The Effect of Anticonvulsants on Bone Mineral Density: Brief Review


Abstract: The effect of anticonvulsants on bone mineral density changes in epileptic patients is an important and relevant scientific question. This brief review focuses on assessing the existing knowledge on how antiepileptic drugs affect bone mineral density. The review examines the various mechanisms that may influence bone mineral density when anticonvulsants are taken. Based on a literature search and analysis, advances in the field are identified and their contribution to the current understanding of the issue is assessed. Overall, this review can serve as an informative resource for understanding the relationship between antiepileptic drugs and bone mineral density and as a direction for future research.

Keywords: epilepsy; bone mineral density; osteoporosis; osteopenia; densitometry; antiepileptic drugs; anticonvulsants.

Introduction

The problem of decreased bone mineral density (BMD) and frequent fractures in epileptic patients with long-term antiepileptic drugs (AEDs) is an important and under-studied issue that reduces quality of life and involves significant economic costs of treatment and rehabilitation. Epilepsy increases the risk of fracture by a number of mechanisms either. This may be due to both direct trauma and unbalanced forced muscle contraction [1, 2]. It has been noted that the incidence of fractures in patients with epilepsy is 2-6 times higher than in the general population [2-4]. The most common cause of fractures in patients with epilepsy are injuries resulting from falls or traumatization during epileptic seizures. The most characteristic injuries in generalized seizures are bilateral posterior shoulder fractures (33%), compression fractures of the thoracic and lumbar spine (29%), skull and mandible fractures (8%), and bilateral femoral neck fractures (6%) [5]. A significant increase in the risk of osteoporotic fractures with long-term drug therapy for epilepsy is a separate important aspect. There are data indicating that the use of first-generation anticonvulsants (such as barbiturates, benzodiazepines, valproates, carbamazepine) leads to a decrease in BMD and, consequently, to the development of osteoporosis and pathologic fractures [6-10]. Information on the effect of new-generation antiepileptic drugs on bone metabolism in epileptic patients is limited, which makes it extremely urgent to study this issue and to develop standardized diagnostic algorithms and tactics for the management of these patients. In addition, in the last decade there has been an increasing focus on the personalization of therapy as an understanding of the need for an individualized approach to every patient. This is a new doctrine of modern healthcare based on practical application of new molecular technologies to improve the estimation of predisposition to diseases (prediction), and their prevention and treatment [11]. Therefore, the actual goal...
of studies in epileptology is to find predictors of response to therapy and to determine the possibility of developing adverse effects of antiepileptic drugs.

**Materials and Methods**

We searched and analyzed scientific papers published on eLibrary, PubMed, Google Scholar on the association between antiepileptic drugs and osteoporosis development, impact on bone metabolism and changes in bone mineral density. For this we used keywords epilepsy, antiepileptic drugs, bone mineral density, osteoporosis, osteopenia, fracture. Only studies that were conducted in humans and published in review journals were included.

