REVIEW ARTICLE

Navigating Bone Health in Epilepsy—A Detailed Review of Anticonvulsant-induced Osteomalacia: Its Mechanisms and Therapeutic Strategies

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Abstract

Anticonvulsants are the drugs given for managing epilepsy and some other types of neurological disorders; however, their long-term use is increasingly suspected of causing adverse skeletal outcomes, including osteomalacia. Osteomalacia is a condition marked by defective mineralization of bone, leading to bone softening, bone pain, muscle weakness, and predisposition to fractures. The disruption of vitamin D metabolism, impaired calcium absorption, and altered bone turnover are mechanisms attributed to several commonly used anticonvulsants, especially enzyme-inducing agents such as phenytoin, carbamazepine, and phenobarbital, in contributing to osteomalacia. Hence, this review aims to provide detailed information about the pathophysiology, clinical manifestations, diagnosis, and treatment of anticonvulsant-induced osteomalacia. The review places further emphasis on the importance of regular monitoring of bone health in individuals receiving long-term antiepileptic treatment, supplementation, lifestyle interventions, and interprofessional care. A proper understanding of this preventable complication will certainly help healthcare providers to minimize the impact in these patients and improve outcomes.

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Introduction

Epilepsy can be a chronic neurological disorder characterized by seizures that recur unprovoked due to abnormal electrical activity in the brain. It affects an estimated 50 million people worldwide, being among the most commonly encountered neurological disorders. The burden of epilepsy is especially felt in shops where diagnosis and treatment cannot be afforded in low- and middle-income countries. Long-term control of seizures is colloquially achieved by the use of anticonvulsant medicines, which, in fact, are the mainstay of therapy.[1]

The anticonvulsant or antiepileptic drug (AED) class contains a wide array of agents including phenytoin, carbamazepine, valproate, phenobarbital, and the newer types such as levetiracetam and lamotrigine. These medications have truly been a blessing in the lives of people living with epilepsy. Long-term use of a drug can cause numerous side effects, one of them affecting bone metabolism. There is emerging evidence in the literature that with prolonged use, some AEDs may cause vitamin D deficiency, hypocalcemia, and consequently arrested bone mineralization, eventually resulting in metabolic bone diseases such as osteomalacia, as shown in Table 1.[4]

Osteomalacia is an endocrine skeletal disorder in adults in which bones soften because of defective mineralization of osteoid matrix mainly due to vitamin D deficiency with phosphate or calcium metabolism abnormalities. Clinicians find evident bone pain, muscle weakness, and easy fractures in patients. In the setting of anticonvulsant therapy, osteomalacia results from a change in vitamin D metabolism, poor calcium absorption, and impaired bone turnover.

As greater awareness grows around bone health issues with long-term anticonvulsant use, an understanding of the mechanisms of osteomalacia, risk factors for it, and prevention will become more important. This is a review to gather present knowledge on this relevant clinical entity, shedding light on the difficult aspects of diagnosing and managing the disorder. Thereby, enhanced awareness can promote better screening and preventive measures by healthcare providers, hence improving long-term safety under anticonvulsant care.[5,6]

Overview of Anticonvulsant Classes

Anticonvulsant drugs are thought to begin their career in the therapeutic field with the onset of action: first, older, or generation, depending upon the classification system, and then, second and third generation. The traditional anticonvulsants still cannot be superseded from their respective uses, ranging over the seizure types. These are the drugs of phenytoin, phenobarbital, carbamazepine, and valproate (Table 2). Although the drugs have been in clinical use for many decades and are still active in numerous seizure types, they have been recognized for their numerous side effects, including effects on bone metabolism and vitamin D deficiency triggered by enzyme induction. Drug burdens include complex pharmacokinetics and numerous drug interactions requiring careful monitoring.[8]

New generation anticonvulsants, such as levetiracetam, lamotrigine, topiramate, oxcarbazepine, and many others, were developed to improve control of seizures with fewer side effects and best tolerability possible (Table 2). They largely have better pharmacokinetic profiles, less interaction potential with other drugs, and some do not induce or inhibit liver enzymes; thus, they avoid certain side effects like bone disease.[9]

Mechanisms of Seizure Control

Seizures are caused when there occurs an abnormal, excessive synchronous activity of neurons within the brain. Various mechanisms are used by anticonvulsants to overmodulate neuronal excitability:

- *Enhancement of inhibitory neurotransmission:* Many anticonvulsants act by potentiating gamma-aminobutyric acid (GABA) neurotransmission. For instance, drugs such as phenobarbital and benzo-

