ELSEVIER

Insights into liaison between antiepileptic drugs and bone

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The adverse effect on bone caused by chronic anticonvulsant therapy causes multiple abnormalities in calcium and bone metabolism, varying from bone turnover, without significant loss of cortical or trabecular bone, to osteopenia/osteoporosis and to osteomalacic disorder. The studies conducted to date have documented anticonvulsant bone disease as a state of increased bone remodeling. With the newer antiepileptic drugs (AEDs) gaining importance and starting to replace conventional medicines, it may be appropriate to compare them with the conventional AEDs and to examine their impact on multiple aspects of bone health. This review focuses on the status of the bony effects of AEDs.

Introduction

Bone strength and integrity is maintained by bone-resorbing osteoclasts and bone-forming osteoblasts. The processes of bone resorption and bone formation work in perfect harmony with each other and any discrepancy in this remodeling balance sets the basis for altered bone mass, thereby triggering numerous bone diseases (i.e. osteoporosis, Paget's disease, bone metastases and osteopetrosis).

The multifactorial risk factors for bone loss enlist pharmacological agents such as antiepileptic drugs (AEDs), which have a strong effect on neuromuscular function and, thus, have been categorized as independent risk factors for bone loss regardless of age, gender and period of treatment. Gross malformations in the bones allied mainly, but not solely, with the cytochrome P450 (CYP450)-inducing AEDs may act as an add-on to risk factors (e.g. seizure-precipitated falls and trauma, sedentary lifestyle) for fractures in epileptics.

Although large quantities of clinical data reporting iatrogenic bone loss with AED medication have been generated over several decades, AED-induced bone loss continues to remain an enormous clinical problem. It may be an inevitable effect but can be mitigated by appropriate selection of AEDs along with the other necessary measures (i.e. supplementation of vitamin D and calcium, weight-bearing exercise, avoidance of alcohol and not smoking).

This review focuses on the multifactorial mechanisms behind AED-associated bone abnormalities. A better understanding of these mechanisms can aid clinicians in identifying and monitoring vulnerable patients and in defining the optimal therapy for all affected patients.

AEDs and bone health

For more than four decades, AEDs have been known to cause serious effects on bone mineral density (BMD) [1–4]. Epilepsy and AEDs intricately modulate the bone microarchitecture and BMD, affecting bone strength. Studies to date have documented antiepileptic bone disease as a state of increased bone remodeling. Antiepileptic therapy causes multiple abnormalities in calcium and bone metabolism, varying from increased bone turnover without significant loss of cortical or trabecular bone to osteopenia/osteoporosis and to osteomalacic disorder [5].

Risk factors

Owing to greater variations in bone turnover patterns among patients, numerous factors account for AED-associated bone loss. The chronic treatment regime, and polytherapy, for epilepsy, which is thought to be tailored to patients' needs, compromises bone mass [6]. Apart from AED medication other factors leading to bone loss are indoor confinement (institutionalized epileptics), old age, reduced physical activity and poor nutrition (see Box 1)

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BOX 1

Risk factors of AED-associated bone loss

- Adverse effects associated with epilepsy: depression; cerebral palsy; trauma
- Age (children and elderly)
- Chronic AED medication
- Cigarette smoking and alcohol intake
- Indoor confinement (institutionalized epileptics)
- Family history of bone disorders such as osteoporosis
- Gender
- History of broken bones
- Menopause
- Polytherapy
- Poor nutrition
- Sedentary lifestyle

BOX 2

Fracture risks linked to epilepsy and AEDs

- Epilepsy

Adverse effects: associated neurologic deficit (e.g. cerebral palsy)
Fall on the onset of seizure (unconscious stage)

- AEDs

Adverse effects: osteopenic/osteoporotic state; ataxia; gait disturbances; somnolence; elevated homocysteine levels

[7,8]. These risk factors promote patient susceptibility to the numerous pathophysiological mechanisms involved in AED-induced bone disease.

