



## Levetiracetam Treatment Does Not Result in Broken Bones

### Effects of Levetiracetam as a Monotherapy on Bone Mineral Density and Biochemical Markers of Bone Metabolism in Patients With Epilepsy.

Koo DL, Joo EY, Kim D, Hong SB. [Published online ahead of print September 30, 2012, *Epilepsy Res.* doi:xxxxxx.]

**PURPOSE:** Antiepileptic drugs (AEDs) may have adverse effects on bone metabolism and bone mineral density (BMD). The aim of this study is to determine the changes of bone metabolism and BMD in epilepsy patients who are undergoing levetiracetam (LEV) monotherapy. **METHODS:** Drug-naïve, sixty-one patients with recent onset epilepsy were recruited (24 female, 37 males; mean age:  $31.0 \pm 13.1$  years) in this study. We measured calcium, phosphate, bone alkaline phosphatase, parathyroid hormone, osteocalcin, insulin-like growth factor (IGF)-1, C-telopeptide, vitamin D3 levels and bone density measurements with DEXA method before and after LEV administration of mean duration  $14.16 \pm 3.36$  months. **RUSULTS:** T score in lumbar spine (L1-L4) was significantly increased with the correction of multiple T tests using Bonferroni's test across LEV monotherapy ( $p=0.0401$ ). However, no significant change was observed in other parameters for BMD and T score. Repeated measures ANOVA with Bonferroni's correction of confounders such as sex, age, and treatment duration revealed significant increase in T score in lumbar spine ( $p=0.0164$ ). The level of average LEV dosage itself did not reveal any significant association with BMD and bone metabolism. **CONCLUSIONS:** We suggest that LEV monotherapy may have no harmful effect on bone strength and metabolism for 1 year.

### Commentary

Persons with epilepsy have a two- to six-fold increased risk of fracture (1). Antiepileptic drug (AED) exposure independently increases the risk (2, 3). Therefore, when choosing an AED, it is important to understand its potential secondary effects on bone. AEDs most commonly associated with adverse effects on bone include phenytoin and phenobarbital (1). Levetiracetam is a broad-spectrum AED used for the treatment of partial and generalized epilepsy syndromes. Whether levetiracetam affects bone has received limited study and is not well understood.

The impact of levetiracetam on bone was previously evaluated in an animal study (4). Rats were treated with low-dose (50 mg/kg) and high-dose (150 mg/kg) levetiracetam. Levetiracetam did not affect bone mass. Low-dose levetiracetam was associated with reduced biochemical strength of the femoral neck, which is predominantly trabecular bone. Trabecular bone is metabolically active bone and contains relatively more cartilage. The femoral diaphysis, which is predominantly cortical bone was not significantly altered. In addition, osteocalcin, a marker of bone formation, was increased in low-dose levetiracetam-treated animals. Increased osteocalcin reflects increased bone turnover resulting in bone loss over time.

An abstract presentation of 16 subjects showed a favorable effect of levetiracetam on bone mineral density (BMD)

and vitamin D concentrations (5). Subjects ranging in age from 20 to 66 had BMD measurements using dual energy x-ray absorptiometry (DXA) and serologic vitamin D concentrations as well as osteocalcin measurements after a minimum of 6 months levetiracetam exposure. DXA is the most commonly used tool to assess BMD. No subject had evidence of low bone mass (osteopenia or osteoporosis). Osteopenia is defined by the World Health Organization as T-scores between  $-1.0$  and  $-2.5$ . Osteoporosis is defined as  $-2.5$  or lower. All subjects had vitamin D concentrations in the normal range. Four subjects had elevated osteocalcin. In the absence of other bone turnover markers, and normal BMD, this finding is of unclear significance. Unfortunately, these results were never published as a peer-reviewed paper.

In contrast, a retrospective cross-sectional study, published as a short communication, found that the incidence of low BMD (either osteopenia or osteoporosis) was higher among levetiracetam monotherapy users compared with users of other AEDs including topiramate, lamotrigine, carbamazepine, and valproate (6). Among 17 subjects treated with levetiracetam, 70% had low BMD. This study is limited by the sample size and lack of evaluation of potential confounders such as diet and exercise.

In order to better understand the effects of levetiracetam on bone, Koo and colleagues designed a prospective study evaluating BMD and bone metabolism among drug-naïve subjects (average age  $31.0 \pm 13.1$  years) with recent onset epilepsy treated with levetiracetam monotherapy (mean duration  $14.16 \pm 3.36$  months) (7). Subjects were recruited from a Korean outpatient epilepsy clinic; among the original 107



recruited subjects, 46 (43%) were excluded. Common reasons for exclusion included loss of follow-up, evidence of osteoporosis, and mental retardation. All subjects initially received either 500 or 1,000 mg per day and were increased to 3,000 mg per day if clinically indicated. The effect of the dose was evaluated. Subjects were grouped into either low-dose (<1,000 mg per day) or high-dose groups ( $\geq 1000$  mg per day). Physical activity and dietary habits were assessed at baseline and every 3 months after levetiracetam administration. Subjects had baseline and repeat DXA scans as well as serologic biochemical bone markers (vitamin D3, calcium, phosphate, bone alkaline phosphatase, parathyroid hormone, osteocalcin, insulin-like growth factor, C-telopeptide). The mean duration of follow-up was  $14.16 \pm 3.36$  months. The average dose of levetiracetam at the last visit was  $1398 \pm 616$  mg per day. There were no significant decreases in BMD at either the lumbar spine or proximal femur. Of interest, there was an increase in BMD at the lumbar spine. This finding is likely related to the age range in this group as opposed to a direct effect of levetiracetam. BMD typically increases until approximately age 30. The age range in this study was 13–55 and therefore included individuals who were continuing to increase BMD. No changes were found in any of the measured biochemical bone markers. The level of levetiracetam dosage (low or high) was not associated with BMD or bone metabolism. The results of this study suggest that levetiracetam monotherapy does not adversely affect bone health.

The currently available data do not support a negative association between levetiracetam and bone health. Two studies suggest there may be an effect on bone strength and BMD. However, one of these studies was an animal study and one was a retrospective study, which had a limited sample size

and did not control for potential confounders. The recently published report by Koo and colleagues adds to the literature as this was a well-designed longitudinal study in drug-naïve persons. Subjects were, however, followed for only a limited time. Well-powered prospective studies in individuals on levetiracetam monotherapy followed for more prolonged periods should be conducted.

by Alison Pack, MD

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