Screening Bone Mineral Density in Epilepsy: A Call to Action, But What Action?

Value of Routine Screening for Bone Demineralization in an Urban Population of Patients with Epilepsy. Lado F, Spiegel R, Masur JH, Boro A and Haut SR. *Epilepsy Research* 2008;78(2–3):155–160. BACKGROUND: Reduced bone mineral density (BMD) is increasingly recognized in patients receiving antiepileptic drug therapy. The precise prevalence is not known due to variability across populations studied. We set out to characterize the prevalence of abnormal BMD in an urban population of patients with epilepsy with the intent to determine the value of routine BMD screening. METHODS: We performed a cross-sectional study of 130 consecutive patients seen thorough our Comprehensive Epilepsy Center. BMD was measured using dual X-ray absorptiometry and was reported as *T*-score and *Z*-score. Additional information collected for each patient included age, race, gender, current and prior AEDs, ambulatory state, menopausal state, concomitant medications potentially associated with reduced bone mineralization, and comorbid illness potentially associated with reduced bone mineralization. Associations between reduced bone mineralization and variables were tested for significance using Fisher's exact test, Student's *t*-test, and Wilcoxon rank sum test. RESULTS: The average age of the entire study population was 43.5 (±12.5) years. Fifty-five percent of patients had *T*-score less than or equal to −1, the WHO criterion for osteopenia in postmenopausal women. The prevalence of *Z*-scores less than −2.0 was 15%, which is more than sixfold greater than expected. The markers for decreased BMD included older age or menopause in women, longer duration of therapy, and a history of use of phenytoin or phenobarbital. Assisted ambulation was also associated with low BMD. CONCLUSION: Our results indicate that reduced bone mineralization is prevalent and a significant health concern in an urban population of patients with epilepsy. Because of the high prevalence of reduced bone mineralization reported in numerous studies including this study, routinely screening for reduced bone mineralization is warranted in patients receiving anticonvulsant therapy.

Bone Health in Young Women with Epilepsy after One Year of Antiepileptic Drug Monotherapy. Pack AM, Morrell MJ, Randall A, McMahon DJ and Shane E. *Neurology* 2008;70(18):1586–1593. OBJECTIVE: Antiepileptic drugs (AEDs) may have adverse effects on bone mineral density (BMD) and metabolism. We previously reported biochemical evidence of increased bone turnover in premenopausal women with epilepsy on phenytoin monotherapy compared with those on carbamazepine, lamotrigine, and valproate. We therefore hypothesized that rates of bone loss would be higher in young women treated with phenytoin. METHODS: Ninety-three premenopausal women with epilepsy receiving a single AED (carbamazepine, lamotrigine, phenytoin, or valproate) participated. Subjects completed nutritional and physical activity questionnaires. Biochemical indices of bone and mineral metabolism and BMD of the proximal femur and lumbar spine were measured at baseline and 1 year. RESULTS: Participants reported high calcium intake (>1,000 mg/day) and were physically active. Significant loss (2.6%) was seen at the femoral neck in the phenytoin group. BMD remained stable in the other AED groups. Bone turnover markers and calciotropic hormones were unchanged after 1 year in all groups except for a significant decline in urine N-telopeptide in the phenytoin group. In women receiving phenytoin, lower serum 25-hydroxyvitamin D concentrations were associated with higher parathyroid hormone, bone alkaline phosphatase, and urine N-telopeptide levels, a biochemical pattern consistent with secondary hyperparathyroidism and increased remodeling. CONCLUSION: In this study, young women treated with phenytoin had significant femoral neck bone loss over 1 year. In contrast, those treated with carbamazepine, lamotrigine, and valproate did not have detectable adverse effects on bone turnover or bone mineral density. These results raise concerns about the long-term effects of phenytoin monotherapy on bone in young women with epilepsy.

COMMENTARY

Antiepileptic drug (AED) therapy for epilepsy is associated with metabolic bone disease and a high risk for fractures. Reduced bone mineral density (BMD) has been reported in 20 to 75 percent of patients taking AEDs in cross-sectional studies (1,2). Patients with epilepsy have a two-fold increased risk of pathological fracture (2) and a five-fold increase risk of hip and spine fracture, compared with the general population (3). At least some of this risk may be secondary to low BMD. Despite these facts, bone health and fracture risk often are inadequately assessed in epilepsy, and guidelines for screening and treatment are not available. The two studies reviewed here provide support for incorporating BMD measurement into clinical care of patients with epilepsy and begin to offer guidance on when BMD screening should be considered.

Dual-energy x-ray absorptiometry (DEXA) scan is the current gold standard for diagnosis of osteoporosis. The *t* score is the difference in the number of standard deviations between the patient's BMD value and the mean value calculated from a population of young controls with peak bone density. The *z* score is the difference in standard deviations between the

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patient's BMD and the BMD measured in an age and gender-matched Caucasian population. The World Health Organization (WHO) defines osteopenia as a t score ≤ -1 and osteoporosis as a t score ≤ -2.5. For patients below age 50, the z score may be a more appropriate measure, with z scores ≤ -2 being "below the expected range for age."

Lado et al. systematically measured the BMD of 130 consecutive patients, seen over a 6-month period in 2005, who had received AEDs for more than 3 years. The investigators found a higher than expected prevalence of clinically significant low BMD; 39% of patients had osteopenia and 16% had osteoporosis. This prevalence is similar to that found by Pack et al., also in a refractory epilepsy population (1). Multivariate analysis identified older age, menopause, phenobarbital or phenytoin use, and duration of AED use of more than 25 years to be associated with low BMD. The strengths of this study are the inclusion of a demographically diverse population, systematic recruitment of subjects, and collection of data on other factors affecting the risk of fracture (e.g., race, ethnicity, ambulatory state, comorbid illness, and concomitant medications). Risk factors, such as diet, smoking, alcohol use, family history of fracture, and prior history of fracture, were not assessed. Most patients had refractory epilepsy and had received multiple AEDs for many years (mean 25.8 years); so, the results cannot be generalized to those with shorter durations of treatment. Because of the cross-sectional design, small numbers of patients taking each AED, and frequency of AED polytherapy, the effects of individual AEDs on BMD was difficult to assess.