Fracture risks

Fractures are one of the sternest effects of perturbations with BMD. BMD is conversely linked with fracture risk, which shows discrepancy with a number of factors that will be discussed below. Falls associated with seizure, accidental trauma or AED-induced ataxia, somnolence and gait disturbances, reduced physical activity caused by epilepsy-associated neurologic deficits (e.g. cerebral palsy or depression) and pathologic fractures resulting from AED-induced bone malformation are certain circumstances that predispose epileptics to fractures [9–11]. When a person does not suffer from epilepsy and enjoys normal physical health the likelihood of fractures is minimal after a fall or slip, but this likelihood increases two- to threefold for epileptics, as a result of altered bone mineralization [12]. Elderly people, especially elderly women, are also more likely to suffer fractures as a result of a fall [13]. A meta-analysis done to assess the effects of epilepsy on fracture risk and changes in BMD in epileptics revealed that the seizures accounted for an increase in fracture risk (approximately 35%) that was much higher than that observed with changes in BMD following AED treatment [14]. The skeleton of community-dwelling and hospitalized epileptics is at risk of fractures [15]. Box 2 summarizes fracture risks linked to epilepsy and AEDs.

Pathophysiology of conventional antiepileptic drug-associated bone disease

Conventional AEDs [i.e. phenytoin (PHT), primidone, phenobarbital and carbamazepine (CBZ)] are potent hepatic mixed-function oxidase (CYP450) inducers including CYP1A2, CYP2C9, CYP2C19 and CYP3A4, as well as glucuronyl transferases and epoxide hydrolase [16]. Valproic acid (VPA) is an enzyme inhibitor. There is a lattice of the pathophysiological mechanisms of AED-induced bone disease that can be either independent or dependent on each other (Fig. 1).

Vitamin D deficiency

Hypovitaminosis D is the major cause for overt bone loss in AED therapy. Hepatic CYP450 hydroxylase enzyme-inducing AEDs accelerate catabolism of vitamin D and inhibition of 25-hydroxylation of vitamin D [17]. This effect is mediated through the pregnane X receptor (PXR), a transcriptional regulator of CYP450. PXR has been reported to mediate induction of CYP24 in cultured cells and *in vivo* in mice [18]. It converts $1,25(OH)_2D$ to its water-soluble, inactive form thereby reducing biologically active vitamin D levels. AEDs can activate PXR, which in turn augments CYP24 expression and is, hence, responsible for PXR-induced vitamin D deficiency [18,19].

In addition, the vitamin D receptor (VDR) gene plays a vital part in regulating BMD, inducing the expression of important proteins in the osteoblasts [i.e. receptor activator nuclear factor-kappa B ligand (RANK-L)] and, thus, osteoclastic activity [20]. It even regulates calcium levels in the endoplasmic reticulum. VDR shares a high degree of homology with PXR indicating that AEDs also activate VDR and, hence, enhance bone metabolism [21]. VDR-null mutant mice have been reported to have a substantial drop in calcium and parathyroid hormone (PTH) levels [22].

In summary, AEDs (CYP450 inducers as well as inhibitors) adversely affect bone health either through PXR or through VDR. Vitamin D deficiency may also result in hypocalcemia owing to the decline in calcium transport across the small intestine contributing to bone loss.

Secondary hyperparathyroidism

PTH activates RANKL in osteoblasts and augments osteoclastic bone resorption. Hyperparathyroidism is associated with an increase in loss of bone mineral. Secondary hyperparathyroidism results from the compensation for lowered circulating calcium owing to hypovitaminosis D [23]. Vitamin-D-related hypocalcemia causes the parathyroid gland to activate osteoclasts that resorb calcium from the bones, ultimately resulting in bone loss [24].

Additionally, PHT and phenobarbital have been proposed to impair cellular response to PTH in fetal rats [25]. The resulting increment in PTH concentration as a feedback mechanism is independent of vitamin D deficiency.

