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Review

An explorative literature review of the multifactorial causes of osteoporosis in epilepsy

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ABSTRACT

Purpose: Patients with epilepsy have a greatly increased risk of osteoporosis and fractures. The literature is diverse and contradictory when dealing with the underlying pathophysiological mechanisms. Consequently, the purpose of this review was to shed light on the multifactorial causes behind the increased occurrence of metabolic bone disease in patients with epilepsy and to identify areas for future research.
Methods: A review of the literature was performed searching PubMed with relevant Medical Subject Headings MeSH terms. The results of the search were evaluated for relevance to the review based on the title and abstract of the publication. Publications in language other than English and publications pertaining only pediatric patients were excluded. For all studies, included reference lists were evaluated for further relevant publications. In total, 96 publications were included in this explorative review.
Results: The high occurrence of metabolic bone disease in patients with epilepsy is multifactorial. The causes are the socioeconomic consequences of having a chronic neurological disease but also adverse effects to antiepileptic drug treatment ranging from interference with calcium and vitamin D metabolism to hyponatremia-induced osteoporosis.
Conclusion: The literature supports the need for awareness of bone health in patients with epilepsy. The pathophysiological mechanisms are many and various wanting for further research in the less well-characterized areas. Furthermore, great responsibility rests on the healthcare professionals in implementing comprehensive patient care and in assuring bone protective measures in clinical practice to prevent bone loss in patients with epilepsy.

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1. Introduction and background

Patients with epilepsy have a greatly increased risk of developing metabolic bone disease. Osteoporosis affects between 11 and 31% of patients with epilepsy and leads to a risk of fractures which is 2 to 6 times increased compared to the background population [1,2]. When epilepsy, in turn, affects between 5 and 10 per 1000 individuals in developed countries [3], the extent and consequences are great.

The finding of increased fracture risk is consistent across the literature from case–control studies to meta-analyses, both when comparing patients with epilepsy to healthy control groups but also when comparing subgroups of patients with epilepsy (Table 1) [4–11]. It has been argued that patients with epilepsy have an increased risk of fractures because of an increased risk of seizure-associated falls. However, it has been shown that only 25% of fractures in patients with epilepsy are known to have occurred during a seizure, and when excluding seizure-related fractures from analysis, an increased fracture risk is still found [5,12]. Likewise, when looking at nonseizure-related fractures in patients with epilepsy, for patients 50 years of age or younger, men were significantly overrepresented in the statistics [7]. Both findings indicate that the increased fracture risk in patients with epilepsy cannot solely be attributed to an increased risk of falls or to traditional risk factors for osteoporosis such as female gender and high age. Interestingly, a study finds the deficit in bone mineral density (BMD) in patients with epilepsy insufficiently in explaining the increased risk of fractures [2]. This finding could be interpreted as support for the hypothesis that increased fracture risk is due to seizures; however, more likely, this represents that secondary forms of osteoporosis, as in patients with epilepsy, increase the fracture risk not by reducing BMD, but by inducing microarchitectural changes resulting in reduced bone strength

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Table 1
Summary of studies of fracture risk in patients with epilepsy.

	Study type	Population	Fractures in patients with epilepsy (N/fractures)	Fractures in control group (N/fractures)	IRR/RR/OR/HR (95% CI)
Meta-analyses					
Vestergaard [2]	Meta-analysis	5 studies of fracture risk in patients with epilepsy	–	–	2.2 (1.9–2.5)
Shen et al. [88]	Meta-analysis	22 studies of fracture risk in patients with epilepsy	–	–	1.86 (1.62–2.12)
Prospective studies					
Persson et al. [89]	Prospective cohort study	Extremity fractures in patients with epilepsy	23/177	–	2.39 (1.52–3.59)[a]
Mezuk et al. [11]	Prospective cohort study	Veterans, 50 years or older from the Veterans Health Administration records			2.42 (2.23–2.63)
Carbone et al. [4]	Prospective cohort study	Postmenopausal women using AEDs vs postmenopausal women not using AEDs	344/1385	22,137/137,282	1.70 (1.53–1.89)[b] 1.44 (1.30–1.61)[b]
Retrospective studies					
Lidgren and Wallöe [90]	Retrospective study	Patients with epilepsy	70/34	–	–
Desai et al. [5]	Retrospective study	Patient with epilepsy vs healthy controls	323/		3.55[c]
Souverein et al. [6]	Retrospective study	Patient with epilepsy vs reference cohort	3478/40,485	3940/80,970	1.89 (1.81–1.98)[b]
Jetté et al. [8]	Retrospective study	Patients with epilepsy and nontraumatic fractures vs age-, sex-, ethnicity- and comorbidity-matched patients with epilepsy	79/15,792	82/47,289	1.24 (1.05–1.47)[b]
Schelleman et al. [91]	Retrospective cohort study	Users of CYP3A4-inducing AEDs vs users of CYP3A4-noninducing AEDs	118/6006[d]	127/7184[d]	1.96 (1.63–2.35)[e] CYP3A4-inducing AEDs 1.77 (1.47–2.10)[e] CYP3A4-noninducing AEDs
Carbone et al. [92]	Retrospective cohort	Anticonvulsant users vs nonanticonvulsant users from the Veterans Affairs Spinal Cord Disease Registry	−/5226	−/2221	1.17 (1.01–1.36)
Nicholas et al. [93]	Retrospective cohort study	Women with epilepsy-prescribed AEDs	4037/138,660		1.22[b] (1.12–1.34)
Cross-sectional studies					
Ahmad et al. [94]	Cross-sectional study	AED users vs non-AED users	7/150	5/506	3.92 (1.08–14.16)[b]
Case–control studies					
Scane et al. [95]	Case–control	AED use in men with symptomatic vertebral fractures vs age-matched controls with no vertebral fracture	–	–	6.1 (1.3–28.4)
Vestergaard et al. [12]	Case–control	Patient with epilepsy and first fracture vs random controls	−/345	−/654	2.0 (1.6–2.5)
Vestergaard et al. [96]	Case–control study	Patients with epilepsy vs age- and gender-matched controls	7091/124,655	10,974/373,962	2.58 (2.53–2.63)
Souverein et al. [9]	Case–control	Patients with epilepsy	/1018	/1842	4.15 (2.71–6.34)[b]
Tsiropoulos et al. [10]	Case–control	Patients admitted with hip fracture vs age- and gender-matched controls	584/7557	1104/27,575	1.31 (1.16–1.48)[b]

