Bone disease associated with antiepileptic drugs

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ABSTRACT

Antiepileptic drugs (AEDs) are associated with bone disease. Early reports found rickets in children and osteomalacia in adults, but those reports were primarily in institutionalized persons. Studies in ambulatory adults and children taking AEDs do not reveal rickets or osteomalacia but do report abnormalities in biochemical indexes of bone mineral metabolism and density. In addition, fracture rates are increased in AED-treated patients. AEDs that induce the cytochrome P450 enzyme system are most commonly associated with abnormalities in bone. Emerging data suggest that valproate, an enzyme inhibitor, may also affect bone, and there is limited information on the newer AEDs. Several theories on the mechanism of AED-associated bone disease have been proposed, but no single one explains all the reported findings. Identifying AED-treated patients who are at risk for or have bone disease is important, as multiple therapies are available.

Antiepileptic drugs (AEDs) can adversely affect bone health in children, adolescents, and adults. The reported effects of AEDs on bone include rickets, osteomalacia, osteoporosis, and fractures. A number of theories have been proposed to explain why AEDs affect bone, but none explains all the reported effects. This article reviews the manifestations of bone disease in AED-treated patients, identifies the AEDs most commonly associated with bone abnormalities, explores the proposed mechanisms of AED-related bone disease, and surveys treatments available for bone disease in AED-treated patients. We conclude with general recommendations for identifying AED-treated patients at risk for bone disease. Identifying these patients is important, given that seizures can put patients at particular risk for falls and fractures.

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BONE HEALTH IS A PROCESS

Maintenance of bone density and bone health is a dynamic process. Bone mass is determined by a balance of bone resorption and bone formation. In children and adolescents, although the rate of bone resorption is high, the rate of bone formation is even higher. After bone mineral density (BMD) peaks in the third decade of life, bone resorption is greater than bone formation, resulting in loss of bone mass. Along with absolute bone mass, the quality of bone is an important component of bone health.

MANIFESTATIONS OF BONE DISEASE IN PERSONS TREATED WITH AEDs

Rickets and osteomalacia

Rickets is a disorder of mineralization of the bone matrix in growing bone, and thus is a pathologic process seen in children.[1] Both the growth plate and newly formed trabecular and cortical bone are affected. Rickets occurs secondary to deficiencies in active vitamin D, calcium, or phosphorus. Clinical manifestations include hypotonia, muscle weakness, and, in severe cases, tetany. Weight bearing produces a bowing deformity of the long bones.

Bone biopsy is the most sensitive method of diagnosis. The biopsy reveals accumulation of unmineralized bone. Biochemical findings include low levels of calcium, phosphorus, and vitamin D metabolites

(25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) and elevated levels of alkaline phosphatase.

Rickets has been reported in children treated with AEDs.[2] However, most of the subjects were institutionalized, and recent reports in ambulatory children have not found evidence of rickets.[3–6]

Osteomalacia, which literally means softening of bone, results from a reduction in bone matrix mineralization.[7] In contrast to rickets, osteomalacia occurs after cessation of growth and involves only the bone and not the growth plate. Drug-induced osteomalacia occurs secondary to either deficiencies in calcium, phosphate, and active vitamin D or interference with their deposition or action in bone.

As with rickets, bone biopsies of patients with AED-induced osteomalacia are histologically characterized by an increase in osteoid or unmineralized bone and reveal a mineralization defect that produces prolonged mineralization lag time. Low calcium, phosphate, and active vitamin D levels are found in serologic studies. Clinically, diffuse muscle pain is the most common presentation, and persons with osteomalacia have an increased risk of fracture.

Early reports described osteomalacia in patients treated with AEDs.[8,9] However, these reports primarily involved institutionalized patients in whom lack of nutrition and lack of sunlight probably influenced outcomes. Evidence of osteomalacia is rarely found in ambulatory persons.[10,11]

Osteoporosis

Osteoporosis is defined by a reduction in bone mass leading to an increased risk of fracture. It is the major cause of vertebral and hip fractures in the United States. Osteoporosis occurs when there is failure to achieve peak bone mass, increased bone resorption, or inadequate bone formation. Multiple risk factors contribute to the development of osteoporosis **(Table 1)**.