Pack et al. examined changes in bone density over a 1-year period in young women on AED monotherapy. Of four commonly used AEDs (carbamazepine, lamotrigine, phenytoin, and valproate), only phenytoin was associated with significant femoral neck bone loss over 1 year. Biochemical analysis suggested secondary hyperparathyroidism and increased bone remodeling as the likely mechanism, as low serum 25-hydroxyvitamin D levels were associated with increased parathyroid hormone, bone alkaline phosphatase, and urine N-telopeptide. These data provide some reassurance that young adults taking AED monotherapy, other than phenytoin, are not at high risk for bone loss, but leave some questions unanswered. There were small numbers of patients in each treatment group. The patients reported good dietary calcium intake, and vitamin D insufficiency was uncommon. These factors may have prevented or ameliorated some of the adverse effects of AEDs on BMD. DEXA scans were repeated at a 1-year interval. While a short study duration minimizes the number of patients who might require a change of AED therapy or who might drop out of the study, 1 year may be too short a time interval to detect bone loss in a small patient sample.

Do all patients with epilepsy need to be routinely screened with DEXA? If so, when and how often? Osteoporosis screening guidelines do not provide specific guidance for practitioners caring for patients with epilepsy (4,5). Many authors propose that 3 to 5 years of AED therapy is a reasonable interval before assessing BMD. The findings of Pack et al. support this interval. The question of how often BMD screening should be repeated has not been addressed in any systematic way, and the answer will likely differ based on patient age, type of AED treatment, the degree of bone loss seen on the first DEXA, and whether the patient is taking an osteoprotective treatment.

In the general population, BMD is only one factor determining fracture risk. Approximately half of patients in the community with fractures do not have osteoporosis by the 1994 WHO BMD criteria. The WHO fracture risk assessment (FRAX) web-based tool (http://www.shef.ac.uk/FRAX/) is designed to assess the 10-year risk of a major pathological fracture (6). The model uses risk factors of age (i.e., 40–90 years), gender, body mass index, previous fragility fracture, history of fracture in parents, current smoking, glucocorticoid use, rheumatoid arthritis, diseases associated with secondary osteoporosis, alcohol use, and BMD at the femoral neck to generate the risk, especially of hip fracture. Other known risk factors, such as nutritional status, falls, and menopausal status, are not included in the model. For the general population, the FRAX tool can be used to determine which patients should have BMD testing and provides risk thresholds at which treatment should be initiated (6).

Unfortunately, the model has limitations for patients with epilepsy; it does not provide estimates of fracture risk in patients younger than 40 years. Patients with epilepsy may have many other risk factors for fractures besides low BMD, including falls during seizures, adverse effects of AEDs on balance, coordination, and vision, as well as concomitant neurologic deficits that increase the risk of falls. To best refine fracture risk estimates, patients with epilepsy should have a comprehensive assessment of fall and other risk factors for fractures with FRAX in addition to a BMD test. Test results will help to define subpopulations of patients with intermediate decreases in BMD in whom treatment should be more aggressive.

Lado et al. proposed that the finding of low BMD in a high proportion of patients with epilepsy justifies DEXA screening of all epilepsy patients as a standard of care. Certainly, their findings serve to call urgent attention to the issue of bone health in epilepsy. The clinical utility of screening tests, however, depends not just on the prevalence of the disease under study, but the ability to diagnose subclinical disease and institute a low-risk therapy that reduces later morbidity and mortality. At this point, the finding of a low BMD usually prompts the question: "Now, what should I do?" as there are no evidenced-based guidelines

for treatment of bone disease for patients with epilepsy. As in other areas lacking clear treatment guidelines, this uncertainty reduces the clinical utility of screening.

What therapy should be started and when? The pathogenesis of bone disease in epilepsy is not well understood and is likely multifactorial. It is difficult to translate guidelines for osteoporosis prevention and treatment in the general population to young patients with epilepsy. For patients with *t* scores between –1.0 and –2.5 (osteopenia), the most common recommendation is to increase weight-bearing exercise and ensure adequate calcium (1200 mg daily) and vitamin D intake (400–800 international units [IU]) (7,8). One could argue that these safe and inexpensive recommendations should be instituted in all epilepsy patients prophylactically, without need for measurement of BMD. A systematic review of the efficacy of vitamin D therapy in the general population showed that vitamin D at doses of over 700 IU daily, plus calcium supplementation, has a small beneficial effect on BMD and reduces the risk of fractures and falls, but an optimal serum 25-hydroxyvitamin D for bone health was difficult to define (10). Similarly, another study demonstrated that 400 IU daily of vitamin D did not lead to improvement in BMD for adult patients with epilepsy, while 4000 IU daily was associated with improvements; whether this protocol translates into decreased fracture risk has not been assessed (9). Bisphosphonates decrease fracture risk in patients over age 50, but their efficacy and long-term adverse effects have not been adequately assessed in younger patients or for patients with AED-associated osteoporosis.

The current studies confirm bone health to be an important long-term health issue for patients with epilepsy. Trials now need to be designed that prospectively evaluate the efficacy of prevention and treatment strategies to improve BMD. Routine screening of BMD in epilepsy will only be useful and cost effective if the detection and treatment of low BMD translates into lowered fracture rates.

by Susan T. Herman, MD

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