This table summarizes the studies of fracture risk in patients with epilepsy. The table includes author, study type, patient population, if listed the fracture incidence in both the patients with epilepsy and in the control group, and the fracture risk expressed as either incidence rate ratio (IRR), risk ratio (RR), odds ratio (OR), or hazard ratio (HR).
[a] Standardized morbidity ratio (observed vs expected numbers of fractures).
[b] Adjusted ratio.
[c] Femoral neck fractures adjusted ratio.
[d] Person-years.
[e] Per 100 person-years.

[13]. This suggests that other aspects of bone metabolism such as vitamin D and calcium homeostasis and bone turnover markers (BTM) are important aspects to focus on. Consequently, the aim of this explorative review was to investigate which pathophysiological mechanisms might be the cause of this increased risk of fractures and metabolic bone disease in adult patients with epilepsy based on already published studies. Moreover, the aim was to identify yet unexplored areas to guide future research within this highly important research area.

2. Method and materials

The study was an exploratory literature review on the pathophysiological mechanisms behind the increased risk of fractures and metabolic bone disease in adult patients with epilepsy. The review was based on a search of PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and included studies from the past 50 years, from 1970 until July 15th, 2019. The following MeSH terms were used to give as a broad range of studies as possible: 'Osteoporosis' or 'Absorptiometry, Photon' or 'Osteoporotic Fractures' or 'Fractures, Bone' or 'Bone Disease, Metabolic' or 'Bone Density' or 'Bone Remodeling' or 'Osteoclasts' or 'Osteoblasts' or 'Osteocytes' and 'Epilepsy' or 'Seizures' or 'Anticonvulsants' or 'Drug-Related Adverse Effects and Adverse Reactions'. On PubMed, the term 'Anticonvulsants' covers drugs used to treat seizures and epilepsy and consequently all commonly used antiepileptic drugs (AEDs). The search was conducted by the first author, and following removal of duplicates, the first author evaluated the studies using the following inclusion and exclusion criteria:

Inclusion criteria:

- Original full-length articles
- Studies describing pathophysiological mechanisms of bone loss in patients with epilepsy
- Studies describing pathophysiological mechanisms or adverse effects of AEDs which could induce bone loss

Exclusion criteria:

- Reviews, case reports, comments, letter-to-the-editor, and conference abstracts
- Articles only describing associations and not going in depth with pathophysiological mechanisms
- Literature pertaining only children or adolescents
- Literature in other language than English

If all inclusion criteria and none of the exclusion criteria were fulfilled, the articles were included. In case of discrepancy between inclusion and exclusion, all coauthors were consulted. All reference lists of included studies were read to find additional relevant studies, all of which were evaluated based on the inclusion and exclusion criteria.

This resulted in a total of 97 publications included in this literature review. The literature search is illustrated in Fig. 1, adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement statement [14].

3. The effects of AEDs

The obvious focus for the increased fracture risk and the common denominator for most patients with epilepsy is the use of AEDs. The most common AEDs, anticonvulsant mechanisms of actions, effect on the livers cytochrome P450 enzyme system, and association with bone loss are summarized in Table 2. Many various pathophysiological mechanisms have been investigated to try and explain the link between AED treatment, reduced BMD, and increased fracture risk. The pathophysiological mechanisms include common AED adverse effects such as confusion, dizziness, and unsteadiness [15], all of which increase the risk of falls and therefore fractures. Antiepileptic drugs, and especially the enzyme-inducing antiepileptic drugs (EIAEDs), affect vitamin D and calcium metabolism. They induce the liver's cytochrome P450 enzyme system resulting in increased hydroxylation of vitamin D and subsequent bone loss, an effect not seen with the nonenzyme-inducing antiepileptic drugs (NEIAEDs). At the same time, AEDs directly affect bone cells and BTM, work as endocrine disruptors and induce