Calcitonin deficiency

Calcitonin, a bone remodeling hormone, is produced by thyroidal C cells. This physiologic antagonist of PTH inhibits bone resorption by blocking the osteoclast PTH receptors and also inhibits osteolysis by blocking osteocytes [26]. AEDs modulate calcitonin-deficiency-related bone loss biology [27]. While some conventional studies demonstrate that AEDs probably intervene with calcitonin release from thyroidal C cells by acting on calcium channels, this subject still remains controversial

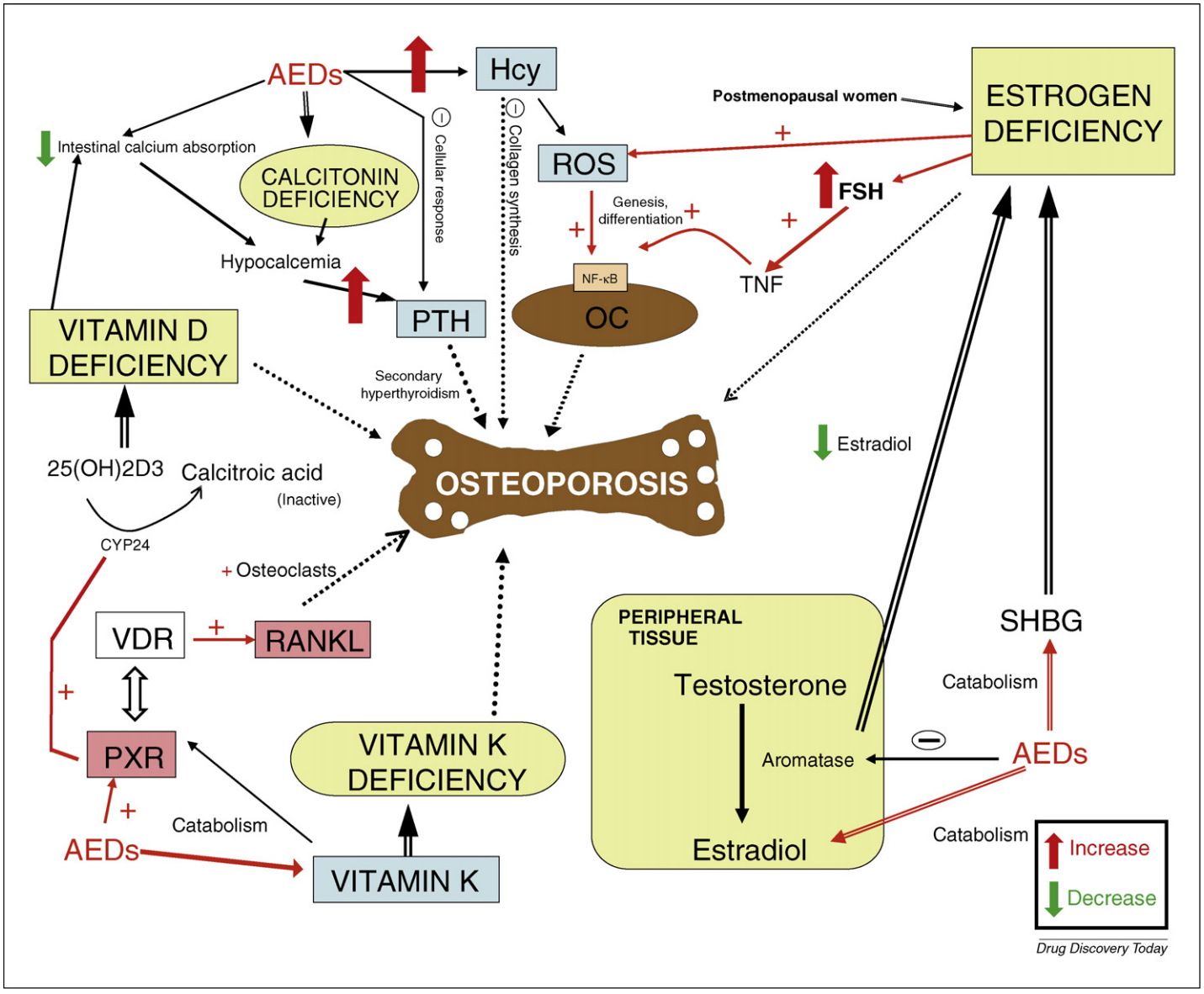

FIGURE 1

Pathophysiology of conventional antiepileptic drug-associated bone disease; AEDs can activate PXR, which in turn augments CYP24 expression. CYP24 converts 1,25(OH)$_2$D to its inactive form, thereby reducing biologically active vitamin D levels. Vitamin D deficiency may also result in hypocalcemia owing to the decline in calcium transport across the small intestine contributing to bone loss. VDR shares a high degree of homology with PXR. AEDs, thus, activate VDR and induce the expression of RANKL. RANKL activates osteoclasts, cells involved in bone resorption. Secondary hyperparathyroidism results from the compensation for lowered circulating calcium owing to hypovitaminosis D. PTH activates osteoclasts that resorb calcium from the bones resulting in bone loss. AEDs probably intervene with calcitonin release. Also, the hypocalcemia consequential to AED therapy might be involved in insufficient calcitonin levels. Vitamin K metabolism is enhanced with AED administration resulting in undercarboxylation of the gla-containing proteins and, thereby, ceasing their calcium-binding ability. Vitamin K has affinity for PXR as well. AED-induced vitamin D deficiency is contemporaneous with the reduced aromatase-induced testosterone conversion to estradiol. Also, AEDs catabolize estradiol and estrone and enhance the synthesis of SHBG. The reduction in estrogen levels outweighs the beneficial effects of estrogen on bone. Estrogen depletion not only downregulates antioxidant pathways but also enhances interleukin-7 (IL-7) production in bone. IL-7 activates T cells and releases interferons (IFNc). The free radicals generated along with IFNc exacerbate tumor necrosis factor (TNF) and RANKL release and, thus, mediate osteoclastogenesis. The age-related