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REVIEW / DERLEME

Effects of Antiepileptic Drugs on Bone Density and Metabolism

Antiepileptik İlaçların Kemik Yoğunluğuna ve Metabolizmasına Etkileri

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Summary

Many studies have demonstrated that both classic (e.g., phenobarbital, carbamazepine, valproate) and new antiepileptic drugs (e.g., oxcarbazepine, gabapentin) decrease bone metabolism. Abnormalities in calcium metabolism often occur on inducing the cytochrome P450 enzyme system, thus decreasing vitamin D levels. However, the reason some antiepileptic drugs that suppress (e.g., valproate) or have no effect on this system also affect vitamin D metabolism is not known. This study explored the effect of classic and new antiepileptic drugs on bone health and calcium metabolism.

Keywords: Antiepileptic drugs; calcium metabolism; decrease in bone mineral density.

Özet

Epilepsi ve epilepsi tedavisine yönelik ilaçların kemik mineralizasyonunu ve kalsiyum metabolizmasına etki ettiğine dair kanıtlar giderek artmaktadır. Klasik (fenobarbital, karbamazepin, VPA vs) ve bazı yeni antiepileptik ilaçlar (okskarbazepin, gabapentin) ile belirgin kemik mineral yoğunluğunda azalma birçok çalışmada gösterilmiştir. Kalsiyum metabolizmasındaki anormalilerin bazı antiepileptiklerin sitokrom P450 enzim sistemini indükleyici etkileri ve böylece D vitamini düzeylerini azaltmaları ile ortaya çıktığı düşünülmektedir. Ancak VPA gibi bu sistemi baskılayan veya bu sisteme etki etmeyen antiepileptiklerin vitamin D metabolizmasına nasıl etki ettikleri bilinmemektedir. Bu yazıda, klasik ve yeni antiepileptik ilaçların kemik sağlığı ve kalsiyum metabolizmasına etkileri gözden geçirildi.

Anahtar sözcükler: Antiepileptik ilaçlar; kalsiyum metabolizması; kemik mineral yoğunluğunda azalma.

Introduction

Epilepsy is a chronic disease that starts in childhood, adolescence, and early adulthood and continues for many years. Many patients require long-term, and sometimes lifelong, use of antiepileptic drugs (AEDs). The risk of osteopenia, osteoporosis, and bone fractures increased in patients with long-term use of AEDs, besides the other side effects of these drugs.[1,2]

The high possibility of bone fractures in patients using AEDs might be related to seizures, besides the side effects of AEDs.[3]

Osteoporosis-related fractures are usually seen in postmenopausal women and old men. The possibility of lifelong bone fractures is 20%–30% and 40%–56% in men and women, respectively.[4] Besides, childhood is a critical period for bone mineralization. Children in high mineralization period tend to have more osteoporosis and bone fractures.[5] AEDs cause a decrease in the density of lumbar vertebra, trochanter, femur neck, and total bone; decrease the amount of

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25(OH)2 D vitamin levels; and increase the alkaline phosphatase levels in the epileptic children.[6]

Apart from AEDs, glucocorticoids, aromatase inhibitors, and anti-androgenic drugs are also associated with osteoporosis. If these drugs are used with AEDs, the risk of a decrease in bone density increases.[4]

Recent studies have demonstrated that the awareness of neurologists regarding the effects of AEDs on bone density is low (28%). It has been reported that a small number of pediatric neurologists (9%) and adult neurologists (7%) prophylactically prescribe calcium and vitamin D together with AEDs.[7]

The negative effects of AEDs on bone density are complex, and their mechanism has not been fully understood. Both enzyme-inducing and non-inducing AEDs may cause abnormalities in bone metabolism.[8–11] The underlying mechanism is thought to be associated with the induction of P450 enzyme activity, increased vitamin D metabolism,[12] increased bone turnover,[13] inhibition of osteocalcin,[14] and reduced intestinal calcium transport.[15]

This study reviewed the effects of AEDs on bone density, their mechanism, and possible precautions.

Epidemiology

A reduced bone density in either vertebra or femur neck was shown in more than half of the patients using AEDs.[16] The relative risk ratios were estimated as 1.3–3.8 for osteopenia, 1.7–3.8 for osteoporosis, and 1.7–6.1 for fractures.[17] A decrease in bone mineral density was also reported in children with epilepsy compared with healthy controls.[18,19] The incidence of rickets was found to be between 6% and 13%.[20,21]

Risk Factors for Bone Mineral Density Impairment in Epileptic Patients

The main risk factors defined for the general population are malnutrition, lack of sun exposure, reduced physical activity, presence of diseases affecting bone metabolism and drug usage, age, and menopause in women. Although these risk factors are valid for epileptic patients, some additional risk factors exist for the bone health, such as increased risk of fall due to the high risks of distracting or causing imbalance.