**Results**

Osteoporosis is a metabolic disease of the skeleton characterized by loss of bone mass, changes in the micro- and macro-architectonics of bones, impaired mineralization, resorption and remodeling of bone tissue and, as a consequence, fractures with minimal or no traumatic agent. Before the development of a low-trauma fracture, osteoporosis has no clinical manifestations. After the development of a fracture, it becomes already a very noticeable problem, which, firstly, has an extremely negative impact on the health and quality of life of the patient, and secondly, is associated with quite high costs of the state for the treatment and rehabilitation of these patients [12]. In addition, osteoporosis is a widespread disease, which is detected in more than 50 million people worldwide, and more than 80% of all fractures after the age of 60 years occur as a result of osteoporotic bone resorption [13]. However, osteoporosis can affect different age groups and occur in younger people. Osteoporosis is most often manifested by vertebral compression fractures, fractures of the distal forearm, proximal part of the femur and proximal part of the humerus, which lead to reduced quality of life and increased medical costs of health care [12]. Bone mass is the main determinant of the mechanical properties of bone tissue and determines up to 75% of its strength. The risk of fracture is directly related to the absolute values of BMD of the spine and femoral neck. Primary and secondary systemic osteoporosis are distinguished. The most common is primary postmenopausal osteoporosis in women, associated with a decrease in estrogen synthesis, the deficiency of which increases bone resorption and leads to a progressive decrease in BMD. Taking certain medications is an important secondary risk factor, especially in the presence of genetic predisposition, along with the main risk factors for osteoporotic fractures, such as low BMD, age, low body weight, frequent falls and fractures in the anamnesis [14]. One of the large groups of drugs, against the background of long-term intake of which osteoporosis can develop, are anticonvulsants. In the current literature there are data indicating a decrease in BMD and increased risk of bone traumatization and fractures in patients receiving long-term antiepileptic therapy [15]. Anticonvulsants are widely used in the therapy of various diseases: epilepsy, migraine, chronic pain, neuropathic pain, psychiatric pathology. The main focus of administration of these drugs is epilepsy, the most common neurological disease affecting about 50 million people worldwide [16]. Earlier studies have shown that compared to healthy people, patients with epilepsy demonstrate an extremely high prevalence of osteoporosis and bone fractures, and bone mineral density decreases on long-term anticonvulsant use [2-4].

Adverse effects of AEDs have a significant affect on the quality of life and effectiveness of treatment. One of the adverse effects of long-term intake of antiepileptic therapy is the development of metabolic effects on the bone system, leading to the development of osteopenia and osteoporosis, and consequently to bone tissue injury. Currently, there
is evidence that taking anticonvulsants such as barbiturates, benzodiazepines, valproates, carbamazepine leads to a decrease in BMD and, consequently, to the development of osteoporosis and pathologic fractures [8-10]. The first scientific reports on the effects of taking antiepileptic drugs on bone mineral density were published more than 50 years ago [17]. Observational studies have shown a decrease in BMD in patients using anticonvulsants compared to normative values, but there is a considerable variation in values. However, the association of increased incidence of low-energy fractures with the intake of AEDs was observed in studies as early as the 90s of the last century [18, 19]. A meta-analysis by Shen C. et al. demonstrated a significant increase in fracture risk for patients taking anticonvulsants. The study found that the use of AEDs was associated with an 86% increase in the risk of fracture at any site and a 90% increase in the risk of hip fracture [10]. There are also studies that have shown a high risk of fractures in the use of anticonvulsants such as carbamazepine, phenobarbital, oxcarbazepine, clonazepam and valproate, depending on the dose of the drug. There have been studies confirming that in young patients, against the background of phenytoin, primidone and phenobarbital decreases BMD [9]. Some researchers have noted that the risk of fractures is higher when taking liver enzyme-inducing anticonvulsants such as phenytoin, carbamazepine, phenobarbital [20]. Most first-generation anticonvulsants are inducers of the cytochrome P450 enzyme system (enzyme-inducing AEDs), which can lead to increased catabolism of 25(OH) vitamin D. This, in turn, leads to decreased intestinal calcium absorption and secondary hyperparathyroidism [14].

Possible mechanisms of anticonvulsant-induced osteoporosis currently include: 1) hepatic cytochrome P450 induction leading to increased vitamin D catabolism and decreased blood content of its bioactive metabolites; 2) decreased effect on bone tissue of endogenous parathyroid hormone with development of secondary hyperparathyroidism; calcitonin deficiency; 3) direct effect of anticonvulsants on the activity of osteoblasts and osteoclasts; 4) inhibition of vitamin K metabolism (phenytoin); 5) suppression of phosphate reabsorption in renal tubules [8, 21].