The diagnosis of osteoporosis currently depends on the measurement of BMD. The present criterion standard for obtaining BMD measurements is dual-energy x-ray absorptiometry (DXA).[12] DXA can measure bone mineral content at multiple sites and can detect a 5% decrement in BMD. The most frequently studied site is the lumbar spine, while others include the proximal femur and the radius. Whole-body measurements of both bone mineral content and body composition may be performed.

DXA results are given as absolute BMD, T score (standard deviation after comparison with a sex- and race-matched population), and Z score (standard deviation after comparison with an age-, sex-, and race-matched population). The World Health Organization uses the T score to define osteopenia and osteoporosis, as follows:

- Normal BMD: T score greater than –1
- Osteopenia: T score between –1 and –2.5
- Osteoporosis: T score less than –2.5.

In clinical practice, osteopenia and osteoporosis define the risk for having a fracture, as prospective studies have found that for each standard deviation below 0, the relative risk of fracture increases 1.5-fold to 3-fold.[13,14]

Markers of bone turnover may be increased in osteoporosis. Bone turnover is determined by bone formation and bone resorption, and both can be affected in osteoporosis. Osteoporosis is usually associated with a net increase in resorption over formation. **Table 2** outlines markers of bone turnover. Markers of resorption are markers of bone degradation and reflect the activity of osteoclasts, cells responsible for bone breakdown. Measurements of bone resorption are in the urine or serum. Markers of bone formation include procollagen markers, bone-specific alkaline phosphatase, and osteocalcin (or bone Gla protein). These markers assess the activity of osteoblasts, cells that form bone.

Two classes of osteoporosis exist: primary and secondary. Primary osteoporosis is the reduction in bone mass and occurrence of fractures in menopausal women or older men and women. Secondary osteoporosis occurs in the setting of a specific pathogenic mechanism.

AEDs are a recognized factor that can contribute to secondary osteoporosis.[15] Several studies have used DXA to measure BMD in adults receiving AEDs, finding significantly reduced BMD at the ribs and spine, femoral neck, and total hip.[16,17] A

TABLE 1
Risk factors for osteoporosis

- Increased age
- Race/ethnicity (white or Asian)
- Family history of osteoporosis
- Small frame
- Menopause
- Poor nutrition
- History of smoking
- Alcohol use
- History of an eating disorder
- Hyperthyroidism
- Hyperparathyroidism
- Liver disease
- Medication use: antiepileptic drugs, glucocorticoids, heparin

TABLE 2
Markers of bone turnover

Markers of bone formation
- Alkaline phosphatase (bone-specific alkaline phosphatase)
- Osteocalcin
- Carboxy-terminal propeptide of type I collagen

Markers of bone resorption
- Hydroxyproline
- N-telopeptide of collagen cross-links
- Cross-linked C-telopeptide of type I collagen

prospective study quantified ongoing bone loss in men receiving AEDs, with the highest rate of bone loss in the youngest men.[17] Use of AEDs is associated with reduced BMD in children as well; reports have described reduced axial, appendicular, and whole-body bone mass.[3–6]

In addition, markers of bone resorption are elevated in patients with epilepsy receiving long-term treatment with AEDs[18] and after recent initiation of therapy.[19,20] Markers of bone formation have also been assessed in patients receiving AEDs. Increases in alkaline phosphatase have been seen in both children and adults receiving AEDs, and in reports that measured the isoenzymes, the increase in total alkaline phosphatase was due mainly to the bone fraction.[21,22] High serum levels of osteocalcin are described with AED treatment, and significant elevations in the C-terminal extension peptide of type I procollagen have been reported in patients taking AEDs.[18–20]

Fracture

The most important clinical sequelae of bone disease are fractures. The consequences of fractures include hospitalization, loss of independence, and death. Both osteoporosis and osteomalacia increase the risk for fracture. In the United States, more than 1 million fractures occur as a result of osteoporosis each year.[23] Vertebral and hip fractures are associated with the most significant morbidity and mortality.[24] Identifying patients with epilepsy who are at risk for fracture is clearly important, particularly when seizure control is inadequate and the patient may be at especially high risk for sustaining a fracture during a seizure.