Bone Fractures and Epilepsy

Many studies investigating the effects of AEDs on the risk of osteoporosis have methodological limitations, making it difficult to reach definite conclusions.[22]

Therefore, although the fracture risk in epileptic patients is not fully known, it increases two to six times compared with the risk in general population,[23] and this increase is especially seen in vertebral bodies and femur neck.[24] Besides the increase in the risk of falls due to seizures, the risk of falls and fractures also increases depending on either the side effects of AEDs, such as sedation, ataxia, and diplopia, or the neurological outcomes of epileptic syndrome.[25] The type of seizure also affects the fracture risk. The risk is higher in patients with tonic–clonic seizures than in patients with other types of seizures.[26] Moreover, a correlation exists between fractures and the duration of antiepileptic treatment. The fracture risk increases as the duration of AED exposure increases.[27]

Relationship Between Antiepileptic Drugs and Bone Mineral Density

AED-related reduction in bone density affects both genders and all age groups. Alterations in bone metabolism during childhood and adolescence, which are important periods for bone growth and mineralization, may cause a decrease in bone density.[28] Moreover, AEDs may trigger age-related bone loss.[28]

Many AEDs inducing cytochrome P450 enzymes, such as phenytoin (PHT), phenobarbital (PB), primidone (PRM), carbamazepine (CBZ), and oxcarbazepine (OXC), are associated with bone metabolism. Of these, PHT is the most effective,[29] whereas CBZ is the least effective. These AEDs cause the conversion of 25(OH)2 D vitamin into its inactive metabolites by increasing the levels of enzymes responsible for vitamin D metabolism.[30] A decrease in 1.25(OH)2 D vitamin level reduces calcium absorption. Subsequently, secondary hyperparathyroidism, increased bone resorption, and bone loss occur.[30]

Other mechanisms might also be responsible for the association between the increase in serum concentration of 25(OH)2 D vitamin with valproate (VPA), which inhibits cytochrome P450 enzymes, and reduced vitamin D metabolites, except the inducing effect of AEDs on cytochrome P450 system (Figure 1).[31–33]

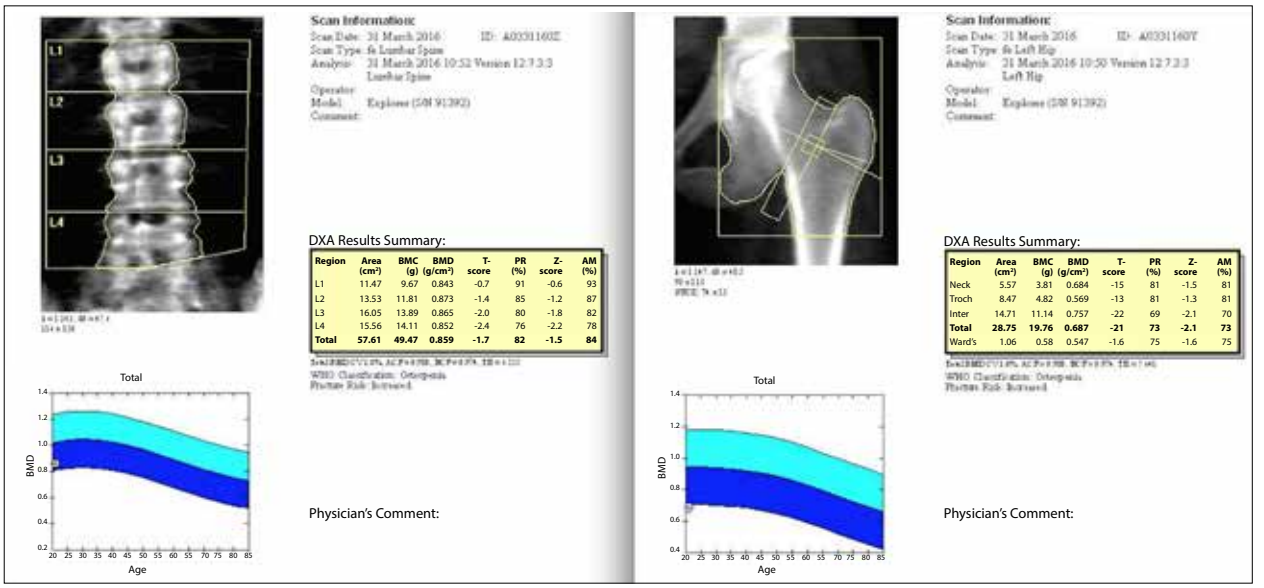

Fig. 1. A 20-year-old female patient admitted to the epilepsy clinic. Her seizures started with fever when she was 2 years old. They continued for 10 years as tonic–chronic seizures. VPA treatment was used and stopped when she was 14 years old. After a period without any drug or treatment, JTK seizures started again while she was watching TV. Bone densitometry performed 6 months after VPA treatment for 10 years revealed osteopenia in the vertebra and femur head.

