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REVIEW

Bone health in people with epilepsy: Is it impaired and what are the risk factors?

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Summary Diseases of the bone are becoming increasingly prevalent. Persons with epilepsy treated with antiepileptic drugs (AEDs) are at greater risk as evidenced by changes in bone turnover, osteoporosis, alterations in bone quality, and fracture. Biochemical indices of bone and mineral metabolism including calcium, vitamin D, parathyroid hormone, and bone turnover markers can be affected. AED exposure is a cause of secondary osteoporosis with decreased bone mineral density (BMD) secondary to poor bone accrual in children or accelerated bone loss in adults. Early reports described osteomalacia, a change in bone quality with increased unmineralized bone. Recent studies do not reveal osteomalacia, but there may be more subtle changes in bone quality. Multiple studies have found an increased risk of fractures in association with epilepsy and AED exposure. Cytochrome P450 enzyme inducing AEDs are most commonly associated with a negative impact on bone, but studies also suggest an effect of valproate. There is limited data regarding the newer AEDs. No single mechanism has emerged to explain all the changes in bone in association with epilepsy and AEDs. Although multiple therapies are available for the treatment of bone disease, there is limited study in persons with epilepsy. It is recommended that all persons obtain adequate amounts of calcium and vitamin D. In addition BMD screening is warranted for persons with long-term AED exposure particularly if they have other risk factors for bone disease.

Contents

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Introduction

Diseases of the bone and joint have been gaining recognition, particularly as the population ages. In the United States, approximately 50% of women and 25% of men will suffer from a fracture.[1] The costs of these fractures are tremendous including loss of daily functioning and jobs, visits to doctor's offices and emergency rooms, hospitalizations, and admissions to nursing homes. The WHO has recognized this growing concern and developed an international initiative to expand awareness and research in this field. Internationally, the years 2000—2010 are the decade of the bone and joint.

Studies suggest that persons with epilepsy treated with antiepileptic drugs (AEDs) may be at an increased risk for bone disease including changes in bone turnover, osteoporosis, alterations in bone quality, and most importantly fracture. Although bone disease is traditionally thought of as a disease in women, the changes associated with epilepsy and AEDs are not gender specific and include both men and women. Unfortunately, despite growing evidence associating epilepsy and AEDs in particular with bone disease, there remains no consensus on whom and when to screen as well as whom and how to treat. This review will highlight current evidence associating epilepsy and AEDs with diseases of the bone.

Biochemical indices of bone and mineral metabolism and bone turnover

Bone structure is composed primarily of calcium and phosphate. Calcium has three definable fractions and the ionized fraction is tightly maintained. The active metabolites of vitamin D function as a regulator of calcium concentration by increasing efficiency of intestinal calcium absorption. In addition, vitamin D recruits stem cells in bone to become mature osteoclasts. Some studies describe reduced calcium concentrations in association with AED treatment,[2] whereas others do not find significant overall reductions in calcium concentrations.[3] There may however, be a differential AED effect with some AEDs significantly reducing calcium relative to others.[4] Similarly some, especially early studies, reported low vitamin D concentrations in association with enzyme inducing AEDs,[2] but more recent studies in ambulatory persons do not consistently find reduced vitamin D metabolites.[4,5]

Calcium and its ionized fraction are regulated by parathyroid hormone (PTH). In response to decreased concentrations of calcium, PTH secretion is increased and the concentration of calcium is increased by increasing the uptake of calcium in the distal renal tubules, improving calcium intestinal efficiency, and finally by increasing bone resorption thereby mobilizing calcium stores in bone. PTH is elevated in some[2] but not all[5,6] studies of persons with epilepsy treated with AEDs.

Bone turnover including osteoblastic (bone formation) and osteoclastic (bone resorption) functions can be assessed by either serologic or urine measurements. Bone formation markers include osteocalcin and bone-specific alkaline phosphatase. Bone resorption markers are measurements of collagen breakdown products in the serum and urine. Elevations of these markers have been reported as being elevated in association with AED treatment.[4,5,7] This elevation suggests a pattern of increased turnover which may result in bone loss over time.

Bone mineral density (BMD)

The life cycle of bone is characterized by several distinct phases. In childhood and adolescence bone is accrued, most significantly in adolescence. Peak BMD is then obtained between ages 20 and 30. In the ensuing years, there is typically a gradual loss of bone. Some time periods are associated with an increased susceptibility to bone loss, for instance in the perimenopausal years.