Increased fracture rates have been described in patients with epilepsy.[25–29] Although some studies have found this increased risk to be related to seizures, AED use may be independently associated with fracture risk. One study in postmenopausal women found that those treated with AEDs had double the rate of hip fracture that controls did.[26] A recent meta-analysis identified AED use as a risk factor with a high-strength association with fracture.[29]

BONE HEALTH IN ADULTS TREATED WITH AEDs

Early reports identified AED use as a risk factor contributing to abnormalities in bone mineral metabolism and BMD in institutionalized adults. Pathologic and serologic findings were often consistent with osteomalacia. It is difficult to clearly understand the effects of AEDs on bone in institutionalized patients, as many confounding factors may compromise these patients' bone health, including inadequate sunlight, nutrition, and exercise. More recent studies in ambulatory outpatients have not found definitive evidence of osteomalacia but have found biochemical abnormalities and reduced BMD.[16–18,30,31]

Reduced BMD has been found in adults receiving long-term AED therapy.[16–18,30,31] The sites of reduced BMD include the lumbar spine and hip. Some reports have identified treatment duration as being correlated with low BMD,[16,17] but this is not a consistent finding.[31,32] Bone loss over 1 year was prospectively identified in one study.[17]

Biochemical abnormalities in adults receiving AEDs include hypocalcemia, hypophosphatemia, reduced levels of active vitamin D metabolites, elevated parathyroid hormone (PTH) levels, and elevated markers of bone resorption and formation.[9,16,18,22,30,33–41] In contrast, one study of patients taking valproate found hypercalcemia.[30] The elevated serum calcium was postulated to reflect increased bone resorption. Although significant reductions in levels of vitamin D metabolites were reported in early studies, more recent reports have not found abnormalities of vitamin D.[16,18,31]

BONE HEALTH IN CHILDREN RECEIVING AEDs

Understanding the effects of AEDs in children is important, as it is during childhood and adolescence that peak BMD is obtained. The first studies describing bone abnormalities in children receiving AEDs found evidence of rickets.[42] Like the early adult studies, these were primarily in institutionalized children. Studies in ambulatory children have not found rickets[3–6] but have found other biochemical abnormalities and decreased BMD relative to

children not treated with AEDs.

Pediatric studies reveal findings consistent with both increased and decreased bone turnover. Elevated markers of bone formation and resorption have been reported.[19,20,43,44] As in recent adult studies, these elevations have been independent of reduced levels of vitamin D metabolites.[11,19,20] In addition, PTH levels are not elevated in some studies in which increased markers of bone turnover are seen.[19,20] Decreased markers of bone formation and resorption have also been described in several pediatric studies.[5,6]

Compared with children not receiving AEDs, children who receive AEDs may have reduced BMD.[3–6] The clinical significance of these findings is not clear, as there are no pediatric BMD reference databases. Further longitudinal studies are needed to understand the long-term effects of AEDs on developing bone.

WHICH AEDs ARE LINKED WITH BONE DISEASE?

AEDs that induce the cytochrome P450 enzyme system (phenobarbital, phenytoin, and carbamazepine) are most commonly associated with abnormalities in bone. Most of the published studies and evidence involve patients receiving these medications.[3,4,18–20,36,41]

Valproate is an inhibitor of the cytochrome P450 enzyme system, and emerging data suggest that it also negatively affects bone. Although early reports evaluating indexes of bone metabolism in patients taking valproate found no significant abnormalities, a recent study of 40 adults receiving long-term valproate monotherapy found increased serum concentrations of calcium, low levels of vitamin D metabolites, increased markers of bone resorption and formation, and decreased BMD.[30] A few small pediatric studies have evaluated bone mass in children taking valproate, finding both reduced BMD[4,5,45] and normal BMD.[46]

Multiple new AEDs have been approved over the past 10 years. Few studies have evaluated the effect of these newer medications on bone mineral metabolism and BMD.[5,31,32] One study in adults looked at the effect of some of the new drugs (gabapentin, lamotrigine, topiramate, and vigabatrin) on bone mineral metabolism and BMD, and found no significant abnormalities.[32] In children, short stature, low bone mass, and reduced bone formation were described in boys and girls treated with lamotrigine either alone or in combination with valproate.[5] Certainly, more studies are needed to determine whether any of these AEDs cause abnormalities in bone.