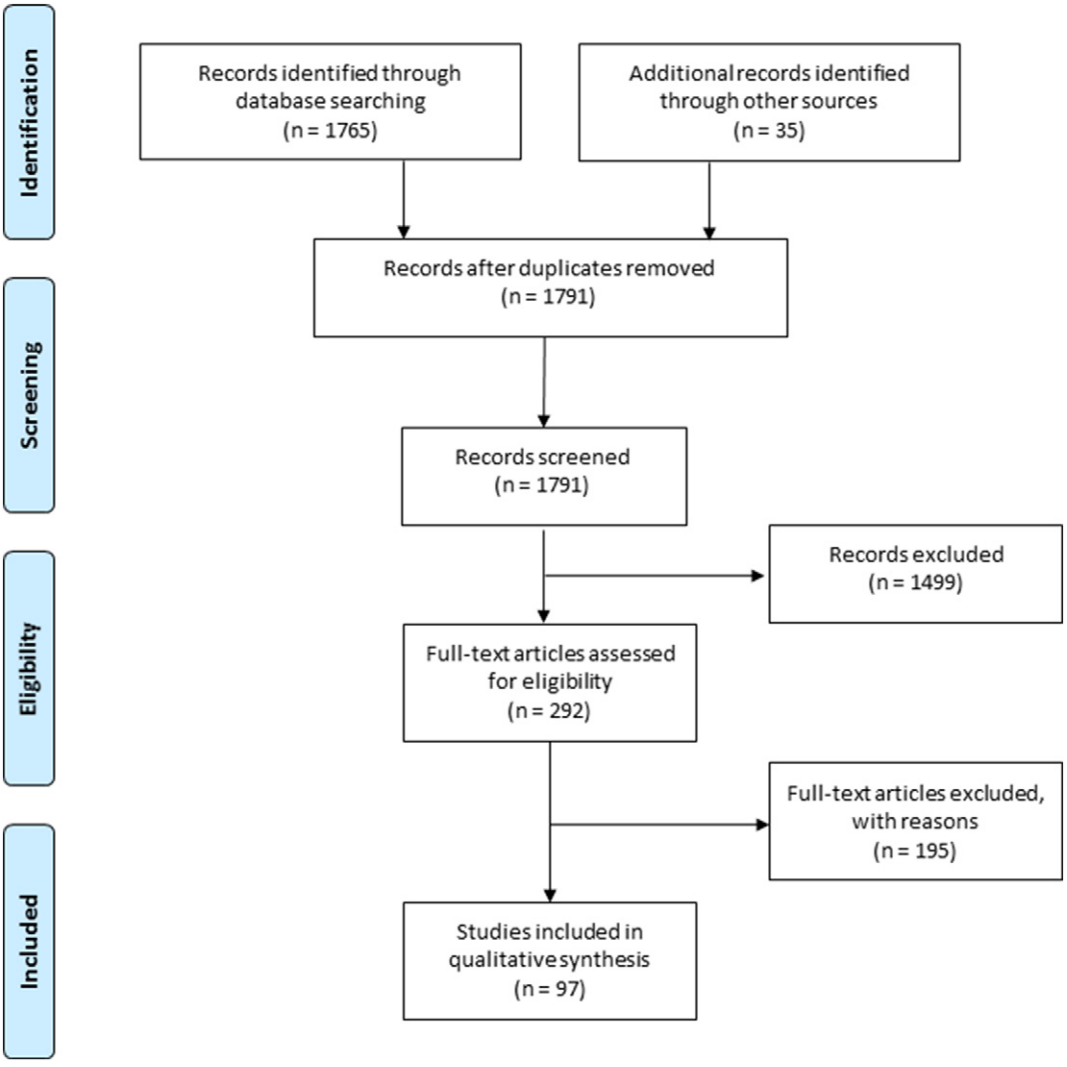

Fig. 1. Illustration of the review's literature search.
Adapted from the PRISMA statement [14].

Table 2
Summarizes the most commonly used antiepileptic drugs.

	Primary anticonvulsant mechanism of action	Interaction with the cytochrome P450 enzyme system	Specific CYPP450 isoenzymes affected	Pathophysiological mechanisms of action in humans
Phenytoin (PHT)	Blocking voltage-sensitive sodium channels	Inducing	CYP1A2 CYP2C9 CYP3A4	Increases hydroxylation of vitamin D Increased BTM Directly affects bone cells
Carbamazepine (CBZ)	Blocking voltage-sensitive sodium channels	Inducing	CYP1A2 CYP2C9 CYP3A4	Increases hydroxylation of vitamin D Increased BTM Hyponatremia-induced osteoporosis Directly affects bone cells
Oxcarbazepine (OXC)	Blocking voltage-sensitive sodium channels	Inducing	CYP3A4	Increases hydroxylation of vitamin D Increased BTM Hyponatremia-induced osteoporosis
Eslicarbazepine acetate (ESL)	Blocking voltage-sensitive sodium channels	Inducing	CYP3A4	Increases hydroxylation of vitamin D[a] Hyponatremia-induced osteoporosis
Topiramate (TPM)	Enhancement of GABA inhibition	Inducing, in dosage >200 mg/day	CYP3A4	Increases hydroxylation of vitamin D[a] Increased BTM
Valproic acid (VPA)	Raises brain levels of GABA	Inhibiting Inducing	CYP2C9 CYP3A4 CYP24	Directly affects bone cells Increases hydroxylation of vitamin D
Lamotrigine (LTG)	Blocking voltage-sensitive sodium channels	No known effect	–	Unknown
Levetiracetam (LEV)	Unknown	No known effect	–	Unknown

This table summarizes the most commonly used antiepileptic drugs, their anticonvulsant mechanism of action, main effect on the cytochrome P450 enzyme system including which specific isoenzymes are affected [97], and by which pathophysiological mechanisms of action they might induce bone loss. Bone turnover markers (BTM).
[a] Due to similar enzyme-inducing properties as PHT, CBZ, and OXC.

hyponatremia-induced osteoporosis. The complex interplay of risk factors for bone loss in patients with epilepsy is illustrated in Fig. 2.