estrogen depletion clubbed with AED intake may suggest a pathway of bone loss via FSH as FSH stimulates TNF. Augmentation of serum Hcy levels with AED intake may or may not be coupled with low serum folic acid. Hcy not only interferes with collagen crosslinking during the bone remodeling process but also stimulates osteoclastogenesis. AED(s), antiepileptic drug(s); FSH, follicle-stimulating hormone; Hcy, homocysteine; OC, osteocalcin; PTH, parathyroid hormone; PXR, pregnane X receptor; RANKL, receptor activator nuclear factor-kappa B ligand; ROS, reactive oxygen species; SHBG, sex hormone-binding globulin; TNF, tissue necrosis factor; VDR, vitamin D receptor.

[28,29]. Thus, there is no direct association between AEDs and circulating calcitonin levels. Calcitonin secretion is, however, largely regulated by ionized calcium concentration via calcium-sensing receptors [30]. The hypocalcemia caused by AED therapy might be involved in insufficient calcitonin levels.

Vitamin K deficiency

The reduced quinol (or hydroquinone) form of vitamin K plays an indispensable part in bone accretion. This hydroquinone is a cofactor for post-translational gamma carboxylation of the glutamate residues of bone matrix gla-containing proteins, a requisite

step to impart the calcium-binding function of the proteins, namely: osteocalcin; matrix gla protein and protein S [31]. Suboptimal vitamin K levels result in under-carboxylation of the gla-containing proteins ending their calcium-binding capability [32,33]. Thus, osteocalcin has a role in mineral maturation and is regarded as a bone formation marker [34]. The epidemiologic and intervention studies on animal models and humans implicated an association of vitamin K deficiency with reduced bone mineralization [35–37]. AEDs are known to interfere with vitamin K metabolism [38]. Vitamin K binds to PXR and mediates a 'bone-friendly' action in a similar way to vitamin D. This further explains the etiology of the resulting bone loss in vitamin K depletion.

Deprived estrogen levels

The nonreproductive function of estrogen is to maintain bone integrity through its autocrine and paracrine activities. It enhances osteoblast differentiation, inhibits osteoclastogenesis, modulates RANK signaling in osteoclastic cells and induces apoptosis of osteoclasts [39–41].