TABLE 3
Proposed mechanisms of AED-related bone disease

- Reduced levels of vitamin D metabolites secondary to induction of the cytochrome P450 enzyme system
- Reduced calcium absorption
- Impaired response to parathyroid hormone
- Hyperparathyroidism
- Impaired bone formation
- Impaired bone resorption
- Vitamin K deficiency
- Calcitonin deficiency

AED polytherapy has been shown to be associated with a higher risk of bone metabolism abnormalities than monotherapy.[16,35,41] No particular combination has emerged as more likely to cause bone disease, but in all of the studies identifying polytherapy as an independent risk factor, treatment included an enzyme-inducing AED as one of the agents.

MECHANISMS OF AED-ASSOCIATED BONE DISEASE

Several theories have been proposed to explain the link between AEDs and bone disease **(Table 3)**.[47] No single theory explains all the reported findings, and there may be multiple mechanisms.

Increased catabolism of vitamin D, resulting from hepatic induction of the cytochrome P450 enzyme system, is the principal mechanism reported. However, it does not explain the findings described in patients receiving other medications, such as valproate (an inhibitor of the cytochrome P450 enzyme system), or the recent evidence of increased bone turnover independent of vitamin D deficiency.

Levels of active vitamin D metabolites may be reduced in persons taking enzyme-inducing AEDs, suggesting that induction of hepatic cytochrome P450 enzymes partially explains the findings in bone.[33,37,41] The AEDs that induce cytochrome P450 enzymes may cause increased conversion of vitamin D to polar inactive metabolites in the liver microsomes, reducing levels of bioavailable vitamin D.[41,48] Reduced levels of biologically active vitamin D lead to decreased absorption of calcium in the gut, resulting in hypocalcemia and an increase in circulating PTH. PTH then increases the mobilization of bone calcium stores and subsequent bone turnover.

Impairment of calcium absorption is another postulated mechanism, as AEDs may interfere with

intestinal absorption of calcium. Impaired absorption would lead to hypocalcemia and feedback hypersecretion of PTH. Markedly decreased calcium absorption was found in rats treated with phenytoin but not in those treated with phenobarbital,[49] suggesting that impaired calcium absorption may play a role in patients treated with phenytoin.

Impaired bone resorption and formation may contribute to AED-associated bone disease. Significant bone resorption was found in neonatal mouse calvaria treated with phenytoin and one of its metabolites (5-[4-hydroxyphenyl]-5-phenylhydantoin).[50] Those calvarias treated with phenytoin and its metabolite had increased bone resorption, as demonstrated by significantly increased calcium in the medium, compared with controls. Proliferation of human osteoblast-like cells was inhibited by treatment with phenytoin and carbamazepine at concentrations equivalent to therapeutic doses for the treatment of epilepsy.[51] These results suggest that both bone resorption and formation may be affected by AEDs.

Inhibition of the cellular response to PTH also may have a role. Fetal rats treated with phenytoin or phenobarbital demonstrated an impaired response to PTH.[42] Inhibition of the bone resorptive response to PTH could lead to hypocalcemia, a frequent finding in patients taking AEDs.

Hyperparathyroidism, as demonstrated in clinical studies, is another possible mechanism. Both male patients with normal vitamin D status[18] and subjects who were vitamin D–repleted[11] have shown evidence of hyperparathyroidism. Hyperparathyroidism can primarily activate bone resorption and, through a coupling phenomenon, secondarily activate bone formation. Increased bone turnover in the setting of hyperparathyroidism is consistent with this theory. However, one study found increased bone turnover and normal levels of PTH.[19,20]

Poor vitamin K status may be an independent risk factor for postmenopausal bone loss, as suggested by accumulating evidence.[52] Vitamin K is a cofactor in the posttranslational carboxylation of several bone proteins, most markedly osteocalcin, a marker of bone formation. Rats treated with phenytoin had more bone loss over a 5-week period than did rats treated with phenytoin and vitamin K_2 (menatetrenone).[53] These findings suggest that insufficiency of vitamin K may contribute to bone loss secondary to phenytoin exposure.

Calcitonin deficiency is a final postulated mechanism, having been associated with AED treatment both in vitro and in vivo.[42,54] Calcitonin, a hormone produced by the thyroid gland, inhibits osteoclast-mediated bone resorption. A deficiency of calcitonin may therefore accelerate bone turnover.