3.1. Lessons from laboratory and preclinical studies

3.1.1. The in vitro studies - the effects of AEDs on cells

For further understanding of the pathophysiologic mechanisms of AED-induced metabolic bone disease, several studies have investigated the effect of AEDs on various bone cells. The main focus has been on AEDs such as phenytoin (PHT) and valproic acid (VPA). Phenytoin, a strong EIAED, has been shown to increase bone nodule formation, enhance the proportion of osteoprogenitor cells, and increase the proportion of functional osteoblasts [16]. Likewise, PHT stimulates osteocalcin secretion through the bone morphogenetic proteins -2 and -4 (BMP-2 and BMP-4) known as osteoinductive proteins in osteoblastic cells [17] suggesting a stimulatory effect of PHT. Somewhat similar is found in a study showing an

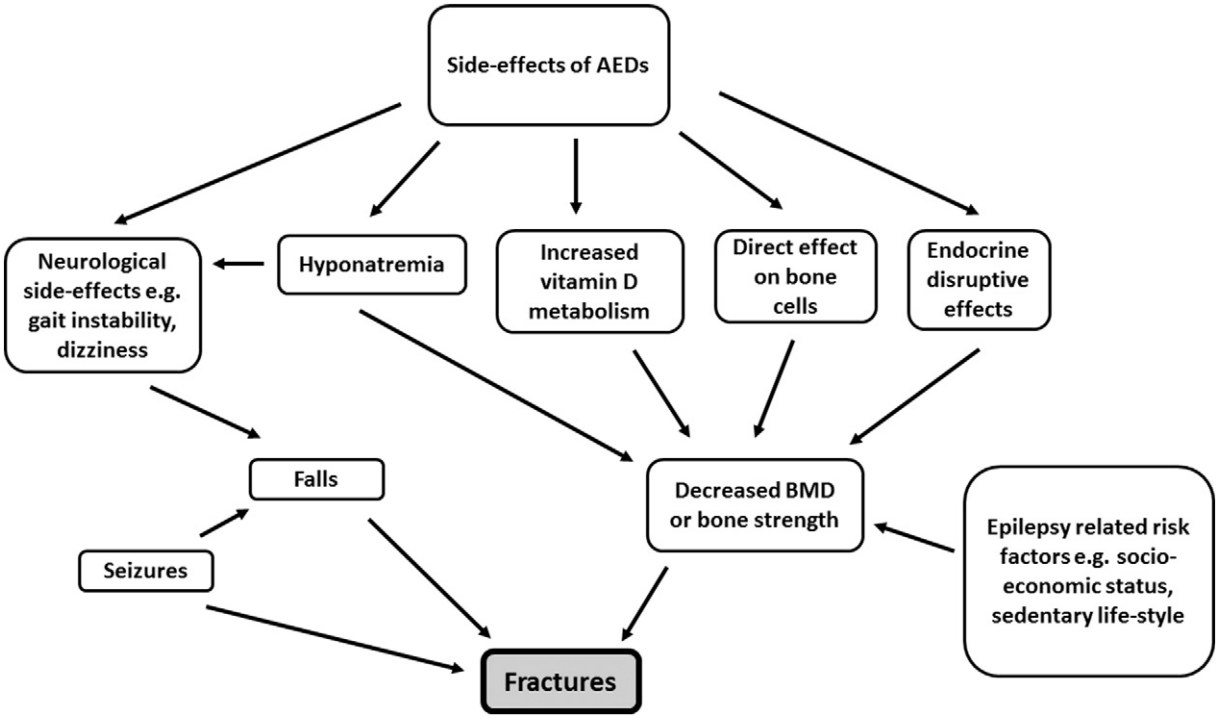

Fig. 2. Illustration of the complex interplay between epilepsy-related risk factors for fractures.

interesting rise in proliferation in human osteoblast-like cells at doses below therapeutic level whereas doses equivalent to therapeutic doses had a negative effect on proliferation. Although some of these findings might seem contradictory, PHT is known to induce connective-tissue disorders resulting in changes in the connective tissue and coarsening of the facial features [18].

Like PHT, the effect of VPA on various bone cells has been studied. Valproic acid is a known histone deacetylase inhibitor and has been found to promote cell proliferation and differentiation in osteoblast-like cells from mice by inducing the Runx2 gene, an important gene for osteoblast differentiation [19,20]. In mouse embryonic mesenchymal cells, a cell line which can differentiate into osteoblasts, chondrocytes, and adipocytes, VPA suppressed cell proliferation in the presence of two known mesenchymal cell proliferation inducers, fibronectin and collagen type I [21]. This likewise suggests that VPA alters bone cell function; however, the effects of these alterations are unknown.

Another interesting pathophysiological mechanism is VPA's ability to potentiate xpression of CYP24 messenger RNA (mRNA) in hepatocytes in the presence of vitamin D. The normal physiological function of CYP24 is to accelerate hydroxylation of 1,25-dihydroxyvitamin D stimulated by the presence of vitamin D_3, as a normal negative feedback mechanism. This process is stimulated by VPA resulting in an accelerated breakdown of vitamin D and lowering biological activity of vitamin D. Valproic acid is not traditionally classified as a known EIAED, but rather an enzyme-inhibiting AED, and is not usually associated with interfering with vitamin D and calcium levels, despite hypovitaminosis D being common in VPA users [22,23].

3.1.2. The in vivo studies – the effects of AEDs in animal models

The effects of various AEDs on bone metabolism have been investigated in animal studies. The studies shed light on aspects of bone which are either very difficult to obtain or not accessible in patients

Table 3
Summary of the preclinical in vivo treatment studies of antiepileptic drugs' effects on bone health in rats.