The aromatase (CYP450)-induced catalytic conversion of C_{19} steroids to estrogens in osteoblasts has an imperative role in BMD maintenance, especially in postmenopausal women [42]. Vitamin D_3 transiently augments the aromatase expression in osteoblasts. AED-induced vitamin D deficiency leads to reduced aromatase expression, a plausible mechanism for reduced BMD. A report published a decade ago showed the beneficial effect of estrogen supplementation on bone accretion in AED-induced bone dematuration [43]. The impeding *in vitro* action of VPA and ethosuximide that was demonstrated leads us to believe that further research is warranted to assess whether this mechanism is the etiology behind the bone loss because of administration of nonenzyme inducer AEDs [44,45].

Furthermore, AEDs are potent stimulators of the microsomal catabolism of estradiol and estrone and the synthesis of sex-hormone-binding globulin (SHBG) [46]. This increased SHBG level results in lowering serum levels of C_{19} steroids [i.e. free testosterone and adrenal androgens (dehydroepiandrosterone and dehydroepiandrosterone-sulfate)]. Thus, this explains one of the possible reasons for estrogen deficit because C_{19} androgenic steroids are aromatized to corresponding estrogens.

Estrogen depletion not only downregulates antioxidant pathways but also enhances interleukin-7 (IL-7) production in bone. IL-7 activates T cells and releases interferons (IFNc). The free radicals generated along with IFNc exacerbate tumor necrosis factor (TNF) and RANKL release and, thus, mediate osteoclastogenesis. Age-related estrogen depletion (along with AED intake) could be a pathway of bone loss via follicle-stimulating hormone (FSH) because FSH stimulates TNF [47]. VPA and CBZ lower serum FSH levels [48].

Modifications in bone cell count

VPA osteoclastogenesis, and antiproliferative and apoptotic effects on osteoblasts, has been explored *in vitro* [49,50]. Also, enzyme-inducing AEDs (e.g. PHT, CBZ and phenobarbital) exhibit antiproliferative and antidifferentiation effects on osteoblasts [51,52]. This imbalance between bone-forming and bone-sorbing cells demonstrates the direct involvement of AEDs in the deterioration of skeletal structures.

Interventions with circulating homocysteine levels

5-Methyl-tetrahydrofolic acid generated from folic acid is essential for homocysteine (Hcy) metabolism. Increase in the serum Hcy level with enzyme-inducing and nonenzyme-inducing (e.g. VPA) AED intake may or may not be coupled with low serum folic acid [53,54]. Hcy not only interferes with collagen crosslinking during the bone remodeling process but also stimulates osteoclastogenesis [55,56]. It shows positive correlation with free radical generation and, consequently, intense bone mass interference [57]. Thus, hyperhomocysteinemia may be among several potential mechanisms involved in pathogenesis of bone malformations.

Other factors

Nonenzyme-inducing AEDs might modify osteoblastic function and lower bone density. Drugs such as VPA could compromise biomechanical bone strength that may or may not be evidenced in the usual BMD or bone mineral content examination [50]. PHT- and phenobarbital-generated hypocalcemia lowers intestinal calcium absorption (which might be the consequence of obstruction of cation transport or impaired vitamin-D-mediated calcium absorption), causing bone turnover and, hence, accelerated bone loss [58,59]. Some researchers reveal no considerable change in circulating calcium levels while others do [60,8]. In addition to the above-mentioned mechanisms, an *in vitro* study illustrated the inhibitory effect of PHT on collagen synthesis in cultured bone [61].

Concisely, the mechanisms of bone loss are multifactorial and the individual risk factors probably amplify the susceptibility to a specific mechanism – namely increased hepatic induction of the CYP450 enzyme system, vitamin D catabolism resulting in hypocalcemia and secondary hyperparathyroidism, impaired calcium absorption and indirect effects of AEDs on bone cells. The induction of the CYP450 system resulting in vitamin D deficiency has been the most important mechanism supported by a large number of clinical reports [5,25,27].

