

MAINTAINING STRONG BONES: STRONG OPINIONS, LITTLE EVIDENCE

Two Randomized Vitamin D Trials in Ambulatory Patients on Anticonvulsants: Impact on Bone. Mikati MA, Dib L, Yamout B, Sawaya R, Rahi AC, Fuleihan Gel-H. *Neurology* 2006;67(11):2005–2014. **OBJECTIVE:** To investigate the effects of two doses of vitamin D given over 1 year on bone density in ambulatory patients on long-term antiepileptic drug (AED) therapy. **METHODS:** We conducted two parallel, randomized, controlled trials in 72 adults (18–54 years old) and 78 children and adolescents (10–18 years) on long-term AED therapy. They received either low-dose vitamin D 400 IU/day or high-dose vitamin D 4,000 IU/day (adults) and 2,000 IU/day (children/adolescents). Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry. **RESULTS:** In adults, baseline BMD was lower than that of age- and gender-matched controls vs either a Western or an ethnically identical population. After 1 year, there were significant increases in BMD at all skeletal sites compared to baseline in the high-, but not in the low-dose treatment group. However, BMD at 1 year remained below normal. In children, baseline BMD was normal vs age- and gender-matched controls and showed significant and comparable increases in both treatment groups. **CONCLUSIONS:** In ambulatory adults on antiepileptic drugs, high-dose vitamin D therapy substantially increased bone mineral density at several skeletal sites. In children, both doses resulted in comparable increases in bone mass.

COMMENTARY

Over the past several years, much attention has been paid to the maintenance of bone health in patients with epilepsy who are taking antiepileptic drugs (AEDs) (1). Studies suggesting a higher risk of bone loss in such patients were first published over 35 years ago but were largely ignored by the medical community (2). The best-documented risks for reduced bone density are associated with enzyme-inducing AEDs, with enhanced vitamin D metabolism being the generally accepted mechanism. But more direct effects of AEDs on bone homeostasis also have been proposed, and reduced bone mass has been observed in patients taking long-term valproate, which is not a cytochrome P enzyme inducer (3). Until recently, however, no serious attempts to quantify the risk of osteoporosis or to reduce it had been made.

Maintenance of normal bone mass depends on proper functioning of a complex network of enzymes, vitamins, and minerals, to ensure an accurate homeostasis of ongoing bone resorption and new bone formation. This process requires adequate dietary calcium and its normal absorption and use, which are facilitated by normal vitamin D serum levels. Vitamin D is derived from the diet, but cutaneous metabolism into its active form is a photosensitive process, normally facilitated through exposure to sunlight.

Osteoporosis (i.e., a bone density T score <-2.5) and osteopenia (T score between -1.0 and -2.5) are remarkably common, with prevalence increasing with age. Other risk factors include female gender, sedentary lifestyle, thin body habitus, Caucasian race, and a positive family history. Extreme inactivity and indoor life (common in those with cerebral palsy or residency in assisted living facilities) are powerfully associated with bone loss; the reported prevalence of osteoporosis is up to 97% in this population (4). The prevalence of osteoporosis in the largely sedentary, general U.S. population is also remarkably high: the lifetime incidence of osteoporosis-related fracture is 30% to 50% in women and 15% to 30% in men (5).

The significant impact of bone loss on the population with epilepsy has been well demonstrated. Already at risk for fractures from falls related to seizures, drug toxicity, and associated neurological disease, patients with epilepsy on enzyme-inducing AEDs or valproate are at a slightly higher fracture risk than the general population, with a detectable dose-response effect (6). However, even as the connection between AEDs and bone loss has become more firmly established, there has been little to guide the clinician hoping to reduce the risk of osteopenia and osteoporosis in patients with epilepsy, who often take AEDs for many years. Confirmation of the efficacy of supplementing vitamin D and calcium to prevent osteoporosis in the general population is scanty (7,8), yet various clinicians writing about long-term exposure to AEDs have recommended supplements of up to 1,500 mg of extra calcium daily. However, there is no evidence-based guidance for the prescribing physician about the efficacy of dietary supplements or the appropriate amounts to recommend.