BMD accumulation and maintenance occur as a function of the coupling of bone resorption and formation. Osteoclasts are the cells responsible for bone resorption whereas osteoblasts are the cells that form bone. An uncoupling of these functions results in either low turnover or high turnover. In childhood these pathologic processes affect bone accumulation, whereas bone loss occurs in the adult years. Osteopenia and osteoporosis are gradations of the same pathology with osteoporosis being more severe. Primary osteoporosis is defined as bone loss in the perimenopausal years and in older men and women. Secondary osteoporosis occurs in association with medical illnesses or medications that results in bone loss (Table 1). AED exposure can result in secondary bone loss. Studies in children find lower BMD when compared to matched controls suggesting poor bone accrual.[8] In adults low BMD has been described in institutionalized and ambulatory populations at multiple sites including the total hip, femoral neck, and lumbar spine.[9] Unfortunately, most studies are cross-sectional and often lack controls, limiting interpretation. One study controlled for genetics by using a sibling/twin pair cohort.[10] The subjects were discordant for treatment with AEDs. BMD analysis revealed significant reduction in

Table 1 Secondary causes of osteoporosis

Gastrointestinal malabsorption
Vitamin D and/or calcium deficiency
Hyperthyroidism
Hyperparathyroidism
Cushing's syndrome
Rheumatoid arthritis and other inflammatory conditions
Alcoholism
Renal disease
Liver disease
Osteogenesis imperfecta
Marfan's syndrome
Homocystinuria
Medications
Glucocorticosteroids
Immunosuppressants (cyclosporine)
Antiepileptic drugs
GnRH agonists
Heparin
Cancer chemotherapy
Depot medroxyprogesterone acetate
Excess thyroid hormone
Diuretics
Metoclopramide
Methotrexate
Antiretroviral therapy for HIV

BMD in those siblings treated with AEDs, with the most significant differences being among those treated with AEDs for greater than 2 years, persons treated with enzyme inducing AEDs, and those older than age 40. Some prospective studies in men and women do find significant bone loss in persons with epilepsy treated with AEDs when compared to controls. For instance a study of men[3] found significant annual BMD loss occurring in young men (24—44) at the femoral neck of the hip, not typically an age group thought to be at risk for bone loss; and in a cohort of postmenopausal women, significant loss occurred in continuous AED users when compared to non-users.[11]

Bone quality

Bone strength is characterized by both bone density and bone quality. Bone quality describes multiple features of bone including structural and material properties as well as biochemical strength. Interestingly, a meta-analysis of both studies of fracture and BMD found that the reported increased fracture risk could not be explained by BMD reports in persons with epilepsy treated with AEDs.[12] Perhaps then changes in bone quality also increase the risk of bone disease and fracture. Osteomalacia is a marked change in bone quality whereby pathologic specimens reveal increased osteoid or unmineralized bone secondary to reduced calcium and/or vitamin D. Osteomalacia and rickets (involving growth plate in children) associated with AED treatment were noted in early studies. Review of these studies finds that most patients were institutionalized and therefore, other confounding variables such as poor diet likely influenced the findings. Biopsy studies in ambulatory persons do not reveal osteomalacia.[2] There may however be more subtle changes in bone quality. Interestingly, bone specimens in rats treated with levetiracetam, phenytoin, and valproate had evidence of changes in bone quality.[13] Biochemical competence was affected in those rats treated with low dose levetiracetam. Further study needs to be done to more definitively assess bone quality in association with epilepsy and AED treatment.

Fracture

Fractures occur as a result of multiple factors including low bone mineral density or osteoporosis, altered bone quality, or a propensity to fall. As already discussed, AED exposure increases one's risk of osteoporosis and may impact bone quality. In addition, persons with epilepsy have an increased risk of falling secondary to either seizures or side effects of AEDs such as poor coordination. Multiple studies have found a 2- to 6-fold increased risk of fractures in persons with epilepsy treated with antiepileptic drugs.[14] A meta-analysis of fracture studies identified AED exposure as a high risk factor with a relative risk or odds ratio (OR) of greater than or equal to 2.0.[15] However, many of these studies are small and poorly controlled. Interestingly, a recent large population-based-controlled registry study found an elevated risk at all sites after controlling for age and sex.[16] The hip was identified as having the highest risk (OR 2.79; 95% CI 2.41—3.24).

