Personalized Psychiatry and Neurology

Review

Perspectives of personalized approach to prevention and treatment of anticonvulsant-induced osteoporosis via action on vitamin D exchange and VDR expression

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Abstract: Anticonvulsant-induced osteoporosis (AIO) and associated pain syndromes and patient disabilities are an important interdisciplinary medical problem generated by various molecular, genetic and pathophysiological mechanisms. AIO are the most important pathological processes associated with chronic pain in adults with epilepsy. Standard approaches to their prevention and treatment do not always solve the problem of the progression of the pathological process and chronicity of AIO. This is the reason for the search for new personalized strategies for the prevention and treatment of AIO. Vitamin D metabolism, expression and specificity of vitamin D receptors (VDRs) may play a key role in the development of AIO and chronic back pain in patients with epilepsy. The aim of the study was to review publications on changes in the vitamin D system in patients with AIO. We searched for articles published in e-Library, PubMed, Oxford Press, Clinical Case, Springer, Elsevier, and Google Scholar. The search was carried out by key-words and their combinations. The role of vitamin D and VDR in the development of AIO and the chronicity of back pain has been demonstrated mainly in animal models and humans. Associative genetic studies have shown that single nucleotide variants (SNVs) of the VDR gene encoding VDR may be associated with the development of osteoporosis of the spine (including those associated with the intake of an anticonvulsants). The prospects for the use of vitamin D preparations for modulating the effect of anticonvulsants used to treat epilepsy are discussed. Genetic association studies of VDR gene SNVs are important for understanding the genetic predictors of AIO and chronic back pain in patients with epilepsy, as well as for developing new personalized pharmacotherapy strategies.

Keywords: *osteoporosis; back pain; anticonvulsant; drug-induced osteoporosis; vitamin D; vitamin D receptor (VDR); VDR gene; genetics; genetic predisposition.*

1. Introduction

Vitamin D, a fat-soluble vitamin, is a group of sterols, which are hormones and precursors of hormones, since it can also be synthesized endogenously [1]. There are two different forms of vitamin D: D3 (cholecalciferol) is the most important isomer produced in the skin, and D2 (ergocalciferol) is of plant origin. The preferred form for use by human of this vitamin is D3. The most important effects are related to the metabolism of calcium, phosphorus and bone mineralization. In recent years, it has been found that vitamin D deficiency plays a key role in the pathogenesis of both the skeletal system and many

chronic diseases [2]. Due to the small amount of foods containing vitamin D, a small proportion (10–20%) of this vitamin is consumed with food. A significant part (80–90%) is synthesized in the skin under the influence of ultraviolet B-rays. The angle at which sunlight hits the earth's surface plays a role in the efficiency of vitamin D synthesis.Vitamin D activation affects several organs. Vitamin D2 or D3, respectively, is hydroxylated in the liver to 25 (OH) D [3].

This metabolite is the main circulating form of vitamin D in human blood, although this form is inactive and must be converted in the kidneys to the biologically active form 1,25 (OH) 2D3. The production of this active metabolite by the kidneys regulates the metabolism of calcium and phosphorus. Importantly, 25 (OH) D can be locally converted to 1,25 (OH) 2D3 in many tissues, which plays an autocrine or paracrine role in regulating various cellular processes such as cell growth, differentiation and apoptosis [4]. Every tissue in the body expresses a vitamin D receptor (VDR) that regulates both genomic and non-genomic responses to 1,25- (OH) 2D3 [5].

1,25- (OH) 2D3 regulates calcium homeostasis through genomic and non-genomic VDR mechanisms. Non-genomic 1,25- (OH) 2D3 -induced calcium influx includes rapid mobilization from the sarcoplasmic reticulum (SR) followed by influx from the extracellular environment via activation of the storage-driven calcium entry pathway (SOCE) and voltage-dependent calcium channels (VDCC) type L [6] Buitrago et al. [7] it has been shown that induced calcium mobilization from SR is regulated by the activation of gamma phospholipase C (PLCγ) and the production of inositol triphosphate (IP3). c-Src and phosphoinositide-3-kinase (PI-3 kinase) are responsible for the activation of PLCγ. Second, the influx of extracellular calcium through SOCE is the result of the release of calcium from the SR and the simultaneous production of diacylglycerol (DAG) [8]. Mobilization of calcium from SR leads to the activation of calmodulin and calmodulin-dependent protein kinase II (CAMKII), as well as protein kinase C (PKC) activation. PKC activation requires both calcium mobilization from SR and DAG production. It has been shown that calmodulin, CAMKII, PKC and other tyrosine kinases activated by PKC are involved in SOCE. Importantly, although 1,25- (OH) 2D3 does activate the cAMP / PKA pathway in skeletal muscle cells, it has not been shown to be involved in SOCE. Later Santillán G. et al. demonstrated that the molecular identity of channels involved in myocyte SOCE may be related to receptor potential transition channel (TRPC)-like proteins [9]. TRPC-like proteins coimmunoprecipitate with VDR after 1,25- (OH) 2D3 treatment, suggesting that VDR may play a direct role in the regulation of channels involved in SOCE.