Antiepileptic drug	Animal strain, age, and sex AED administration route and dose, treatment duration	BMD/BMC	Biomechanical testing	Bone turnover markers
Phenytoin (PHT)				
Simko et al. [27]	Albino Wistar, 8 weeks-old, male. Standard laboratory diet enriched with PHT for 12 weeks.	→BMD	→Strength	↓Formation →Resorption
Nissen-Meyer et al. [30]	Wistar, 80 days-old, female. Gastric feeding, twice daily, 50 mg/kg, for 90 days.	↓BMD and BMD	→Strength	→Resorption
Kanda et al. [32]	Sprague–Dawley, age unspecified, male. Gastric feeding, 20 mg/kg, for 12 weeks.	↓BMD	↓Strength	→Formation ↑Resorption
Valproic acid (VPA)				
Gold et al. [24]	Sprague–Dawley, age unspecified, male. Intraperitoneally, 250 mg/kg, for 8 weeks.	↓BMD and BMC	↓Strength	Not measured
Nissen-Meyer et al. [30]	Wistar, 80 days-old, female. Gastric feeding, twice daily, 300 mg/kg, for 90 days.	↓BMD and BMC	→Strength	↑Formation ↑Resorption
Lamotrigine (LTG)				
Simko et al. [26]	Wistar orchidectomized, age unspecified. Standard laboratory diet enriched with LTG for 12 weeks.	↓BMD and BMC	↓Strength	→Formation ↓Resorption
Simko et al. [27]	Albino Wistar, 8 weeks-old, male. Standard laboratory diet enriched with PHT for 12 weeks.	→BMD	→Strength	→Formation ↓Resorption
Kanda et al. [31]	Sprague–Dawley, 5 weeks-old, male. Gastric feeding, 2 or 10 mg/day, for 12 weeks.	→BMD	→Strength	→Formation →Resorption
Levetiracetam (LEV)				
Fekete et al. [28]	Wistar orchidectomized, age unspecified. Standard laboratory diet enriched with LEV for 12 weeks.	↓BMD and BMC	→Strength	↓Formation ↑Resorption
Nissen-Meyer et al. [30]	Wistar, 80 days-old, female. Gastric feeding, twice daily, 50 mg/kg, for 90 days.	→BMD and BMC	↓Strength[a]	↓Formation →Resorption
Kanda et al. [32]	Sprague–Dawley, age unspecified, male. Gastric feeding, 20 mg/kg, for 12 weeks.	→BMD	→Strength	Not measured
Karesova et al. [34]	Wistar, 8 weeks-old, male. Standard laboratory diet enriched with LEV for 12 weeks.	↑BMD	→Strength	↑Resorption
Topiramate (TPM)				
Simko et al. [26]	Wistar orchidectomized, age unspecified. Standard laboratory diet enriched with LTG for 12 weeks.	↓BMD and BMC	↓Strength	→Formation →Resorption
Kanda et al. [31]	Sprague–Dawley, 5 weeks-old, male. Gastric feeding, 5 or 20 mg/day, for 12 weeks.	→BMD	→Strength	↓Formation →Resorption
Zonisamide (ZNS)				
Takahashi et al. [25]	Wistar, age unspecified, male. Subcutaneous, 80 mg/kg, 5 weeks.	↓BMD	Not measured	→Formation ↑Resorption
Lacosamide (LCM)				
Simko et al. [33]	Wistar orchidectomized, age unspecified. Standard laboratory diet enriched with LCM for 12 weeks.	↓BMD	→Strength	↓Formation →Resorption
Gabapentin (GBP)				
Kanda et al. [32]	Sprague–Dawley, age unspecified, male. Gastric feeding, 30 or 150 mg/kg, for 12 weeks.	→BMD	→Strength	Not measured

This table summarizes the details of the preclinical in vivo treatment studies of antiepileptic drugs' (AEDs) effects on bone health in rats sectioned by AED. This includes strain of animal, age, gender, route of administration of AED, dose, and duration of treatment. Furthermore, the table summarized the effect on bone mineral density (BMD), bone mineral content (BMC), biomechanical properties (strength), and bone turnover markers (markers were categorized as either formation or resorption). The arrows indicate whether the study found the parameter increased (↑), unchanged (→), or decreased (↓).

[a] Histomorphological analysis showed a clear trend towards increased content of cartilage in the metaphysis of LEV-treated rats.

and provide valuable mechanistic information for understanding the pathophysiology of AED-associated bone disease.

Several studies investigated the changes in BMD, bone mineral content (BMC), biomechanical properties, and BTM in relation to treatment with various AEDs in animal models. Table 3 summarizes the results of preclinical in vivo treatment studies on bone turnover in rats [24–34]. The results are conflicting when it comes to studies of the same AED. This possibly reflects the variation between the studies: the use of different strains of animals, differences in AED doses, administration form, and duration of treatment. Furthermore, the difference in results also represents different pathophysiological mechanisms of EIAEDs and NEIAEDs including very different timespans for the mechanisms of action. It is possible that direct effects on bone cells are seen faster than secondary effects on bone seen through an impact on the vitamin D and calcium metabolism. An interesting finding by Nissen-Meyer and colleagues showed an increased proportion of cartilage to calcified tissue in rat femur treated with levetiracetam (LEV) and a resulting decrease in bone strength despite no affect was seen on BMD or BMC [30].

The postmenopausal decline in estrogen accelerated bone loss and could make postmenopausal women a more vulnerable target for AED-induced bone loss. This aspect was investigated in an ovariectomy model in rats with the following AEDs: carbamazepine (CBZ), VPA, and LEV. The study found that for all treatments, the combined effect of AED and estrogen withdrawal significantly increased bone loss [35]. However, the study did not compare the results to a vehicle or sham group, impairing the possibilities for further comparisons and conclusions of pathophysiological mechanisms.

