



# Bones & Fat: metabolic side effects of chronic antiepileptic use?

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**P**atients with epilepsy are often required to take anti-epileptic medication (AED) for prolonged periods of time. This means that they can experience the very important benefits of treatment of epilepsy due to prevention or reduction of seizures, but also that some may experience side effects of medications and also co-morbidities (a second condition associated with epilepsy itself). Two conditions which are potentially associated with epilepsy and its treatment are bone fragility and cardiovascular disease.

## Bone Health

Studies have shown that patients with epilepsy have a risk of bone fractures approximately twice that of the general population. The increased fracture rate may be due to bone disease, and increased falls and fractures either during seizures or at other times. There are also increasing numbers of patients taking AED to treat conditions other than epilepsy. Low trauma fractures are associated with increased risk of mortality in older patients<sup>1</sup>, and are predicted to create an increasing cost burden to the community.<sup>2</sup>

In the 1950s to the 1970s, studies of bone health in patients with epilepsy demonstrated rickets and osteomalacia (where the bones are softened due to inadequate mineralization). However, the nature of the bone disease in these studies was probably influenced by factors other than AED therapy as most of the patients studied resided in institutionalized settings at that time. These patients were subjected to many influences that may impair bone health (e.g. lack of sunlight exposure,

nutritional factors, exercise, smoking, etc.).<sup>3-5</sup> Whether the results would be similar in community-dwelling epilepsy patients is a question which is the subject of ongoing research.

One method of assessing bone health is by measuring the bone mineral density (BMD) with a DXA scanner. The results of this test can then be compared against normal values for healthy young adults (deriving a T-score) to determine whether the bone density is normal, or whether a patient may have low bone density, i.e. conditions such as osteopenia and osteoporosis.

Recent studies of patients with epilepsy, the majority of whom now live independently in the community, have shown a fracture risk of at least twice that of the general population in patients taking AED.<sup>6</sup> This risk may be higher than the risk of fracture for patients taking glucocorticoids, in whom the problem is well-recognized and routinely monitored.<sup>7</sup> However, the increased fracture rate is not entirely explained by a deficit in BMD<sup>6</sup>, and the difference may be due to other factors including injuries during seizures, and balance impairment, leading to falls and fractures.<sup>8</sup>

Our previous study of community-dwelling female twins and siblings, where one of each pair had been prescribed AED for epilepsy or another condition, and the other had no exposure to AED (and no reason to be taking AED, for instance a condition such as epilepsy, chronic pain or bipolar disorder) found that some AED users have significantly lower BMD in clinically-relevant sites for fracture risk, when compared to the non-AED-

using twin/sibling.<sup>9</sup> In particular, women who had taken enzyme-inducing AEDs (e.g. phenytoin, carbamazepine, phenobarbitone and primidone), who were aged over 40 years and had longer-term use of AEDs (and the underlying condition requiring AEDs) had on average, reduced BMD compared to their twin or sibling. Whether this association of AEDs with low bone density is related to epilepsy, AEDs, a genetic susceptibility, use of newer or older AEDs, use of particular AEDs or other factors remains to be established.

There is increasing use of AEDs in the community, not only for epilepsy, but for psychiatric conditions such as bipolar disorder, and also for treating migraine and neuralgias. Therefore, it is of great importance to these patients to establish the nature of the association of AED usage and increased fracture rate, and for clinicians to better understand the problem, and identify effective, evidence-based, methods for intervening and preventing this important problem, thereby reducing the burden of morbidity and mortality due to fractures and their cost to the patient and the community.

## Weight and Cardiovascular Health

AED use is sometimes associated with a change in total body weight. For instance, some patients taking valproate or carbamazepine may experience weight gain. Theories as to why this may occur include an increase in food intake, an increase in insulin levels or changes in the metabolism of insulin. The associations with weight gain, such as effects on cardiovascular health, may also be of concern, particularly

insulin resistance and type II diabetes and increased blood pressure, all predisposing to the development of cardiovascular disease. It is known that patients with epilepsy have higher rates of ischaemic heart disease.<sup>10</sup>

Reasons for this are not entirely clear, but some studies suggest that patients with epilepsy may have lower rates of exercise, increased body fat and a higher rate of smoking compared to the non-epileptic population.

Other AEDs, such as topiramate are associated with weight loss in some patients, possibly via a loss of appetite. The mechanisms for AED-associated weight changes remain to be fully established, and it is likely that individual genetic characteristics may play an important role in determining which patients are most likely to be affected. Studies examining specific AEDs for side effects alongside genetic profiles are underway and may reveal a genetic predisposition to some drug side effects.

It is recognized that changes in the distribution of body fat have important health implications which are independent of total body weight, specifically the association of increased proportion of abdominal fat as a risk factor for cardiovascular disease. While many studies have examined the magnitude of weight gain, few have considered the distribution of fat in AED users. In a recent study (unpublished data) we observed an association with increasing abdominal fat percentage with long term use of valproate, when compared to a twin or sibling not on treatment. This increased abdominal fat also had some correlation with increases in blood pressure. Of interest in this Australian population, there was not a significant difference in rates of exercise or smoking between the participants who were taking the AEDs and their twins or siblings who did not have epilepsy or did not take AED. In other studies of women taking phenytoin and carbamazepine, there have been reports of central obesity with estrogen deficiency. A recent study found two or more cardiovascular risk factors in 52% of adult epileptic patients, compared to 28% of the general community, and recommended screening for cardiovascular risk in this population.<sup>11</sup> Weight distribution in epilepsy and

cardiovascular risk is an issue which requires further study; however it would be prudent for patients with epilepsy to discuss their cardiovascular health and risk factors with their doctor.

For women with epilepsy, there are a number of special issues, including an association between epilepsy (and some epilepsy medication) with polycystic ovarian syndrome and changes in hormone levels and sometimes some fertility issues. Epilepsy and pregnancy is another special issue which is outside the scope of this article, but all women of childbearing age who have epilepsy should discuss this with their doctor.

Possible links between epilepsy and its treatment with bone health and cardiovascular health include:

- reduced physical activity which can affect bones, cause weight gain and cardiovascular health problems;
- changes in hormone levels associated with epilepsy, fat distribution and bone health (such as low estrogen levels)
- smoking, which can cause osteoporosis, reduce exercise capacity and is a risk factor for cardiovascular disease, and
- low vitamin D levels, which is discussed in more detail here.

### **Vitamin D, bone health and cardiovascular risk**

There has been a strong interest in the role of vitamin D in many disease processes in recent times. In addition to the known role of low vitamin D levels in the development of bone disease, there have also been associations of low vitamin D with obesity, high blood pressure, insulin resistance and type II diabetes, and cardiovascular disease, to list some of the metabolic associations. Whether the associations of low vitamin D levels seen in some studies of AED-users<sup>12-15</sup> may be associated with the metabolic syndrome and increased cardiovascular risk requires further study.

For patients with epilepsy, the first and foremost concern still needs to be effective control of epilepsy, which often requires long-term use of anti-epileptic medications. An awareness of some of the possible conditions that may be associated with of epilepsy and its treatment is of value for patients so that they may discuss ways of monitoring

and optimizing their bone health and vitamin D status as well as reducing their cardiovascular risk factors with their treating doctor, while further research into prevention and treatment of these problems is carried out.

*This article does not constitute clinical advice. For more information, please speak with your treating doctor or neurologist.*

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