Finally, the 1,25- (OH) 2D3 -induced entry of extracellular calcium through VDCC is mediated by the cAMP / PKA and PLC / PKC pathways. Studies confirm that adenylyl cyclase can be activated through 1,25- (OH) 2D3 - induced phosphorylation and inhibition of Gαi, rather than Gs activation. It has been suggested that PKC may be responsible for Gαi phosphorylation [10]. Indeed, calcium influx into VDCC requires PKC activation, which, in turn, cross-interacts with the cAMP / PKA pathway [11]. Therefore, calcium influx through VDCC includes both PKA and PKC. Thus, 1,25- (OH) 2D3 -induced calcium fluxes in cultured skeletal muscle cells involve rapid mobilization from SR via PLC / IP3 followed by extracellular calcium influx via SOCE and VDCC. SOCE activation includes calmodulin, CAMKII, and PKC, while extracellular calcium influx via VDCC includes the cAMP / PKA and PLC / PKC pathways. In addition, activation of the cAMP / PKA pathway also results in the expression of calmodulin, which is likely to promote 1,25- (OH) 2D3 -induced calcium signaling. 1,25- (OH) 2D3-induced calcium fluxes and alterations in calcium signaling may play a role in regulating muscle contractile force in differentiated muscle fibers and play a role in myoblast proliferation and differentiation among a variety of other cellular processes that may be influenced 1.25 - (OH) 2D3, which is very important in the processes of bone tissue regeneration in case of spinal injury.

Table 1. Enzyme-inducing AEDs that may predispose to osteoporosis [17].

Drug (generic name)	Available as (brands include)
Carbamazepine	Tegretol
Eslicarbazepine acetate	Zebinix
Oxcarbazepine	Trileptal
Phenobarbital	no brand name
Phenytoin	Epanutin
Primidone	no brand name
Rufinamide	Inovelon
Topiramate	Topamax
Perampanel	Fycompa

Numerous data support the opinion that vitamin D is included in the endocrine system, which includes the active hormone vitamin D 25 (OH) D, dihydroxyvitamin D3), receptors and enzymes involved in the production of biologically active forms of vitamin D. This system is involved in the modulation of various biological processes including metabolism of the bone, immune systems, detoxification, oxidative stress, proliferation and differentiation of various cell types [12]. In addition, it is known that vitamin D is involved in bone and cartilage metabolism [13, 14], since the presence of VDR is evident in the cells of the intervertebral disc, more precisely, in the nucleus of the pulpous and annular fibrous cells, which make up two different main parts of the intervertebral disc [15].

Biological interactions of intervertebral disc cells with vitamin D metabolites may be critical to disc health, and altered vitamin D signaling may play a role in the pathophysiology of intervertebral disc degeneration and spinal disease [16].

Many drugs (for example, anticonvulsants) additionally interfere with intestinal absorption of vitamin D or alter the functional activity of the VDR (Table 1, Table 2). Until now, the most controversial issue of the role of drugs in the development of vitamin D metabolic disorders and VDR expression is anticonvulsant-induced osteoporosis (AIO).

The aim of the study was to review publications on changes in the vitamin D system in patients with AIO.

Table 2. Non-enzyme-inducing AEDs that may predispose to osteoporosis [17].

Drug (generic name)	Available as (brands include)
Acetazolamide	Diamox
Brivaracetam	Briviact
Clobazam	Frisium, Tapclob
Clonazepam	no brand name
Ethosuximide	no brand name
Gabapentin	Neurontin
Lacosamide	Vimpat
Levetiracetam	Desitrend, Keppra
Piracetam	Nootropil
Pregabalin	Alzain, Lyrica
Sodium valproate	Epilim, Episenta
Stiripentol	Diacomit
Tiagabine	Gabril
Vigabatrin	Sabril
Zonisamide	Zonegran

2. Materials and Methods

The search strategies of this thematic review:

- We used keywords “osteoporosis”; “back pain”; “anticonvulsant”; “drug-induced osteoporosis”; “vitamin D”; “vitamin D receptor (VDR)”; “VDR gene”; “genetics”; “genetic predisposition” and their combinations, for the

search full-text articles in PubMed, Springer, Wiley Online Library, Taylor & Francis Online, APA PsycInfo, CORE, Science Direct, and eLIBRARY.RU databases.

- We analyzed placebo controlled studies, cross-sectional studies, case-control studies, case studies, systematic reviews, meta-analyzes, and Cochrane reviews. Articles published from January 2011 to September 2021 were analyzed. The final date of the search was 10 September 2021.
- Analyzed data have been pre-selected from identified studies by the titles and abstracts or from the entire publication if titles and abstracts did not provide sufficient information on the type of study.
- English and Russian languages were included.
- Duplicate articles were excluded from the analysis.