TREATMENT OF AED-ASSOCIATED BONE DISEASE

Multiple therapies for bone disease are available, but vitamin D supplementation is the only modality studied specifically for the treatment of bone disease in persons taking AEDs.[55,56] Other approved therapies for bone loss include calcium supplementation, bisphosphonates, hormone replacement therapy (HRT), selective estrogen receptor modulators, and calcitonin. Although not approved by the US Food and Drug Administration (FDA), vitamin K supplementation is being studied as a potential treatment for bone loss.

High-dose vitamin D supplementation normalized 25-hydroxyvitamin D levels in one study of AED recipients[55] and improved biochemical indexes of bone mineral metabolism and BMD in another.[56] The dosages ranged from 400 to 4,000 IU/day. The recommended daily allowance is 400 to 800 IU.

Calcium supplementation can slow the rate of bone loss in elderly women not taking AEDs who have inadequate dietary calcium intake.[24] The recommended daily allowance varies according to age, sex, and reproductive status (1,000 mg to 1,500 mg). Because most people do not achieve adequate calcium intake from their diet, supplementation is usually necessary.

Bisphosphonates are potent inhibitors of bone resorption. Given the findings of increased bone resorption associated with AEDs, bisphosphonates may be an effective treatment for bone disease in patients receiving AEDs.[24] Alendronate and risedronate are two FDA-approved bisphosphonates. For treatment of osteoporosis, the dosage of alendronate is 10 mg/day or 70 mg/week; for prevention of osteoporosis, the dosage is 5 mg/day or 35 mg/week. Risedronate is given at a dosage of 5 mg/day.

Hormone replacement therapy. Data also support the efficacy of HRT in stopping bone loss in postmenopausal women.[24] However, HRT has multiple reported side effects, including increased risk for breast cancer, cardiovascular events, and venous thromboembolism,[57] and women with epilepsy should be aware that HRT may increase seizure activity.[58]

Selective estrogen receptor modulators. Raloxifene is an FDA-approved selective estrogen receptor modulator that acts as a partial agonist in bone.

In postmenopausal women not taking AEDs, raloxifene increases bone mass and reduces the risk of vertebral fracture by 40% to 50%.[59,60] Its side effects include an increased risk of deep venous thrombosis and an increase in hot flashes. Raloxifene is given at a dosage of 60 mg/day.

Calcitonin may be an effective treatment in persons with bone disease receiving AEDs, since studies have associated reduced calcitonin levels with AED use. In a study of postmenopausal women not taking AEDs, intranasal salmon calcitonin at a dosage of 200 IU/day reduced the rate of vertebral fracture but not of peripheral fracture.[61]

Vitamin K supplementation. Interventional studies have shown retardation of bone loss with increased vitamin K intake (via vitamin K_1 and vitamin K_2 supplement formulations) in postmenopausal women.[52,62] Similarly, growing rats treated with phenytoin and menatetrenone (vitamin K_2) had higher BMD than did animals treated with phenytoin alone.[53] Vitamin K_2 may therefore have a therapeutic benefit in AED-induced bone loss.

IMPLICATIONS AND RECOMMENDATIONS

Few physicians are aware of the long-term effects of AEDs on bone. A recent survey of US board-certified or board-eligible pediatric and adult neurologists highlights this lack of awareness.[63] Although the length of time needed for AEDs to affect bone is not known, several prospective studies have found changes in markers of both bone turnover and BMD after 1 year of treatment.[17,19,20]

We recommend evaluating bone by quantifying BMD as measured by DXA after 5 years of AED treatment and before AED treatment in postmenopausal women. We recommend proceeding as follows:

- If the T score is greater than –1, encourage calcium and vitamin D supplementation and weight-bearing exercise.
- If the T score is between –1 and –2, also encourage supplementation and weight-bearing exercise, and repeat the study in 1 to 2 years.
- If the T score is less than –2, further intervention may be required and the treating neurologist may wish to refer the patient to an internist or an endocrinologist.

Vitamin D supplementation in high doses has been shown to improve biochemical indexes of bone mineral metabolism and BMD in patients taking AEDs. In addition, other therapeutic options are available for the treatment of bone loss and may be effective for AED-associated bone disease.

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