3.2. Lessons from clinical studies

3.2.1. AEDs' effects on calcium and vitamin D metabolism in patients with epilepsy

Numerous studies have investigated the effects of AEDs on vitamin D and calcium metabolism. In several of the first studies on the topic, the term 'anticonvulsant osteomalacia' was introduced. This term, which only applies to AED-treated patients, includes decreased levels of 25-OH-vitamin D, hypocalcaemia, and increased levels of alkaline phosphatase (ALP). The combination of decreased levels of vitamin D and calcium combined with elevated ALP is classical for osteomalacia. The pathophysiology behind the 'anticonvulsant osteomalacia' is thought to be the result of treatment with EIAEDs. The EIAEDs induce various isoenzymes of the cytochrome P450 enzyme system in the liver and cause an increased hydroxylation of vitamin D and thus reduced levels, resulting in development of hypocalcemia and consequently a physiological condition similar to that of secondary hyperparathyroidism and an increased bone loss [36–40]. Several AEDs influence isoenzymes (Fig. 3) which are essential for the vitamin D synthesis in the liver and could be a likely explanation for the hypovitaminosis D and subsequent metabolic bone disease we see in patients with epilepsy. However, not all studies find the classical biochemical representation of secondary hyperparathyroidism in relation to treatment of EIAEDs despite findings of decreased BMD [41]. Furthermore, a cross-sectional study showed normal BMD and 25-OH-vitamin D levels in patients treated with the strong enzyme-inducer CBZ as monotherapy compared to healthy controls [42]. One single cross-sectional study showed that, in patients with ambulatory epilepsy receiving chronic AED treatment, hypocalcemia and osteopenia occurred despite normal levels of 25-OH-vitamin D and 1,25-OH-vitamin D [43]. This indicates that the cytochrome P450 enzyme system induction and subsequent 'anticonvulsant osteomalacia' cannot solely explain the bone loss seen in patients with epilepsy, and that AEDs might influence bone turnover by other mechanisms. This is supported by an interesting study of intestinal calcium absorption in chronic AED users. In a small prospective study, patients with AED-treated epilepsy and matched controls were given a daily oral dose of 0.5 μg of 1,25-OH-vitamin D or a daily oral dose of 10 μg of 25-OH-vitamin D for 10 days [44]. Independently of vitamin D dose, the patients had a reduced fractional intestinal calcium absorption compared to controls suggesting a direct inhibition of the intestinal calcium absorption by the AEDs. Both patients and controls had equal increases in fractional intestinal calcium absorption in response to 1,25-OH-vitamin D supplement indicating that patients had normal sensitivity to exogenous 1,25-OH-vitamin D and that the decreased intestinal calcium absorption is caused mainly by reduced tissue concentration of active vitamin D metabolites [44].

That the interplay between AEDs and vitamin D is complex is further illustrated by a prospective study of the dose of vitamin D required to correct low 25-OH-vitamin D levels in patients with epilepsy. The study consisted first of a titration phase to obtain serum values of vitamin D within the normal reference range and a subsequent 12 months follow-up period with a continuation of the same dose of vitamin D. The vitamin D intervention required to obtain normal serum levels ranged from 400 to 4000 D_3 IU/day with normal levels only persisting in one out of 11 patients [45]. This suggests a dynamic interaction of AEDs on vitamin D metabolism that is yet unexplained.

That an independent effect of AEDs exists is, however, supported by findings of accelerated bone loss in patients using AEDs for other indications than epilepsy [46,47].

3.2.2. AEDs' effects on serum bone turnover markers in patients with epilepsy

Several studies have investigated the effect of various AEDs on BTM to understand how treatment directly affects the activity of bone cells and bone loss. The serum BTM primarily measured in relation to AED treatment studies are osteocalcin and C-terminal extension peptide of type 1 procollagen (P1CP), both biochemical markers for bone formation, and C-terminal cross-linking telopeptide of type I collagen (CTX), a marker for bone resorption. The studies and their findings on BTM are summarized in Table 4. Only three studies show significant changes in serum BTM. In a study by Välimäki et al., PHT and CBZ increased levels of osteocalcin, P1CP, and CTX. The finding was independent of low levels of vitamin D indicating that bone turnover was accelerated independently of hypovitaminosis D [48]. Another study by El-Haggar et al. found a significant decrease in osteocalcin levels following 6 months of monotherapy treatment with LEV but not with lamotrigine (LTG). Whereas, 6 months of polytherapy with LTG and VPA or LEV and VPA resulted in significant increases in osteocalcin levels [49]. However, it

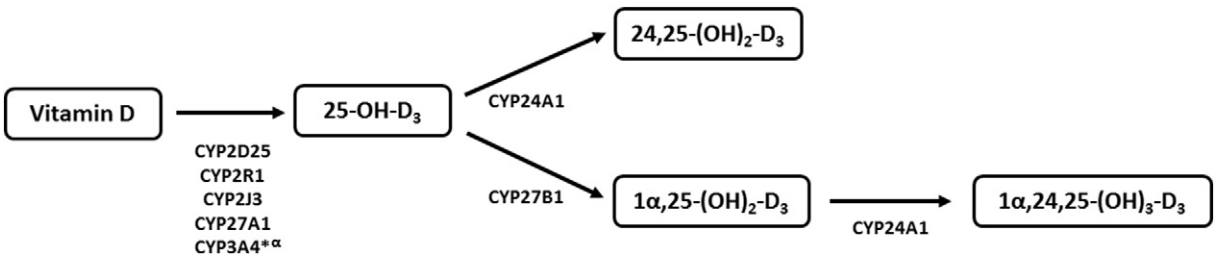

Fig. 3. Illustration of the steps in hydroxylation of vitamin D including the cytochrome P450 isoenzymes responsible for the specific steps. *The isoenzyme CYP3A4 is induced by phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine acetate, topiramate. αThe isoenzyme CYP3A4 is inhibited by valproic acid.

Table 4
Summary of the clinical studies of the effects of AEDs on serum bone turnover markers.