Several articles published previously to this period were also included into the review due to their high scientific value. We analyzed 78 studies in this thematic review.

3. Results

3.1. The Role of Vitamin D and VDR in the Development of Osteoporosis

Osteoporosis is characterized by a decrease in bone mineral density and an increased risk of fractures [18, 19]. Age is one of the risk factors for fractures: over 55 for women and over 65 for men [20]. Boonen et al. showed that 22% of men and 47% of women over 50 will have an osteoporotic fracture for the rest of their lives [21, 22].

The metabolism of osteoblasts and osteoclasts is influenced by sex hormones, thyroid and parathyroid hormones, gonadotropins, insulin-like factor, vitamin D [23] Vitamin D is involved in the absorption of calcium and phosphate in the intestine, but acts primarily on osteoblasts [24]. VDR expression occurs in both osteocytes and osteoblasts. VDR expression in osteoblasts leads to an increase in bone mass induced by vitamin D. Increased vitamin D levels induce bone formation through osteoblast differentiation [25].

Intestinal calcium absorption is reduced in the elderly with vitamin D deficiency. Decreased calcium absorption is exacerbated by the development of intestinal resistance to 1,25 (OH) 2D [26, 27]. Age-related decline in kidney function in the elderly leads to a violation of the hydroxylation of 25-hydroxyvitamin D (25 (OH) D) to 1,25-dihydroxyvitamin D (1,25 (OH) 2D3) [26, 28]. The efficiency of calcium reabsorption in the kidney is reduced due to a decrease in the expression of VDR and epithelial calcium (Ca 2+) TRPV5 channels in the kidney [29].

Thus, human age is associated both with a decrease in dietary vitamin D intake and a decrease in its absorption in the gastrointestinal tract, and with a decrease in the expression of VDR in the intestine and kidneys. Vitamin D deficiency is exacerbated by shorter sun exposure for older people due to reduced mobility and reduced levels of insolation in some regions of residence.

AEDs-induced vitamin D deficiency is likely mediated through the orphan nuclear receptor, pregnane X receptor (PXR) [30]. The PXR shares 60% homology in their DNA binding domains with VDR. PXR has been shown to mediate induction of isoenzymes of CYP2 and CYP3 subfamily of the cytochrome P450, which metabolize the most of AEDs. Furthermore, PXR can be activated by a variety of AEDs including phenytoin, phenobarbital and carbamazepine [30]. PXR activators can increase the expression of the CYP24, a VDR target gene in cultured cells and in vivo in mice. An isoenzyme CYP24 directs the side chain oxidation and cleavage of 25 (OH)2 D3 and 1β, 25 (OH)2 D3 to carboxylic acid end products (calcitroic acid), resulting in lower cellular concentration of active vitamin D [31]. This induces a state of vitamin D deficiency and results in hypocalcemia, secondary

hyperparathyroidism and increased bone turnover predisposing to AED-induced osteoporosis [30, 32]. However, does not explain the deficiency of vitamin D with valproic acid reported in some studies as valproates are inhibitors of P450 isoenzymes and is not among the known activators of PXR [31].

PXR mediated the catabolism of vitamin D in humans. PXR is activated by various AEDs and other drugs and induces isoenzyme CYP24, which metabolises active vitamin D3 to inactive form. The homology between VDR and PXR is conceivable that the effects of PXR activation by AEDs may be not be limited to inactivation of vitamin D and may potentially interfere with many other VDR controlled physiological processes including cellular and bone effects. These processes may affect growth and maturation of osteoclasts and function of osteoblasts leading to ADRs of AEDs on bone mineralization [31].

3.2. Anticonvulsant-Induced Osteoporosis

AEDs are known to alter vitamin D metabolism in patients with epilepsy. In this connection, vitamin D preparations are considered as a component of symptomatic therapy for AED-induced adverse drug reactions (ADRs). It has now become obvious that long-term use of AEDs (more than 2 years) is associated with a decrease in bone mineral density (BMD), especially when using enzyme-inducing AEDs in persons over 40 years of age. According to a population study conducted in Sweden (1991-1995), the incidence of bone fractures of the extremities in patients with epilepsy in the older age group was quite high - 23.8 cases per 1000 patients, while the standardized morbidity rate (Standardized Morbidity Ratio - SMR) was 2.39 (95% CI: 1.52-3.59). Significant risk factors include age over 45, male gender, and generalized / bilateral tonic-clonic seizures (GTCS / BTKP) [33]. In recent years, AED-induced osteoporosis has been described in patients taking enzyme-inhibiting AEDs. The long-term (more than 1 year) intake of valproic acid (VA) drugs leads to a decrease in BMD in adult patients with epilepsy, although a multivariate analysis did not demonstrate a statistically significant association between changes in BMD and PTH, and serum alkaline phosphatase (ALP) and phosphorus (P) levels [34, 35]. The VA effect is mainly associated with a decrease in the level of calcium (Ca) and a decrease in osteoblast activity [36]. An increase in vitamin D metabolism in bone tissue and an increase in bone resorption have been described in patients receiving AEDs [37]. Many biochemical abnormalities have been shown be associated with the use of AEDs such as hypocalcemia, hypophosphatemia, reduced serum levels of vitamin D (biologically active metabolites), and increase in parathormone (PTH) levels [38].

