Bone health in epilepsy

It is not often that neurologists consider bone health when caring for patients with epilepsy, although there may be good reason to. About 40% of women and 13% of men over the age of 50 years will sustain an osteoporotic fracture at the hip, spine, or forearm.[1] Osteoporotic fractures have a devastating effect on quality of life and societal burden; 30% of patients with a hip fracture die within 1 year of the injury.

Although fractures typically occur in the elderly, the beginnings of osteoporosis can be traced back to young adulthood. Bone mineralisation increases to a maximum at age 20 years. This peak bone mass is then maintained until around age 40 years, after which mineralisation steadily declines, and fractures arise in old age.[2] Heritable factors explain 80% of the variability of bone density; white women are at the highest risk and African-American males at the lowest risk of osteoporotic fractures.[3] For osteopenia to be detectable on radiography, loss of bone mineralisation has to exceed 50%. Dual energy X-ray absorptiometry is a more sensitive method of measuring bone-mineral density. Absorptiometry readings 1–2·5 SD below normal values are deemed osteopenic, whereas values lower than 2·5 SD below normal are classified as osteoporosis.

There are three main epilepsy related factors that adversely affect bone: seizure-related trauma and medication-associated uncoordination lead to falls and fractures; symptomatic epilepsy-associated hemipareisis, cerebral palsy, and epilepsy-associated depression reduce physical activity and therefore promote future osteopenia; and antiepileptic drugs (AED) may cause osteomalacia and rickets. These osteopenic factors are typically silent for many decades before fractures occur.

AED-associated osteopenia affects patients of all ages. In childhood and adolescence, increased bone turnover during a critical period of mineralisation can result in lower peak bone mass and long-lasting consequences. In adults, factors that increase bone turnover could contribute to an earlier decline in mineralisation. In elderly patients, drug treatment can exacerbate the decline in mineralisation, which leads to osteoporotic fractures at an earlier age.

The association between AEDs and bone disease has been known for over 30 years. Given these long-standing concerns, it is interesting to note the findings of a recent prospective longitudinal study, which reported that AED use increased bone-loss rates at the heel and hip in women with epilepsy age 65 years and older.[4] The authors concluded that, if unabated, the loss of bone was sufficient to increase the risk of hip fracture by 29% over 5 years. This risk was increased for phenobarbital and carbamazepine, but was highest for phenytoin. The risk is estimated at 1·8% decline in bone density per year of phenytoin treatment. Similar findings in cross-sectional studies have been reported with the old AEDs in children and young adults, and in both women and men, which suggests that although women are at particular risk, osteopenia associated with AED use happens at all ages in both sexes. Unfortunately, none of the patients in the recent study were taking the new AEDs and therefore judgment of the osteopenic effects of these drugs awaits further investigation.

Although seizure related falls and physical limitations are not easily amenable to intervention, the risk of osteopenia related to AEDs can be reduced by changing to a treatment that does not have osteopenic adverse effects. Drugs that seem to be osteopenic include the enzyme-inducing agents phenytoin, phenobarbital, and carbamazepine, which reduce vitamin D concentrations and result in a high bone turnover. Valproic acid, although not an enzyme-including agent, interferes with osteoblastic function and is associated with reduced bone mineral density.[5] Although the newer AEDs do not seem to have either of these effects, it remains to be determined which, if any, of these new drugs is "bone friendly". The lack of an obvious mechanism does not prevent a new AED from having osteopenic effects.

At present it is not clear what interventions may be effective. Calcium and vitamin-D supplementation alone, although needed to meet normal nutritional guidelines, may be inadequate to prevent bone loss in epilepsy.[1] Recently, it was shown that more than 50 times the recommended vitamin-D supplementation given intravenously is required to overcome the enzyme-inducing effects of phenytoin. Osteoporosis can be effectively treated with bisphosphonates. These drugs disrupt osteoclastic bone resorption and cause apoptosis of osteoclasts. The bisphosphonates are effective in the treatment of bone loss associated with other chronic diseases and with other bone-depleting drugs, although their role in AED-associated osteopenia has not been investigated. Potential therapeutic interventions, however, clearly require randomised prospective studies.

Exposure to AEDs is large and growing. AEDs are increasingly used to treat neuropsychiatric disorders other than epilepsy and the number of people taking them has increased nearly twofold since 1991. Prevention of the devastating effect of fractures requires two broad approaches. Awareness of the importance of bone health in epilepsy is essential. Equally essential, however, is the investigation of effective therapeutic strategies to help maintain bone health in the young and to prevent bone loss in the elderly. A search for AEDs without an osteopenic effect would offer neurologists, and patients, an alternative treatment strategy.

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Conflict of interest

RDS sits on advisory boards for GlaxoSmithKline and Ortho-McNeil, and is a consultant for GlaxoSmithKline, Ortho-McNeil, UCB Pharma, and Novartis.

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