Using the same database and a nested case control study design, long-term AED use was associated with an increased risk of fracture, particularly in women.[17]

AEDs

Cytochrome P450 enzyme inducing AEDs are most commonly associated with a negative impact on bone.[9] Although carbamazepine is an enzyme inducing AED, data is more conflicting. Some studies find changes in bone density and turnover whereas others do not. One study suggests a change in bone turnover markers[5,6] in children treated with carba-

mazepine. Prior to initiation of carbamazepine treatment, adolescents had an evaluation of calcium, vitamin D metabolites, PTH, and bone turnover markers and were compared to age, sex, and pubertal matched controls. Significant changes in turnover markers and not PTH or vitamin D metabolites were found after 1 and 2 years after treatment suggesting that these adolescents may have long-term effects on bone density secondary to elevated turnover. Similarly a 6-month longitudinal study found significant BMD reductions in persons treated with carbamazepine.[18] Oxcarbazepine at higher doses is also an enzyme inducer. Interestingly adults treated with this AED had reduced vitamin D metabolites and elevated PTH that was most significant at higher doses.[19]

Although valproate is a cytochrome P450 enzyme inhibitor, studies do suggest an effect on bone.[7,18,20] BMD has been found to be reduced in both children and adults at multiple sites. In addition, bone turnover markers may be elevated.

Data regarding lamotrigine's effects on bone are mixed. Children treated with lamotrigine had shorter stature when compared to matched controls.[21] The investigators speculated that this finding was explained by significantly reduced exercise. Another prospective study found elevated osteocalcin, a marker of bone formation, in association with lamotrigine treatment.[18] In contrast, premenopausal women treated with lamotrigine did not have significant reductions in BMD or changes in bone turnover markers.[4]

Topiramate and zonisamide's effects on bone have received limited study. As both are carbonic anhydrase inhibitors resulting in renal acidosis there may be secondary abnormalities on bone. Interestingly though, carbonic anhydrase potentiates the action of osteoclasts and therefore, inhibitors may have a bone sparing effect. This hypothesis is supported by findings in women with glaucoma treated with acetazolomide, another carbonic anhydrase inhibitor.[22] A double blind randomized preliminary study of topiramate as treatment for obesity did not find significant changes in bone turnover markers compared to placebo controls.[23]

Limited data also exists on levetiracetam's effects on bone. A preliminary study of a limited sample size finds no effects.[24]

Mechanisms

As most evidence associates cytochrome P450 enzyme inducing AEDs with abnormalities in bone, the induction of these enzymes has been proposed as being the main mechanism to describe this effect. This induction potentially increases catabolism of vitamin D to inactive metabolites resulting in reduction of calcium, a subsequent elevation in PTH, and elevation in bone turnover. These clinical findings are supported by recent basic studies evaluating the effect of these AEDs on the expression of specific cytochrome P450 isoenzymes involved in vitamin D metabolism. Phenobarbital, phenytoin, and carbamazepine are among a class of drugs known as xenobiotics. Xenobiotics activate a nuclear receptor known as either the steroid and xenobiotic receptor (SXR) or pregnane X receptor (PXR). One study found that xenobiotics upregulate 25-hydroxyvitamin D3-24-hydroxylase (CYP24) in the kidney through activation of PXR. This enzyme catalyzes the conversion of 25-hydroxyvitamin D to its inactive metabolite, 24,25-dihyroxyvitamin, rather than to its active metabolite, 1,25-dihyroxyvitamin D.[25] Other investigators found that xenobiotic activation of PXR did not upregulate CYP24 but did increase expression of a different isoenzyme, CYP3A4, in the liver and small intestine.[26] This enzyme converts vitamin D to more polar inactive metabolites. Despite some of the clinical and basic studies' findings, the biochemical findings supporting this mechanism are not consistently found in ambulatory persons. In addition, valproate, an enzyme inhibitor may also negatively impact bone. Animal studies suggest other potential mechanisms including effects on bone quality and reduced calcium absorption.[13,27] Other potential mechanisms may also explain described abnormalities in bone (Table 2).[28,29] Further animal and clinical studies are needed to elucidate potential mechanisms associating AEDs with abnormalities in bone.

Screening

No official clear recommendations for screening bone health in persons with epilepsy treated with AEDs are available. Currently the most sensitive predictor of fracture is BMD and therefore, it is

Table 2 Possible mechanisms of AED related bone disease

Hepatic induction of cytochrome P450 enzymes leading to increased metabolism of vitamin D
Direct action of AEDs on osteoblasts
Impaired calcium absorption
Elevated homocysteine
Inhibition of response to PTH
Hyperparathyroidism
Reduced reproductive sex hormones
Reduced vitamin K

reasonable to consider obtaining BMD measurements in person at risk. Multiple risk factors increase one's risk of osteoporosis and fracture (Table 1). In addition to the secondary causes of osteoporosis listed in Table 1, a family history of osteoporosis, Caucasian or Asian races, tobacco use, and small body frame increase one's risk of osteoporosis. Importantly, the more risk factors that are present the higher one's risk of fracture especially if BMD is low.[30] If a person has prolonged exposure to AEDs, particularly with those AEDs commonly associated with abnormalities in bone (enzyme inducing AEDs and valproate), BMD screening as assessed by dual energy X-ray absorptiometry should be performed. There is no defined role for obtaining bone turnover markers although they may be useful if available.