Nagarjukonda et al. conducted a study of the serum level of the active metabolite of vitamin D (25 (OH) D3) in patients with epilepsy on the background of monotherapy and polytherapy with AED and in the control group of healthy individuals. The authors also analyzed the degree of exposure to sunlight, physical activity and dietary characteristics of the subjects included in this study. Among patients with epilepsy, 41% had a deficiency, 49% had a moderate decrease in serum 25 (OH) D3, and only 9% had a normal level of this metabolite. However, the authors did not find statistically significant differences in the serum level of 25 (OH) D3 depending on the sex of patients with epilepsy and people without epilepsy, and also did not find a relationship with mono and polytherapy of AED and the degree of resistance of epileptic seizures to AED ($p > 0.05$). As a result, the authors concluded that people with epilepsy need to correct vitamin D deficiency in more than 40% of cases [39].

Data from adult patients with epilepsy who received various antiepileptic drugs show that long-term treatment with gabapentin can lead to bone loss in the hip and lumbar spine [33]. A recent study in 108 patients concluded that newer generation (lamotrigine, topiramate, and clonazepam) AEDs are associated with low BMD. Several studies have also reported decreased 25 (OH) D levels, increased markers of bone resorption and a significant decrease in BMD when using oxcarbazepine [40].

In patients receiving topiramate, mild to moderate metabolic acidosis has been reported, leading to the development of kidney stones, osteomalacia and / or osteoporosis [41]. Another study involving 36 women who received topiramate monotherapy for a long time showed lower levels of PTH, moderate hypocalcemia, and an increase in bone metabolism [42].

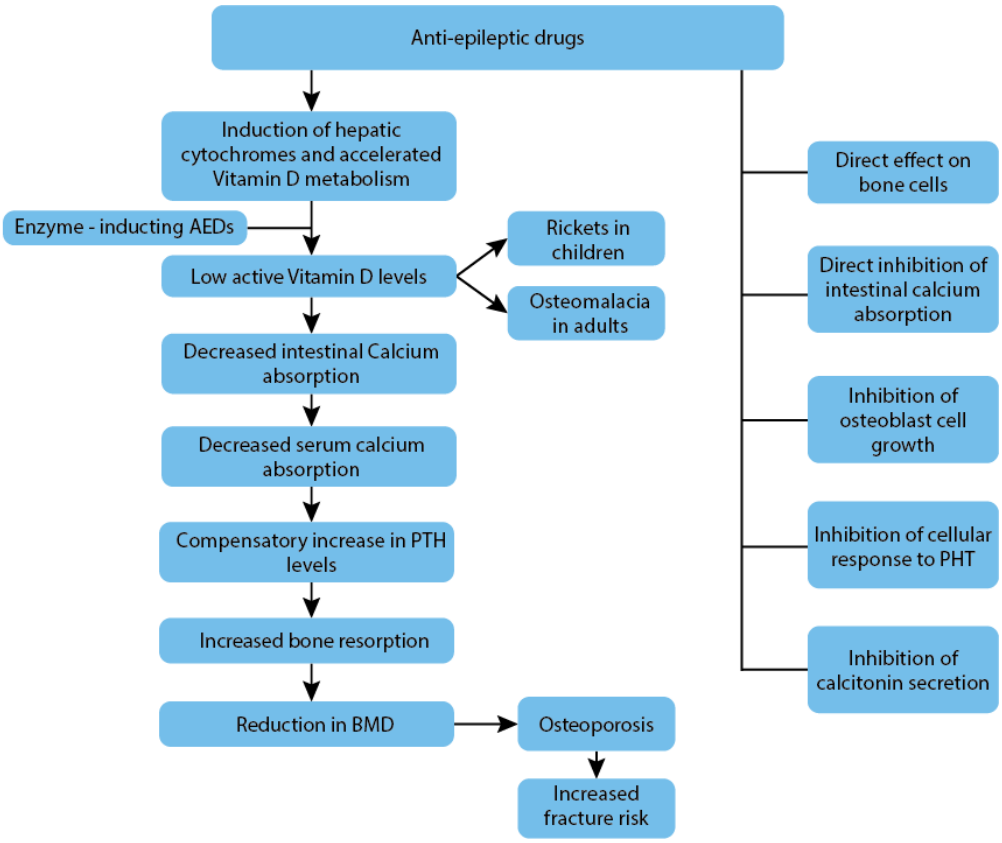

Figure 1. Proposed mechanisms contributing to antiepileptic drug-induced osteoporosis.

As shown in Figure 1, vitamin D deficiency is one of the leading causes of AIO.