Study	Study type	AED	Duration of treatment	BTM	Change (%)			
Brämsvig et al.	Prospective	Healthy men on CBZ	10 weeks		CBZ:			
				Osteocalcin	22% ↓			
				CTX	1% ↓			
Koo et al.	Prospective	Drug-naïve patients with new-onset epilepsy on OXC	11 months (median)		OXC:			
				Osteocalcin	8% ↓			
				CTX	19% ↓			
Koo et al.	Prospective	Drug-naïve patients with new-onset epilepsy on LEV	13 months (median)		LEV:			
				Osteocalcin	18% ↓			
				CTX	16% ↓			
El-Haggar et al.	Prospective	Patients with epilepsy	6 months		LTG:	LEV:	VPA + LTG:	VPA + LEV:
				Osteocalcin	12% ↓	31% ↓[a]	100% ↑[a]	94% ↑[a]
Välimäki et al.	Case–control	PHT, CBZ or PHT and CBZ	21 years (median)		Female:		Male:	
				Osteocalcin	13% ↑		66% ↑[a]	
				P1CP	27% ↑[a]		63% ↑[a]	
				CTX	46% ↑[a]		22% ↑[a]	
Lyngstad-Brechan et al.	Case–control	All patients: various AEDs EIAEDs: PHT, PB, CBZ, OXC	Unknown		All patients:	EIAED:	CBZ:	
				Osteocalcin	6% ↑	6% ↑	2% ↑	
				CTX	30% ↑	39% ↑	42% ↑	
Heo et al.	Case–control	Premenopausal women on monotherapy with CBZ, TPM, or VPA	2.8–6.6 years (mean)		VPA:	TPM:	CBZ:	
				Osteocalcin	15% ↑	25% ↑	2% ↓	
				CTX	20% ↓	24% ↑	20% ↓	
Suljic et al.	Case–control	Patients on CBZ monotherapy	6 years (mean)		CBZ:			
				Osteocalcin	33% ↑[a]			

This table summarizes the details of the clinical studies of the effects of antiepileptic drugs (AEDs) on serum bone turnover markers (BTM). This includes study type, the AEDs investigated, duration of treatment, measured BTM, and change in percentage. The arrows indicate whether the study found the parameter increased (↑) or decreased (↓). Phenytoin (PHT), carbamazepine (CBZ), phenobarbital (PB), oxcarbazepine (OXC), topiramate (TPM), valproic acid (VPA), lamotrigine (LTG), levetiracetam (LEV), C-terminal extension peptide of type 1 procollagen (P1CP), C-terminal cross-linking telopeptide of type I collagen (CTX).
[a] Significant finding.

should be noted that all treatment groups, except LTG monotherapy, had significant decreases in their BMD during the 6 months of treatment. Suljic et al. found increased levels of osteocalcin in patients on CBZ monotherapy compared to healthy controls accompanied by lower levels of vitamin D and BMD [50]. Despite the significance, similar studies have not been able to reproduce the findings [51–53]. New AEDs such as topiramate (TPM) with little or no effect on the cytochrome P450 enzyme system have also been investigated. Topiramate, a weak enzyme-inducer in doses above 200 mg/day, did not significantly change levels of osteocalcin or CTX compared to healthy controls [54,55].

3.2.3. AEDs' effects as endocrine disrupters in patients with epilepsy

Antiepileptic drugs are known to have endocrine adverse effects in both men and women, several of which can also increase bone turnover. The EIAEDs increase catabolism of sex steroids including estradiol and testosterone as well as increasing sex-hormone-binding globulin levels thereby reducing levels of bioavailable hormones [56,57]. Both testosterone and estradiol are essential for bone health, and decreased levels will lead to increased bone loss. Likewise, decreased thyroid function and thyroid hormones have been found in patients using AEDs [58,59] which can also affect bone turnover. Antiepileptic drugs are also known to affect levels of vitamin K, leptin, homocysteine, and insulin-growth factor 1 [60,61], and although these factors' role in bone loss is debatable, the possibility exists that AEDs exert an effect through these.

3.2.4. AED-induced hyponatremia and osteoporosis in patients with epilepsy

Patients treated with AEDs can develop chronic hyponatremia as a common adverse effect in relation to treatment with EIAEDs, such as CBZ and oxcarbazepine (OXC). Studies have found that 7–46% of patients receiving one or both of these drugs develop hyponatremia [62–64]. Not only is chronic hyponatremia seen in relation to treatment with older EIAEDs but case reports have shown that it occurs with newer EIAEDs as eslicarbazepine acetate (ESL), but also with NEIAEDs as LEV and VPA [65–69]. The chronic hyponatremia is thought to be caused by a mechanism similar to syndrome of inappropriate antidiuretic hormone secretion (SIADH), where the AEDs independently of the presence of antidiuretic hormone (ADH) can stimulate the tubule cells of the kidneys to increase water reuptake [70–72]. During the past decade, accumulating evidence has demonstrated that hyponatremia is associated with increased risk of osteoporosis and fractures [73,74]. To our knowledge, there is to date only one study linking hyponatremia in patients with epilepsy to the increased risk of osteoporosis. In a cross-sectional study, a decreased T-score was significantly associated with mild and severe hyponatremia (p-Na ≤ 129 mmol/L) when correcting for known risk factors for osteoporosis in patients with epilepsy [75]. This finding suggests that the effects of hyponatremia-induced osteoporosis are also seen in patients with epilepsy and that hyponatremia should not be left unattended.

Furthermore, it should be noted that chronic hyponatremia is also associated with gait instability and falls [76] which could be another mechanism by which hyponatremia additionally increases the risk of fractures in patients with epilepsy (Fig. 2).