Alterations of bone metabolism by newer antiepileptic drugs

In an attempt to eliminate adverse effects of classical established AEDs, the next-generation AEDs are starting to replace the classical ones. Still, these rationally designed moieties – vigabatrin, lamotrigine (LTG), topiramate (TPM), tiagabine, gabapentin, oxcarbazepine (OXC), levetiracetam (LVT) and zonisamide (ZNS) – are categorized as second-line drugs. Despite better tolerability profiles providing a beneficial edge to these drugs, none of them is free from the so-called 'bony' adverse effects. It remains to be determined whether any of these newer drugs can be termed as osteoprotective. The current need is to explore the various mechanisms that deteriorate skeletal health of patients treated with newer AEDs. The underlying mechanisms explored to date have been mentioned in this review (see Table 1).

Carbonic anhydrase inhibition

Carbonic anhydrase (CA) is a ubiquitous zinc enzyme. One isozyme (CA II; abundant in human cells) catalyzes the reversible hydration of carbon dioxide to give bicarbonate and proton ions. These proton ions provide an acidic environment during the bone resorption phase of the bone cycle and, thus, CA II is implicated in

TABLE 1

Possible pathophysiological mechanisms of next-generation AEDs

	Aromatase inhibition	Carbonic anhydrase inhibition	CYP450 induction	Estrogen depletion	Folate antagonism	Low vitamin D and secondary hyperparathyroidism
LTG	+				+	
LVT				+		
OXC	+		+ (partial)			+
Tiagabine	+					
TPM		+	+			+
ZNS		+				

LTG, lamotrigine; LVT, levetiracetam; OXC, oxcarbazepine; TPM, topiramate; ZNS, zonisamide.

osteoclast differentiation. Although CA II inhibitors have been explored as antiepileptics and antiosteoporotics, the metabolic acidosis caused by CA II inhibitor use has the propensity to effect bone health. The AED TPM is an inhibitor of most of the CA isozymes (except CA III and CA I). Recent clinical evidence indicates that ZNS forms an enzyme–inhibitor complex with cytosolic CA II and mitochondrial CA II (VA and VB) [62,63]. This mechanism has not been reported with conventional AEDs.

CYP450 induction

Even next-generation AEDs are not free from CYP450 induction. TPM is a dose-dependent hepatic CYP3A4 inducer at concentrations ranging 50–500 μM [64]. Resultant activation of its transcriptional regulator, PXR, initiates the cascade of events responsible for bone loss. OXC (a partial CYP450 inducer) induces CYPC1 and CYPC24, following the steps that disrupt the normal bone cycle [65]. OXC therapy has been reported to be associated with low serum vitamin D levels and secondary hyperparathyroidism [66].

Miscellaneous causes

LVT has a neutral response toward CYP450 yet it influences serum estrogen at low doses [67,68]. This may be the rationale behind skeletal disturbances occurring secondarily to low serum estrogen. BMD may not be influenced during LVT treatment but its influence on biomechanical bone strength is alarming [50].

Tiagabine and LTG inhibition of aromatase *in vitro* increase the likelihood that they might affect vitamin D levels in postmenopausal women. OXC has also inhibited aromatase *in vitro* [45], and whether this inhibitory mechanism attributes to bone malformation in the cases of tiagabine and LTG needs further confirmation. It has been reported that LTG changes neither serum nor RBC folate concentrations but inhibits dihydrofolate reductase (an enzyme involved in folic acid synthesis) [69] (http://www.drugs.-com/mmx/lamotrigine.html). Further studies are necessary to establish whether or not LTG has any correlation with circulating Hcy levels.

Few clinical studies have used the term 'bone-friendly' for newer AEDs and the ongoing research has put a question mark over this term. The affect of these next-generation drugs on children and the 'young' epileptic bone is debatable.