Vitamin D deficiency, which is required for bone growth and remodeling, is commonly described as a cause of bone loss in patients with epilepsy [43]. Induction of the CYP450 system in the liver has been found to accelerate the catabolism of vitamin D to its polar inactive metabolites, decreasing biologically active forms of vitamin D. Reduced serum 25 (OH) D levels are observed in both adults and children [44]. However, detection of vitamin D deficiency is not always observed in all studies evaluating the effects of AED on bone health, and some studies have shown evidence of increased bone metabolism even in the absence of vitamin D deficiency [45]. Thus, it has been suggested that AEDs of the first and second generation can influence bone metabolism through mechanisms not only associated with the induction of hepatic enzymes.

Fan et al. found that more than 50% of patients with epilepsy taking AED reported bone abnormalities. Cytochrome P450 (liver CYP450) isoenzymes are induced by AEDs, especially classical ones such as benzodiazepines (BZD), carbamazepine (CMZ), phenytoin (FT), and VA. Induction of CYP450 isoenzymes can cause vitamin D deficiency, hypocalcemia, an increased risk of fractures and changes in bone metabolism, which leads to a violation of BMD. Newer AEDs such as levetiracetam (LEV), oxcarbazepine (OXC), lamotrigine (LTG), topiramate (TPM), gabapentin (GP), and vigabatrin (VB) are broader spectrum, safer and better tolerated than classic AEDs. However, the effects of these AEDs on vitamin D metabolism and bone health are controversial. Particular attention is paid to the study of the effect of AED on bone growth and metabolism of Ca^{+} and P in the bones

of the skeleton, which emphasizes the need for alertness of neurologists, epileptologists and psychiatrists regarding the timely detection of a clinically significant decrease in serum vitamin D levels in patients with epilepsy, requiring timely administration of vitamin D preparations for correction. its deficiency, requiring a dose reduction or cancellation of these AEDs in order to avoid serious impairments to the health of patients and their quality of life [46].

Because low serum 25 (OH) D3 levels are often induced by AED, osteoporosis and epilepsy are common comorbital conditions.

In elderly patients, the incidence of anticonvulsant-induced osteoporosis is higher than the population mean [47].

Despite the increasing prevalence and incidence of osteoporosis with age, few studies specifically investigate the risk of decreased BMD and spinal osteoporosis in people taking AED [48]. In a review by Lee et al. authors consider hypotheses of the pathogenesis of BMD loss caused by AED intake, and also presents an analysis of the risk of AIO and fractures in elderly people with epilepsy. Several studies have shown an association between the use of AEDs, a decrease in BMD, and an increased risk of AIO.

Chandrasekaran et al. conducted a cross-sectional study of AIO. The authors showed that the quality of bone tissue, assessed using BMD and quantitative ultrasound of the heels, is lower in men (24-73 years old) compared with women (21-94 years old) taking AED. In this regard, the authors concluded that monitoring bone health and early diagnosis of AIO osteoparosis in AED users is warrante.

The biological mechanism, although not yet fully understood, may involve the interaction of AEDs with vitamin D metabolism and subsequent bone metabolism [49]. Ensrud et al. in a prospective cohort study of more than 8,000 women over 65 years of age showed that women taking AEDs were 75% more likely to fall than those who did not use AEDs [50]. Sedentary mobility and reduced levels of insolation, along with AEDs intake, increase the risk of vitamin D deficiency in patients with epilepsy who are hospitalized for a long time. It has been shown that more than half of inpatients have hypovitaminosis D and AIO. Patients with epilepsy with frequent epileptic seizures who have to stay at home for a long time are at a higher risk of anticonvulsant-induced vitamin D deficiency due to insufficient exposure to sunlight. In addition, sun exposure is often restricted in users of enzyme-inducing AEDs such as CMZ to reduce the occurrence of sun-induced rashes [51].

Number of enzyme-inducing AEDs can increase vitamin D catabolism, resulting in hypophosphatemia and hypocalcemia [38]. Major effects include hypocalcemia, hypophosphatemia, decreased serum vitamin D levels, increased PTH levels, and changes in markers of bone metabolism. AEDs that induce the CYP450 enzyme such as PH, PB, CMZ and primidone are the most common AEDs associated with bone disease (Table 1), while data on the effects of VA and newer AEDs such as LTG, GP, VB, LEV and TPM (Table 2), bone metabolism and bone density are scarce and inconsistent [33].

Despite the recognition of the effect of certain AEDs on BMD and the development of AIO, there are limited data on the monitoring and treatment of AIO in patients with epilepsy [49].

Vitamin D deficiency is commonly described as the cause of bone loss in patients with epilepsy, while others are decreased calcium absorption, increased PTH levels, inhibition of calcitonin secretion, etc.