Treatment

Multiple therapies are available for the treatment of bone disease (Table 3). Some are recommended in specific clinical situations. For instance hormone replacement therapy may be useful in a menopausal woman with other significant symptoms including hot flashes. However, if the woman has epilepsy she may be at risk for an increased seizure activity.[31] Bisphosphonates are known to increase BMD and reduce the risk of fracture but are not routinely recommended in premenopausal women particularly as the teratogenic potential is unknown. Limited study is available on these treatments in persons with epilepsy treated with AEDs. A recent randomized double blind trial over 1 year compared low dose (400 IU/day for adults and children) and high dose (4000 IU/day for adults and 2000 IU/day for children) vitamin D supplementation.[32] In the adults, the baseline BMD was reduced at all sites when compared to age and gender matched controls. After 1 year, there were significant increases in BMD at all sites in those receiving high dose but not low dose vitamin D. The children had normal BMD when compared to age and gender matched controls and had significant and comparable increases in BMD in both treatment groups. This study suggests that persons with epilepsy treated with AEDs, should be counseled about adequate vitamin D intake. For those taking enzyme inducing AEDs, higher doses of vitamin D than currently recommended are suggested. In addition, adequate calcium intake and supplementation if necessary are advised.

Table 3 Available treatments for osteoporosis

Calcium and vitamin D supplementation
Bisphosphonates
Alendronate sodium
Alendronate sodium plus 2800 IU vitamin D3
Ibandronate sodium
Risedronate sodium
Risedronate sodium plus 500 mg calcium carbonate
Hormone therapy
Selective estrogen receptor modulators
Raloxifene
Parathyroid hormone

Recommendations

Epilepsy and in particular AEDs are associated with adverse affects on bone including elevated bone turnover, reduced BMD, potential changes in bone quality, and fracture. The increased fracture risk may be a result of multiple factors including the discussed adverse effects in bone as well as an increased propensity to fall secondary to the seizures themselves or side effects of medications (e.g. poor coordination). Enzyme inducing AEDs and valproate in multiple studies results in these bone abnormalities. There is limited data regarding the newer AEDs. It is recommended that all persons obtain adequate amounts of calcium and vitamin D. In addition BMD screening is warranted for persons with long-term AED exposure particularly if they have other risk factors for bone disease.

References

1. U.S. Department of Health and Human Services. *Bone health and osteoporosis: a report of the surgeon general*. Rockville, MD: U.S. Department of Health and Human Services, Office of the Surgeon General; 2004.
2. Weinstein RS, Bryce GF, Sappington LJ, King DW, Gallagher BB. Decreased serum ionized calcium and normal vitamin D metabolite levels with anticonvulsant drug treatment. *J Clin Endocrinol Metab* 1984;**58**:1003—9.
3. Andress DL, Ozuna J, Tirschwell D, Grande L, Johnson M, Jacobson AF, et al. Antiepileptic drug-induced bone loss in young male patients who have seizures. *Arch Neurol* 2002;**59**:781—6.
4. Pack AM, Morrell MJ, Marcus R, Holloway L, Flaster E, Doñe S, et al. Bone mass and turnover in women with epilepsy on antiepileptic drug monotherapy. *Ann Neurol* 2005;**57**:781—6.
5. Verrotti A, Greco R, Morgese G, Chiarelli F. Increased bone turnover in epileptic patients treated with carbamazepine. *Ann Neurol* 2000;**47**:385—8.
6. Verrotti A, Greco R, Latini G, Morgese G, Chiarelli F. Increased bone turnover in prepubertal, pubertal, and postpubertal patients receiving carbamazepine. *Epilepsia* 2002;**43**:1488—92.
7. Sato Y, Kondo I, Ishida S, Motooka H, Takayama K, Tomita Y, et al. Decreased bone mass and increased bone turnover with