Assessment of AED-induced bone abnormalities

Since 1968 researchers and the clinicians have gathered large quantities of data reporting AED interference with the bone resorption process [1], although no official screening or treatment guidelines are available. Therefore, bone strength should be appraised on a routine basis throughout therapy to assess the changes in the bone [14,27]. BMD measurement and the biochemical markers of bone resorption and formation are indicative of AED intervention with organization, texture and mass of bone. These techniques facilitate early prediction of bone dysfunction and the overt fracture risk associated with and without fall.

BMD can be measured using densitometry and the most widely used method is dual-energy X-ray absortiometry (DEXA). DEXA has been recognized as the 'gold standard' because even levels as low as 2–5% bone loss can be detected. The *T*-score obtained is indicative of the bone health status and is based on peak BMD of a healthy 30-year-old adult. Similarly, the *Z*-score is also based on the BMD of a healthy 30-year-old adult. Because the *Z*-score can be misleading at times (especially for older adults), *T*-score is currently the WHO-recognized basis for categorizing the bony status of a patient: *T*-score >-1.0 indicates healthy bone; *T*-score <-1 and >-2.5 signifies the osteopenic state; and *T*-score <-2.5 implies osteoporosis [14].

Table 2 summarizes the known markers of bone turnover. While talking about bone health, the bone mass (mineral content), bone features (micro-architecture, geometry and matrix composition) and bone turnover should be grouped together and evaluated before drawing a conclusion regarding the malformed state.

Reasons for the need of comparison among AEDs in regard to bone health

Research is undertaken with the aim of producing superior and better products than those already in the market. As is the case with new drugs, which are developed with the aim that they are superior to old drugs, especially in the context of any adverse affect profile or pharmacokinetic properties. It is evident that none of the newer AEDs induces or inhibits CYP450 to the extent as the older AEDs. Therefore, it becomes pertinent to explore the bony adverse effect of newer drugs. The mechanisms mentioned in this review could be the first steps in this direction. To illustrate, a study recently demonstrated the biphasic dose response of LEV toward skeletal abnormalities [50]. OXC and LTG have been shown to possess mechanisms that might affect bone (mentioned earlier).

In 2007, during the American Epilepsy Society 61st Annual Meeting, a piece of research was presented that showed that the prevalence of AED-associated bone abnormalities is 46.2% for enzyme inducer AEDs and 34.2% for nonenzyme inducer AEDs

TABLE 2

Markers of bone turnover[a]

Biochemical bone markers	Formation (F) or resorption (R)	Remarks	Assay type	FDA approval
Aminoterminal crosslinking telopeptide of bone collagen (NTX)	R	Collagen-based; a fragment of the protein matrix; osteoclastic activity based	ELISA	+
Bone sialoprotein	R	Noncollagenous bone matrix constituent; found in mineralized tissues; mineralization initiator	Reversed-phase HPLC; RIA	–
Bone-specific alkaline phosphatase (B-ALP)	F	Produced during the bone formation by osteoblasts; indicative of metabolic bone activity	Immunoassay; heat stability; electrophoresis; wheat-germ lecithin precipitation	+
Carboxyterminal crosslinking telopeptide of bone collagen (CTX)	R	Collagen-based; a fragment of the protein matrix; osteoclastic activity based	ELISA; RIA; automated electrochemiluminescent sandwich antibody assay (ECLIA)	–
Free lysyl-pyridinoline (deoxypyridinoline) (DPD)	R	Collagen-based; generated during post-translational processing of lysine and hydroxylysine residues	Reversed-phase HPLC with fluorescence detector; ELISA	–
Hydroxy-proline (Hyp)	R	Collagen-based; not very specific	HPLC; calorimetric	–
Carboxy-terminal telopeptide of type I collagen (ICTP)	R	Derived from degradation of type I collagen molecules of collagen fibers	RIA	–
Osteocalcin (OC) or bone gla-protein (BGP)	F	Secreted by osteoblasts; vitamin K-dependent protein; most abundant of all noncollagenous protein (26%)	Chemiluminescence; radioimmunoassay; ELISA; RIA	–
Procollagen I carboxyterminal propeptide (PICP)	F	Procollagen I extension peptide; produced during the incorporation of type I collagen into bone	ELISA	–
Procollagen I aminioterminal propeptide (PINP)	F	Collagen-based; indicator of osteoblastic activity	ELISA	+
Pyrilinks	R	Composed of pyridinoline and deoxypyridinoline crosslinks; these crosslinks are released from bone undergoing resorption; excreted in urine	ELISA; immunoassay	–
Pyridinoline crosslinks (PYD)	R	Collagen-based; a group of collagen breakdown products that includes DPD	Reversed-phase HPLC with fluorescence detector; enzyme immunoassay	–
Tartrate-resistant acid phosphatase (TRACP)	R	Secreted by osteoclasts; lack of specificity; instable in frozen samples, and the presence of its inhibitors in serum makes it prone to degradation	Electrophoresis; ELISA; with the help of analyzer	–