3.3. Association of the VDR Ggene's SNVs with the Development of Osteoporosis

As mentioned earlier, vitamin D affects bone mineralization processes indirectly through the VDR, which encodes the VDR gene of the same name (Figure 2). Associative genetic studies have shown that the most common single nucleotide variants (SNVs) of the VDR gene associated with the development of osteoporosis in various ethnic groups are ApaI, BsmI, TaqI, FokI, and Cdx2 [52]. Analysis of polymorphisms of the VDR gene makes it possible to early identify the risk of osteoporosis or an individual predisposition

to its development. Carriage of individual SNVs of the VDR gene is associated with the risk of AIO [53].

Thus, Bell et al. studied the degree of BMD and the risk of fractures in carriers of these SNVs of the VDR gene: FokI (alleles F / f, C> T, rs2228570), BsmI (alleles B / b, G> A, rs1544410), ApaI (alleles A / a , C> A, rs17879735) and TaqI (alleles T / t, T> C, rs731236). The authors showed that in Australian residents, SNV ApaI is associated with a decrease in the BMD of the lumbar spine, while the BMD was lower in men with homozygous aa genotype compared with homozygous AA genotype by 6.7% [54]. At the same time, studies in Turkey, Korea and Spain showed a statistically significant association of ApaI carriage with a decrease in BMD in menopausal women [55, 56, 57]. Zhao et al. showed that BMD of the lumbar vertebrae was significantly lower in menopausal Han women with homozygous aa genotype compared to heterozygous Aa genotype of ApaI polymorphism [58].

Wu et al. studied the association between the three SNVs of the VDR gene and the risk of osteoporosis. Only SNV ApaI (rs17879735) is associated with the risk of osteoporosis in the Chinese Han population [59].

Marozik et al. (2021) studied the effects of carriage of VDR gene variants (ApaI rs7975232, BsmI rs1544410, TaqI rs731236, FokI rs2228570, and Cdx2 rs11568820) on BMD, 25 (OH) D level and risk of osteoporosis in Belarusian women. The study found that rs7975232 A / A, rs1544410 T / T and rs731236 G / G and their ATG haplotype showed a significant association with an increased risk of osteoporosis (ATG, OR = 1.8, p = 0.0001) and a decrease in BMD (ATG, -0.09 g / cm 2, p = 0.0001). Carriage of the A allele rs11568820 had a protective effect on BMD (+0.22 g / cm 2, p = 0.027). A significant dose effect of 25 (OH) D was found for the rs1544410, rs731236, and rs11568820 genotypes. 25 (OH) D deficiency has been associated with the rs731236 A / A polymorphism [60].

Figure 2. Localization of the VDR gene on chromosome 12q13.11.

Carriage of the homozigous genotype TT rs2228570 gene and the homozigous genotype CC rs731236 of the VDR was associated with the presence of osteopenia

and decreased BMD along with impaired vitamin D function in young healthy women in Saudi Arabia [61].

Homozygous carriage of the TT TaqI polymorphism has been associated with low BMD in postmenopausal women with osteoporosis in North India. TaqI polymorphism of the VDR gene is an important factor determining the risk of developing osteoporosis [62].

Iranian researchers have found a significant relationship between the carriage of the FF genotype of the FokI VDR polymorphism and vitamin D deficiency and musculoskeletal pain syndrome [63].

3.4. Prospects for the Use of vitamin D and Other Drugs to Modulate the Effect of Vitamin D and VDR Activity Used for the Prevention and Treatment of Anticonvulsant-Induced Osteoporosis

Despite the recognition of the effect of certain AEDs on BMD and the development of AIO, data on the monitoring and treatment of AIO in patients with epilepsy are limited [49]. In this connection, we have found single official recommendations for practicing physicians on the prevention of osteoporosis in patients taking AED [33, 64]. Vitamin D deficiency is commonly described as a cause of bone loss in patients with epilepsy, while others are decreased Ca absorption, increased PTH levels, inhibition of calcitonin

secretion, etc. However, there is no formal practice guideline for bone management in patients with epilepsy. Evidence-based strategies for monitoring, preventing and treating AIO are needed in patients receiving AED.

The National Institute for Health and Care Excellence (NICE) recommends that all adults taking enzyme-inducing AEDs test their serum levels of the active metabolite of vitamin D every 2–5 years to ensure that their bones are healthy. A BMD scan can test bone strength in patients with epilepsy and provide information to the neurologist as to whether the patient is indicated for medical correction of AIO. Adding Ca and vitamin D supplements to mainstream therapy can help replenish natural bone loss in Ca [65].

A number of therapeutic options are available for the prevention and treatment of low BMD in patients with epilepsy, including calcium and vitamin D supplements, bisphosphonates, selective estrogen receptor modulators, hormone replacement therapy, recombinant parathyroid hormone, and calcitonin. However, there are very few studies on the prevention and treatment of bone disease in patients with epilepsy who are taking long-term AEDs [66].