Even more disturbing is the lack of guidance for the practitioner wanting to monitor the bone health of patients. The National Osteoporosis Foundation and the United States Preventive Services Task Force guidelines stipulate bone density scans for all women over the age of 65. Those women with risk factors, such as a family history of osteoporosis, fractures, low body weight, and smoking, are considered for scanning after age 50 years. No consistent guidelines are available for males, neither are there data that indicate when to measure bone density in patients with epilepsy exposed to years of enzyme-inducing or other types of AEDs.

Mikati et al. decided to examine the effects of vitamin D supplementation in adults and children taking AEDs. Their study has the advantages of relative long duration (1 year), prospective design, well-balanced comparison groups, a community-based population, and carefully measured vitamin D serum and bone density levels. Its shortcomings include an unblinded study design and a high subject dropout rate (25%), with only a vague description of the reasons for the latter. It seems largely to be attributed to gastrointestinal distress in those on high-dose vitamin D. In addition, the study is underpowered for the detection of any dosage effect in the pediatric group, thus offering no grounds for a rational method of choosing a dose for vitamin D supplementation. Finally, the formulation of the supplement (liquid rather than tablet), probably chosen for easier acceptance by the pediatric group, would unlikely to be adopted for daily use by adults.

After 1 year of therapy with vitamin D, the percentage of adult patients with normal serum levels increased from 20% to 69% and the percentage of children from 41% to 50%. The more clinically significant value of bone density increased significantly at three of five bone sites in the treated adult group. In the pediatric group, lumbar spine bone density, total body bone mineral content, and total body bone mineral density all increased in treated subjects; however, all of the children started the study with normal bone mineral densities. In contrast, the adult group as a whole had lower bone mineral density at all sites at the beginning of the study.

Possible variations in risk arising from different AEDs were not detected in this study, which simply divided the drugs into enzyme inducers and all the other agents, leaving open the question of whether the results would change significantly if those taking valproate were reassigned to the enzyme-inducing

group. The study was not powered to detect significant differences among individual enzyme-inducing AEDs. Furthermore, the element that makes the study least applicable to ordinary clinical practice is the omission of calcium supplementation—despite the judgment that dietary calcium in the study subjects was judged to be “suboptimal.” Perhaps the improvements in bone density that were seen in the treated groups would have been more significant had calcium intake been supplemented as well.

This paper includes a revealing tabulated literature review, exposing the bewildering variations, contradictions, and limitations of previous studies of calcium and/or vitamin D supplementation for patients with epilepsy. The neurology community and their patients must still wait for a study that may help determine the utility of such supplements, the most appropriate time to introduce them, and the most useful dosages.

by Donna C Bergen, MD

References

1. Pack AM, Morrell, MJ. Epilepsy and bone health in adults. *Epilepsy Behav* 2004;5(suppl 2):S24–S29.
2. Dent CE, Richens A, Rowe DJ, Stamp TC. Osteomalacia with long-term anticonvulsant therapy in epilepsy. *Br Med J* 1970;4:69–72.
3. Oner N, Kaya M, Karasalihoglu S, Karaca H, Celtik C, Tutunculer F. Bone mineral metabolism changes in epileptic children receiving valproic acid. *J Paediatr Child Health* 2004;40:470–473.
4. Henderson RC, Lark RK, Gurka MJ, Worley G, Fung EB, Conaway M, Stallings VA, Stevenson RD. Bone density and metabolism in children and adolescents with moderate to severe cerebral palsy. *Pediatrics* 2002;110(1 pt 1):e5.
5. Tucci JR. Importance of early diagnosis and treatment of osteoporosis to prevent fractures. *Am J Managed Care* 2006;12(suppl 7):S181–S190.
6. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. *Epilepsia* 2004;45:1330–1337.
7. The Cochrane Collaboration. Vitamin D with calcium supplements reduces the risk of fracture in some older people. www.cochrane.org/review/en/ab000227.html, accessed 12 May 2007.
8. Shea B, Wells G, Cranney A, Moher D, Adachi R, Treleaven D, Peterson J, Tugwell P, Henry D. The effect of calcium supplementation on bone loss in postmenopausal women. www.cochrane.org/colloquia/abstracts/oslo/Oslo32.htm, accessed 12 May 2007.