Over the past decades, a large number of new-generation anticonvulsants have emerged that position themselves as drugs with a positive pharmacological profile, lower side effects, while maintaining high efficacy. Also, newer anticonvulsants should theoretically have less effect on bone density because they are less certain to induce liver enzymes. However, a review of the scientific literature shows that data on specific effects of the new AEDs, such as bone remodeling, are limited by controversial results. In one study, oxcarbazepine, gabapentin and levetiracetam were found to be associated with changes in bone metabolism [22]. In another study of adult patients with epilepsy, it was shown that long-term treatment with gabapentin can lead to bone loss in the hip joints and lumbar spine [23]. In a cross-sectional comparative study, a decrease in BMD was observed in patients with long-term lamotrigine treatment compared to a control group of healthy donors [24]. Low bone mass and reduced bone formation have also been reported in children aged 3-17 years treated with lamotrigine, alone or in combination with valproic acid [25]. However, in a study of children treated with lamotrigine monotherapy, bone mass was similar to that of healthy control subjects [25]. In patients receiving topiramate, metabolic acidosis of mild to moderate severity was registered, leading to the development of kidney stones, osteomalacia and osteoporosis [26]. Conversely, the data of a retrospective cohort study conducted on 560 patients showed that patients who were prescribed newer non-enzyme-inducing anticonvulsants were less likely to have osteoporosis in the lumbar spine, femoral neck and hip joint, indicating that newer anticonvulsants are not associated with a decrease in BMD [27]. There is evidence that enzyme-inducing AEDs, such as carbamazepine, phenytoin, phenobarbital, primidone, are involved in dysregulation of vitamin D metabolism and calcium-phosphate metabolism, contribute
to increased levels of alkaline phosphatase, a marker of bone damage, resulting in decreased bone strength [28]. However, in recent years, anticonvulsant-induced osteopenia has also been described in patients taking enzyme-inhibiting AEDs. It was shown that the severity of skeletal bone mineralization and density disorders in patients with epilepsy increases with long-term combined use of valproate and lamotrigine [29]. According to the results of meta-analysis including 12 studies with high literature quality (including 629 epileptic children and 627 control subjects), it was shown new antiseizure medication decreased bone mineral density (MD: −0.05, 95% CI, −0.09, −0.02; P = 0.004) [30].

Adverse effects of anticonvulsants have a significant impact on the quality of life of patients with epilepsy [31]. Antiepileptic therapy is prescribed for a long time, so it is important to consider possible metabolic disorders associated with the use of AEDs. This is important because often BMD changes in this patient group remain subclinical for long periods of time and may take years to manifest clinically. Older generation anticonvulsants such as barbituates, benzodiazepines, valproic acid, and carbamazepine have been identified as a separate risk factor for drug-induced osteoporosis, but there are no similar reports for newer generation antiepileptic drugs [21]. In addition, the assessment of cumulative risk of drug-induced osteoporosis in patients with epilepsy is still difficult in clinical practice, as there are no algorithms to identify patients at high risk of drug-induced osteoporosis caused by anticonvulsants.

Conclusions

There are no specific data on the effect of new generation antiepileptic drugs on the development of osteoporosis in patients with epilepsy, which makes it extremely important to develop standardized diagnostic algorithms and change the tactics of management of this category of patients. In this context, the question of clarifying the risk factors for the development of drug-induced osteoporosis is raised. The identification of clinical, laboratory and radiological markers for the subsequent early diagnosis and prevention of osteoporosis, which is widespread among patients with epilepsy, corresponds to the trend of personalized medicine. In clinical practice, early diagnosis and prevention of osteoporosis in this population will reduce the risk of pathological fractures and injuries in patients with epilepsy, significantly reduce associated disability rates, and reduce economic costs of treatment and rehabilitation. Thus, it is needed to conduct research aimed at solving the fundamental problem of studying the complex mechanisms of osteoporosis development and developing a prognostic model of its risk in patients with epilepsy, long-term users of antiepileptic therapy, including “new generation” anticonvulsants, taking into account gender and age specifics.

Author Contributions: Conceptualization, N.A.S.; methodology, I.V.A.; investigation, V.P.R., I.Yu.T., L.V.L.; data curation, R.F.N.; writing—original draft preparation, V.A.M; writing—review and editing, G.E.M.; project administration, N.A.S. All authors have read and agreed to the published version of the manuscript.


References