The Agency for the Regulation of Medicines and Health Products recommends that prophylactic vitamin D supplementation be considered for at-risk patients receiving AEDs [67]. All patients with epilepsy can receive prophylactic doses of vitamin D up to 2000 IU / day at the start of antiepileptic therapy. It is also necessary to ensure adequate intake of Ca in doses of 600-1000 mg / day. In the case of AED - induced osteopenia or AIO, it is advisable to prescribe treatment with 2000-4000 IU of vitamin D per day. In addition, vitamin D doses may be increased in osteomalacia [68].

Bisphosphonates are commonly prescribed to treat patients with AIO and a high risk of fracture. In addition, bisphosphonates may be required when an inadequate response to vitamin D is found. In a recent study in AED patients, the addition of Ca and vitamin D supplements to risedronate resulted in an improvement in BMD in more than 69% of cases [69].

4. Discussion

According to Gao et al. the molecular biology of osteoporosis includes control mechanisms bone remodeling through osteoblasts, osteocytes, and osteoclasts [70]. At the same time, it was shown that anticonvulsant-induced decrease in vitamin D3 levels and changes in VDR expression can affect various mechanisms of AIO development (Table 3) [31].

So, this thematic review suggests that the molecular mechanisms of vitamin D metabolism disorders in patients with epilepsy are important for science and clinical practice, since long-term use of most AEDs of I and II generation leads to impaired bone mineralization and the development of AIO. At the same time, both enzyme-inducing and enzyme-inhibiting AEDs can lead to the development of osteoporosis, as a frequent ADRs However, the molecular mechanisms of AIO development when taking enzyme-inhibiting and enzyme-inducing AEDs may differ. Treatment of AIO is currently being actively discussed, but no consensus has been reached. Treatment may include a diet high in vitamin D, nutrients, and medications that contain vitamin D and calcium. The second way of treating AED-induced vitamin D deficiency may be VDR modulation, but this way is currently not well understood. At the same time, in patients who carry the SNVs of *VDR* gene, leading to a decrease in its expression and or specificity due to conformational changes (for example, due to folding disorders), the therapeutic response to vitamin D preparations may decrease.

Table 3. Main molecular mechanisms of anticonvulsant-induced osteoporosis.

Mechanism of osteoporosis	Reference
Alteration of bone remodeling	[31], [72], [73], [74]
Estrogen deficiency-induced bone loss	[74], [75], [76]
Increase bone resorption	[37], [40], [42], [77]
Discharge in early osteoblast differentiation	[77], [78]
Alteration of expression on signaling molecules are produced by osteocytes (sclerostin, cathepsin K, Wnts, DKK1, DMP1, IGF1, and RANKL/OPG)	[79], [80], [81]
Disfunction in osteoblast activity (decrease of aromatase activity in osteoblasts)	[36], [78], [82], [83]
Decrease level of calcium and vitamin D in serum	[36], [37], [38], [39, [40], [42], [84], [85], [86]
Inhibition of osteocalcin secretion	[31], [87]
Secondary decrease of parathyroid hormone level (increase bone turnover and predispose to low bonemass)	[38], [42]
Inhibition of proliferation of osteoblast-like cells	[78], [88]
Stimulation of osteoclast activity	[87]

Nevertheless, there is no doubt that patients receiving high doses of AEDs in monotherapy or polytherapy should be advised to monitor the level of active metabolites of vitamin D, Ca, P, ALP, PTH in serum every 6-12 months. It is also recommended to conduct a bone density scan Dual-Energy X-ray Absorptiometry (DEXA scan) before initiating AEDs in all high-risk adult patients such as post-menopausal women or patients with multiple risk factors and then periodically at 1–2-year intervals. Patients at high risk of AED-induced vitamin D deficiency and AIO also include homozygous carriers of SNVs ApaI, BsmI, TaqI, FokI, and Cdx2 of the *VDR* gene, therefore, genetic testing can be recommended for all patients with epilepsy and high environmental risk factors for osteoporosis to clarify the carriage of the above SNVs.

Patients with epilepsy can be classified as intermediate risk if they receive long-term AEDs (Table 1, Table 2) in monotherapy with moderate doses, if they are homozygous or heterozygous carriers of the SNVs ApaI, BsmI, TaqI, FokI, and Cdx2 of the *VDR* gene and have one environmental risk factor for osteoporosis. These patients should be advised to test serum markers of AIO and DEXA scan every 24 months.

Patients with epilepsy can be classified as a low-risk group: they receive low-dose AED monotherapy and are homozygous carriers of the wild variant or full-functional SNVs of the *VDR* gene and do not have environmental risk factors for osteoporosis. These patients can be recommended DEXA scan once every 5 years while taking AEDs [31, 72].

Patients with epilepsy with AED-induced vitamin D deficiency and abnormal serum markers of osteoporosis or low BMD on DEXA scan require joint supervision by a neurologist (epileptologist) and an endocrinologist.

Recommendations for the treatment of AEDs associated vitamin D deficiency depend on the severity of the bone disease.