[a] These markers may be highly variable both within the individual but also between individuals, which may hamper their use in individual analyses.

(http://www.medscape.com/viewprogram/567073). It is more interesting to note that the nonenzyme inducers belonged to next-generation AEDs (with VPA as an exception) and enzyme inducers belonged to classical AEDs (with OXC as an exception). It is possible that these drugs may find links to the pathophysiological mechanisms of bone malformation shown by the older AEDs or take a longer duration to emerge in a quantitative manner.

To date, neurologists emphasize vitamin D and calcium supplementation for prophylaxis and treatment of bone loss [27]. But the question is whether this supplementation is justifiable in terms of efficacy for newer AED-induced bone deterioration. Since the pathway of induction of bone loss by the newer AEDs may or may not have similarity with the conventional AEDs, this supplementation might not prove to be useful. Infact, there are experimental studies demonstrating no alteration in serum calcium following LTG [70], LVT [50] or ZNS [60] administration, although changes in biomechanical bone strength rather than on BMD were observed with LVT [50]. Administration of ZNS has also been reported to decrease BMD significantly [60]. Is it rational to use this supplementation for AEDs that are not affecting serum vitamin D and serum calcium levels? A novel treatment strategy should be put in place and screened in clinical trials.

There is a dearth of data regarding the modification of an antiosteoporotic regime (mainly on bisphosphonates, raloxifene, among others) if, in later years, the patient is diagnosed with epilepsy syndrome. The goals of therapy for treating bone loss will differ between antiepileptic patients and the patients diagnosed with neurologic disorders requiring AED treatment. It is interesting to note that hormone therapy (e.g. SERMs) and bisphosphonates are equally likely to be selected as first-line treatment drugs for osteoporosis [71]. Since 1968, when this overt effect was reported [1], hardly any research has been carried out with the other FDA-approved antiosteoporotic agents. Therefore, it is necessary to carry out further research aimed at discovering novel

antiosteoporotic supplements that can be prescribed alongside AEDs.

To add more, the Standard and New Antiepileptic Drugs Study (SANAD) recommended the first-line usage of next-generation AEDs (e.g. LTG and OXC) for adults and children with focal epilepsy [72]. This further necessitates the comparison of scarcely available postsurveillance data relating to bony adverse effects of the next-generation AEDs. There is a pressing need for the comparison of this adverse affect profile among AEDs.

Concluding remarks

This article raises as many queries as it does answers. Closer monitoring of vulnerable groups is suggested to evade long-term adverse effects. Although such effects are inevitable, the choice of AED and the correct supplementation initiated at the right time can shield the bony skeleton. It has been proposed that research should be carried out beyond the conventional supplementation of vitamin D and calcium for AED-associated bone loss.

Performing extensive research on the pathogenesis of AED-associated bone disease and providing reliable data to evaluate the risk associated with specific AED regimens, and defining the therapeutic strategy for all affected patients, require the utmost attention. By way of an explanation to this is the expanded role of AEDs in other neuropsychiatric disorders.

Finally, several theories have been proposed to explain the link between AEDs and bones but conclusions regarding the degree of effect produced by each AED, pathogenesis and definitive guidelines for evaluation and the optimal therapy have yet to be determined.

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