valproate therapy in adults with epilepsy. *Neurology* 2001;**57**:445—9.
8. Sheth RD. Bone health in pediatric epilepsy. *Epilepsy Behav* 2004;**5**(Suppl. 2):S30—5.
9. Pack AM, Morrell MJ. Epilepsy and bone health in adults. *Epilepsy Behav* 2004;**5**(Suppl. 2):S24—9.
10. Petty SJ, Paton LM, O'Brien TJ, Makovey J, Erbas B, Sambrook P, et al. Effect of antiepileptic drug medication on bone mineral measures. *Neurology* 2005;**65**:1358—65.
11. Ensrud KE, Walczak TS, Blackwell T, Ensrud ER, Bowman PJ, Stone KL. Antiepileptic drug increases rates of bone loss in older women: a prospective study. *Neurology* 2004;**62**: 2051—7.
12. Vestergaard P. Epilepsy, osteoporosis, and fracture risk—a meta-analysis. *Acta Neurol Scandanavia* 2005;**112**:277—86.
13. Nissen-Meyer LS, Svalheim S, Taubøll E, Reppe S, Lekva T, Solberg LB, et al. Levetiracetam, phenytoin, and valproate act differently on rat bone mass, structure, and metabolism. *Epilepsia* 2007;**48**:1850—60.
14. Mattson RH, Gidal BE. Fractures, epilepsy, and antiepileptic drugs. *Epilepsy Behav* 2004;**5**(Suppl. 2):S36—40.
15. Espallargues M, Sampietro-Colom L, Estrada MD, Solà M, del Rio L, Setoain J, et al. Identifying bone-mass related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. *Osteopor Int* 2001;**12**:811—22.
16. Souverein PC, Webb DJ, Petri H, Weil J, Van Staa TP, Egberts T. Incidence of fractures among epilepsy patients: a population-based study retrospective cohort study in the General Research Database. *Epilepsia* 2005;**46**:304—10.
17. Souverein PC, Webb DJ, Weil JG, Van Staa TP, Egberts AC. Use of antiepileptic drugs and risk of fractures: case control study among patients with epilepsy. *Neurology* 2006;**66**:1318—24.
18. Kim SH, Lee JW, Choi KG, Chung HW, Lee HW. A 6-month longitudinal study of bone mineral density with antiepileptic drug monotherapy. *Epilepsy Behav* 2007;**10**(2):291—5.
19. Mintzer S, Boppana P, Toguri J, DeSantis A. Vitamin D levels and bone turnover in epilepsy taking carbamazepine or oxcarbazepine. *Epilepsia* 2006;**47**(3):510—5.
20. Sheth RD, Wesolowski CA, Jacob JC, Penney S, Hobbs GR, Riggs JE, et al. Effect of carbamazepine and valproate on bone mineral density. *J Pediatr* 1995;**127**(2):256—62.
21. Gou CY, Ronen GM, Atkinson SA. Long-term valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. *Epilepsia* 2001;**42**(9):1141—7.
22. Pierce Jr WM, Nardin GF, Fuqua MF, Sabah-Maren E, Stern SH. Effect of chronic carbonic anhydrase inhibitor therapy on bone and mineral density in white women. *J Bone Miner Res* 1991;**6**(4):347—54.
23. Leung A, Ramsay E. Effect of topiramate on bone resorption in adults. *Am Epilepsy Soc Abstr* 2006;**2**:150.
24. Ali II, Herial NA, Horrigan T, Kellough L, Tietjen GE. Measurement of bone mineral density in patients on levetiracetam monotherapy. *Am Epilepsy Soc Abstr* 2006;**3**:211.
25. Pascussi JM, Robert A, Nguyen M, Walrant-Debray O, Garabedian M, Martin P, et al. Possible involvement or pregnane X receptor-enhanced CYP 24 expression in drug-induced osteomalacia. *J Clin Invest* 2005;**115**(1):177—86.
26. Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, et al. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. *J Clin Invest* 2006;**116**(6):1703—12.
27. von Borstel Smith M, Crofoot K, Rodriguez-Proteau R, Filtz TM. Effects of phenytoin and carbamazepine on calcium transport in Caco-2 cells. *Toxicol In Vitro* 2007;**21**(5):855—62.
28. Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. *Epilepsy Behav* 2004;**5**(Suppl. 2):S3—15.
29. Elliott JO, Jacobsen MP, Haneef Z. Homocysteine and bone loss in epilepsy. *Seizure* 2007;**16**(1):22—34.
30. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *New Engl J Med* 1995;**332**(12):767—73.
31. Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, et al. Hormone replacement therapy in women with epilepsy: a randomized double-blind, placebo-controlled study. *Epilepsia* 2006;**47**(9):1447—51.
32. Mikati MA, Dib L, Yamout B, Sawaya R, Rahi AC, Fuleihan Gel-H. Two randomized vitamin D trials in ambulatory patients on anticonvulsants: impact on bone. *Neurology* 2006;**67**(11): 2005—14.