Patients with epilepsy with normal bone mass (T score> -1) should be encouraged to follow good bone health practices in addition to vitamin D and Ca supplementation and or specific diet high in vitamin D (fatty fish, fish liver oils, and egg yolk) [89].

Patients with epilepsy and AED-induced osteopenia (T score <-1 and> -2.5), in addition risk modification as above, antiresorptive treatment may be indicated for those with significant disease (T score <-1.5) and multiple risk factors for low bone mass. These patients may benefit from a specialist evaluation.

Adult epileptic patients with AIO (T score <-2.5) and or fragility fractures, treatment with antiresorptive drugs is indicated in addition to vitamin D and calcium supplementation. These patients should preferably be evaluated by endocrinologist and secondary causes for low bone mass ruled out as appropriate.

In postmenopausal women with epilepsy, hormone replacement therapy may retard the bone loss but the possibility of increase in seizure activity needs to be seriously considered in addition to risk of thromboembolism and breast cancer [31].

Anti-resorptive agents such as Bisphosphonates (BPPs), estrogen replacement therapy and denosumab have been proven effective in some patients [90]. BPPs (alendronate, risedronate, ibandronate and zoledronic acid) [91] may be considered for adults with significant AED-induced osteopenia or AIO although there are no established data for its use in AEDs induced bone loss specifically. For patients who cannot tolerate oral bisphosphonates, treatment with parenteral drugs such as zoledronic acid, or ibandronate sodium may be considered [91]. The mainstay of current treatments is still anti-resorptive drugs, particularly, BPPs, in most developing countries [92]. However, such therapy should be offered only after consideration of potential risks and benefits and should be appropriately individualized.

Vitamin D insufficiency should be treated prior to starting BPPs.

BMD with DEXA scan should be monitored at regular intervals of 12–18 months to monitor the response to therapy. Bone resorption markers such as N-telopeptide (NTX) may also be used to monitor the response to therapy as an adjunct to BMD testing in patients with AIO.

Vitamin D recommendations from various medical organizations which are focused on the care of patients with or at increased risk of osteoporosis generally recommend higher intakes or higher 25 (OH)D levels than recommended daily allowances for seniors. International osteoporosis foundation (IOF) recommends that older adults aged 60 years and over take a supplement at a dose of 800 to 1000 IU/day, as this is associated with greater muscle strength and improved bone health In people at risk, vitamin D supplements alone may reduce the risk of fracture and of falling provided the daily dose of vitamin D is greater than 700 IU. In contrast, studies with large annual doses of vitamin D have reported an increased risk of falls and hip fracture. Thus, a yearly regimen of vitamin D high-dose supplementation should be avoided [93]. There is no single supplementation regimen in patients with 25-hydroxyvitamin D deficiency. Table 4 shows the regimen recommended by the panel for both the general population and for patients with osteoporosis or other populations at risk of 25-hydroxyvitamin D deficiency, whether opting for cholecalciferol or calcifediol (Table 4) [94].

Table 4. Recommended doses of cholecalciferol in patients with osteoporosis and other population groups at risk of vitamin D deficiency [94].

Serum 25(OH)D level	Recommended doses of vitamin D
Severe vitamin D deficiency: 25(OH)D <10 ng/ml.	50.000 UI/week for 6-8 weeks, than continue with the insufficiency regimen
Mild vitamin D deficiency: 25(OH)D = 21–30 ng/ml.	50.000 UI/month or 1.000-2.000 UI/day

5. Limitation

There are several limitations in our thematic research. We studied only English-language and Russian-language publications. It is likely that taking different AEDs can have a variable effect on the decrease in the level of various biomarkers of discharge of vitamin D metabolism in serum and/or urine. Men and women may respond differently to the development of a AIO and have different levels of studied serum biomarkers of AIO. Further studies are needed to study the effect of modifiable (medications for primary osteoporosis treatment in AEDs monotherapy and polytherapy, comorbid diseases, dietary habits, etc.) and unmodifiable (gender, age, genetic predisposition) predictors of AIO in humans. Further studies are needed to investigate the effects of carriage of SNVs/polymorphisms of *VDR* gene in patients with AIO. Further research is needed to confirm the role of mutations of the gene as biomarkers of AIO using knockout mice.

6. Conclusions

This thematic review demonstrates the importance of updating our knowledge of the molecular and clinical aspects of anticonvulsant-induced disorders in vitamin D metabolism and reception and, as a consequence, the development of AIO. Epilepsy is a common neurological disease: according to the World Health Organization, the number of patients with epilepsy in the world is more than 30 million. 60-80% of them require lifelong intake of AED. This explains the importance of developing new personalized approaches to predicting, preventing and treating AIO and improving the quality of life of patients with epilepsy by reducing the risk of fractures and chronic pain syndrome. Such a personalized approach is impossible without translating the results of fundamental studies of the molecular mechanisms of AIO and stratification of patients with epilepsy into AIO risk groups based on the homozygous and heterozygous carriage of previously studied SNVs of the *VDR* gene.

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