Possible mechanisms underlying the effects AEDs on bone density, not mediated by vitamin D, are thought to be a reduction of calcium absorption in the intestine (PHT), resistance against parathyroid hormone (CBZ), calcitonin deficiency (PHT and PRM), interaction with vitamin K metabolism (PHT), and a direct effect on bone cell functions (PHT, CBZ, and VPA).[34] Moreover, AEDs may have some indirect effects such as hormonal alterations, increase in homocysteine level, and reduction in growth factors.[35]

A limited number of studies exist on the effects of AEDs on bone metabolism. Some of the studies have demonstrated no effects of lamotrigine (LTG), gabapentin (GBP), topiramate (TPM) and tiagabine (TGB) on bone metabolism. However, a few studies have shown that the aforementioned drugs induce changes in bone mineral density.[36]

GBP is not metabolized and does not induce or suppress hepatic enzymes. No study has directly investigated the effect of GBP monotherapy on bone metabolism. However, it has been shown that long-term GBP treatment induces fractures in hip, femur head, and lumbar vertebral bones.[8,24] Further, it has been shown that GBP significantly increases the fracture risk.[37] However, GBP's mechanism of action on bone density or fracture risk is not known yet. It is also unclear whether GBP is directly related to bone metabolism or is associated with reduced mobility, as it is used in chronic pain syndrome.

The direct correlation between LTG and fracture risk has not been explored yet. However, the effects of LTG on bone density in children and postmenopausal women have been investigated in some studies.[38] As a result, LTG is less effective on bone density compared with other antiepileptics. It has been shown that bone formation in children decreased and a low bone density was found to be associated with short stature when VPA and LTG were used together.[33]

Although the effect of levetiracetam (LEV) on bone metabolism is unclear, a preclinical study showed that rats treated with low-dose LEV showed a decrease in bone strength of femur head. However, the mineral content of bone and bone density did not change.[39]

OXC is a weak hepatic enzyme inducer. It was thought to be associated with decreased 25(OH)2 D vitamins levels, increased bone resorption, and bone turnover.[40,41]

Carbonic anhydrase inhibitors (TPM, zonisamide, and acetazolamide) can affect bone metabolism by causing metabolic acidosis.[2,42]

Further studies are needed to better understand the effects of new AEDs on bone metabolism. Also, a significant relationship exists between drug-related loss of bone density and duration of AED usage.[8] The decrease in bone mineral content is found to be 20%–65% in patients with long-term AED usage,[18] and the most significant correlation is seen in the patients using AEDs for more than 12 years.[27]

Moreover, the use of AEDs as polytherapy or monotherapy is controversial because of their effects on bone metabolism. Combination therapies increase the risk of bone metabolism caused by AEDs.[27]

Protection and Treatment Options

A limited number of studies have investigated the treatment of osteoporosis and the reduction in AED-related bone density. Consequently, no guideline exists on these issues. However, some well-accepted suggestions are available. Regular bone densitometry measurements should be performed on individuals using AEDs (PHT, PB, PRM, CBZ, and VPA) who are at high risk in terms of bone densitometry impairments. However, no ideal screening time has been defined.

People who are at high risk due to both AED usage and bone density impairments should be followed up more closely, and the measurements should be done more frequently. A balanced nutrition, regular physical activity, avoiding smoking and alcohol, and sufficient amount of sun exposure should be recommended for all patients using AEDs in terms of decreasing or preventing risk factors.[43]

The serum 25(OH)2 D levels of patients who use enzyme-inducing AEDs for a long time should be measured regularly (before treatment, every 6–12 months). The diagnostic value of biochemical markers showing bone turnover in patients using AEDs is low, and their usage in clinic routine is not recommended.[44]

The pros and cons of the treatment should be considered, and the seizure-inducing effects should be taken into account before starting a hormone replacement therapy in the postmenopausal epileptic patients using AEDs.[45]

Recent studies showed that calcium (between 1000 and 1500 mg/day) and the combination of calcium and vitamin D (between 500 and 750 IU/day) supplementation increased the bone density. Also, a low dose of vitamin D had no effects on the bone density of adults. Although evidence on ideal supplement regime and dose is still not available, daily intake of 1000–2000 IU vitamin D may be enough for the patients using AEDs not inducing enzymes.[46] Patients using AEDs inducing enzymes should use a higher dose of vitamin D (2000–4000 IU) as a protective treatment.[47]

Drug treatment is indicated if the fracture risk increases. Therefore, drug treatment is recommended especially in patients who had a vertebral or hip fracture or an absolute increase in risk for 10 years. The risk of individual fracture can be assessed using the "Fracture Risk Assessment Tool" of the World Health Organization.[48]

Preparations that inhibit bone resorption, especially bisphosphonates or selective estrogen receptor modulators (raloxifene), are used for treating osteoporosis. This treatment should last at least 3–5 years, and both vitamin D deficiency and osteomalacia should be excluded before starting drug treatment.

Conclusions

The assessment of the risk factors affecting bone density in the epileptic patients using AEDs and regular bone density follow-ups are required for protecting patients from the side effects of AEDs on bone density and their treatment.

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