4. Non-AED-related risk factors in patients with epilepsy

4.1. Cognitive, physical, and socioeconomic risk factors for osteoporosis

A chronic neurological disease like epilepsy, where seizure-induced loss-of-control might be a common symptom, has many adverse effects for the patients' general health. In a telephone interview study on the health status of adult patients with epilepsy, a higher frequency of smoking and alcohol consumption was found, and likewise were the patients less likely to report exercise within the past 30 days, all factors which individually have negative effects on bone health. Moreover, the patients were less likely to have completed college, were more likely to be unemployed, and have significantly lower annual household income [77]. Despite the limitations of self-reporting, stigmata leading to underreporting and the lack of a causal relationship between the

epilepsy and health outcome, the factors are all aspects which negatively influence bone health. Likewise, the consequences of epilepsy could be a more sedentary indoor lifestyle and less sunlight exposure which can also lead to lower levels of vitamin D and consequently biochemical changes similar to those of 'anticonvulsant osteomalacia'. Interestingly, none of the 'anticonvulsant osteomalacia' biochemical changes were seen in studies conducted in Florida and Brazil, suggesting an effect of sunlight exposure in patients with epilepsy [78,79]. In addition to this confounding factor, it is also possible that the patients are taking other medication with adverse effects on bone such as corticosteroids.

Likewise, factors pertaining to epilepsy, other than effects of AED use, are associated with reduced BMD. This includes occurrence of generalized seizures and duration of epilepsy [80,81], and although we do not believe in a causal relationship, the associations should be seen as surrogate markers indicating that at least for the seizures, well-treated epilepsy is a key component in bone health.

Not only does epilepsy affect patient's general health behavior but it independently also poses a barrier to the prevention and diagnosis of osteoporosis. Physical functioning barriers, such as seizures, or other concomitant neurological disorders frequently seen in relation to epilepsy, as cerebral palsy or spasticity might prevent or complicate undergoing dual-energy X-ray absorptiometry (DXA) scan just as cognitive barriers as mental retardation or cognitive impairment might pose a barrier [82]. Additional to physical and cognitive barriers, the patient's own knowledge is of great importance when it comes to improving awareness of bone health and inspiring bone protective behavior. Studies have shown that the patients' perceived benefits from taking calcium supplements and doing regular exercise are important in preventing bone loss and for later taking up exercising and taking calcium supplements [83,84]. This also indicates that the physician plays an important role when informing the patient about benefits of vitamin D and calcium supplements and when promoting bone protective behavior. A survey found that 75% of patients felt that they were not given enough information about the adverse effects of AED use nor were they told of the fact that AEDs can cause osteoporosis. However, of those that had been informed, the information came from their epilepsy specialist [84,85], which stresses the importance of the physicians role in adequately informing their patients. Unfortunately, routine evaluation of BMD in AED-treated patients is only performed by 28% of neurologists [86]. Thus, increasing the professionals' awareness and focus on regularly monitoring bone health could greatly benefit the patients. This is supported by a study showing that patients who had undergone a DXA scan reported significantly higher rates of regular intake of calcium and vitamin D than those reporting not having undergone a DXA scan, and this seemed not to be influenced by the actual result of the DXA scan [87].

5. Discussion and conclusion

As this review shows, patients with epilepsy are heavily burdened by the high occurrence of metabolic bone disease and subsequent high risk of fractures. However, the underlying pathophysiological mechanisms are far from clear, only that there exist multiple mechanisms are certain. It can be related both to socioeconomic consequences of having a chronic disease like epilepsy as well as the use of AEDs. There can be no doubt that the AEDs play an independent and marked role in the development of bone loss in patients with epilepsy. However, whether this is due to the 'anticonvulsant osteomalacia' is questionable since adverse effects on bone are seen independently of vitamin D levels in humans and moreover, are the findings in preclinical animal models and cell cultures not limited to EIAEDs but also demonstrate effects of NEIAEDs. Adverse effect of VPA appears to be quite consistent from preclinical experiments and clinical studies; however, the underlying mechanisms are unknown, warranting for further studies. The picture is further complicated by the diversity of findings in BTM spanning effects of both EIAEDs and NEIAEDs but also including several studies showing no effects of AEDs on BTM. Although BTM are gaining ground in clinical use, the consequences and implications in patients with epilepsy remain unknown.

As thus demonstrated, the classic hypothesis on the underlying pathophysiology of AED-induced bone loss is not supported by the findings in the review. This emphasizes the importance of investigating new pathophysiological mechanisms as the consequences of AEDs as endocrine disruptors and inducers of hyponatremia-induced osteoporosis. Future research on the pathophysiological mechanisms with a more standardized approach should be carried out to increase reproducibility and generalizability of the results. Likewise, translational studies are to be encouraged along with an increased focus on the newer AEDs and on potential new mechanisms of action such as endocrine adverse effects and hyponatremia-induced osteoporosis. All of which could increase our knowledge on the adverse effects of AEDs on bone health.

The review demonstrates that there exist several socioeconomic consequences to epilepsy which can greatly affect bone health indicating the importance of comprehensive patient care, i.e., doctors (often specialists) prescribing AEDs but also nurse specialists and caregivers who have a key role in the prevention and follow-up of comorbidities to epilepsy and adverse effects to AEDs in their patients with epilepsy.

In conclusion, the literature supports the need for awareness of bone health in patients with epilepsy. Healthcare professionals should be aware of the adverse effects of AEDs, of the possible benefits of implementing preventive measures in clinical practice, and of adequately informing patients about adverse effects to AED treatment so all possible measures in preventing bone loss are taken. Furthermore, the literature supports the need for further research in the area and with emphasis on newer and less well-described pathophysiological mechanisms.

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