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Table 1: Risk factors

Risk factor	*Description*
Long-term anticonvulsant use	Long-term use (ranging from months to years) of enzyme-inducing antiepileptic drugs (e.g., phenytoin, carbamazepine, phenobarbital) interferes with vitamin D metabolism
Type of anticonvulsant	Usage of enzyme-inducing AEDs tends to increase vitamin D catabolism, whereas the nonenzyme inducers usually have less detrimental effects on bone
Vitamin D deficiency	Pre-existing low vitamin D levels due to inadequate sunlight exposure, poor diet, or malabsorption syndromes
Poor nutritional status	Deficiency in calcium, phosphate, or protein intake can diminish bone mineralization
Limited sunlight exposure	UV-B radiation deficiency lowers the synthesis capacity of vitamin D in the skin
Age	Those who are very old or very young are at an increased risk of bone disorders because their bone density and vitamin D status are impaired naturally
Gender	Women are vulnerable, especially postmenopausal ones, due to hormonal changes that influence bone metabolism
Coexisting medical conditions	Conditions such as chronic kidney disease, malabsorption syndromes (e.g., celiac disease), or liver disease may worsen vitamin D metabolism and bone health
Reduced mobility	Physical inactivity or immobility lessens mechanical stimulation of bone, therefore promoting bone loss
Concurrent medications	Concurrent use of other drugs disruptive to bone metabolism (i.e., glucocorticoids, heparin) only thickens the plot of risk of vitamin D deficiency[2,3]

Table 2: Commonly prescribed anticonvulsant drugs associated with osteomalacia

Drug name	*Classification*	*Enzyme induction*	*Impact on bone health*
Phenytoin	Hydantoin	Strong inducer of CYP450	Accelerates vitamin D catabolism: vitamin D deficiency, hypocalcemia, secondary hyperparathyroidism, osteomalacia
Carbamazepine	Dibenzazepine derivative	Strong inducer of CYP450	Similar to phenytoin, reduces vitamin D levels: impaired bone mineralization and increased fracture risk
Phenobarbital	Barbiturate	Strong inducer of CYP450	Increases vitamin D metabolism: osteomalacia and bone demineralization
Valproate	Fatty acid derivative	Weak or no enzyme induction	Less commonly linked; may cause bone loss by indirect mechanisms
Lamotrigine	Phenyltriazine derivative	No significant induction	Minimal impact on vitamin D metabolism and bone health
Levetiracetam	Pyrrolidone derivative	No significant induction	Minimal evidence of bone metabolism disruption
Topiramate	Sulfamate	Weak inducer	Potential mild effects on bone; data limited[7]

diazepines augment GABAergic activity that inhibits neuronal firing.

- I*nhibition of excitatory neurotransmission:* Several anticonvulsants diminish the activity of excitatory neurotransmitters, such as glutamate, thus averting the spread of seizures.
- *Modulation of ion channels:* Sodium and calcium ion channels are essential for the generation and propagation of electrical impulses in neurons. Phenytoin, carbamazepine, and lamotrigine block voltage-gated sodium channels, thereby stabilizing neuronal membranes and preventing repetitive firing. Other drugs may block T-type calcium channels, thereby reducing excitability.

By these diverse mechanisms, anticonvulsants restore the excitatory-inhibitory balance in the CNS and control seizures.[10,11]

Hepatic Enzyme Induction vs Noninduction

The liver microsomal cytochrome P450 enzymes CYP3A4 and CYP2C9 remain a principal set of enzymatic mediators which are induced during the use of anticonvulsants.

- With enzyme-induced drugs such as phenytoin, carbamazepine, and phenobarbital, the induction results in a thousand-fold increase in the activity of liver enzymes metabolizing a variety of compounds, including vitamin D, by accelerating the metabolism of vitamin D metabolites, thus diminishing the serum levels of active vitamin D. Decrease in active vitamin D concentration leads to vitamin D deficiency, lowering the calcium absorption in the gut and consequently causing secondary hyperparathyroidism and bone resorption that may result in osteomalacia.[12]
- Nonenzyme-inducing anticonvulsants such as levetiracetam, lamotrigine, and valproate do not alter liver enzyme activity to any extent; hence, they may not interfere with vitamin D metabolism and bone health to a great extent. Long-term treatment is an important consideration for this distinction, especially for those at risk of bone disease.[13]

Overview of Osteomalacia

Osteomalacia is the softening of bone due to improper bone mineralization in adults, usually caused by a deficient amount of calcium, phosphate, or vitamin D in the blood. An important difference between osteoporosis and osteomalacia is that with the former there is a decrease in the intrinsic matrix of the bone while with the latter, the matrix is intact. Osteomalacia can cause pain in the bones, weakness in the muscles, and susceptibility to fracture (Table 3). In children, the condition is called rickets. Osteomalacia can be caused by dietary deficiencies, malabsorption, renal forms of tubular acidosis, or drug-induced forms, mainly arising from the administration of anticonvulsants that interfere with vitamin D metabolism.[15]

Pathophysiology

The major aspect in osteomalacia is the impairment of mineralization of the osteoid (newly formed unmineralized bone matrix) secondary to any deficiency or dysfunction of

Table 3: Clinical features

Clinical feature	*Description*
Bone pain and tenderness	Diffuse dull pain, aching in the lower back, pelvis, hips, and legs; increases with activity
Muscle weakness	Proximal muscle weakness, mainly affecting the pelvic and shoulder girdles, rendering standing or climbing stairs difficult
Skeletal deformities	Bone softening leads to deformities such as bowed legs (genu varum/valgum), pelvic deformities, and spinal curvatures (kyphosis)
Fractures	With minimal trauma, there is an increased risk of insufficiency fracture in looser zones; common sites include ribs, femoral neck, and pubic rami
Neuromuscular symptoms	Hypocalcemic cramps and tetany and paresthesias caused by increased neuromuscular excitability
General symptoms	Fatigue, malaise, and reduced ability to perform daily activities[14]

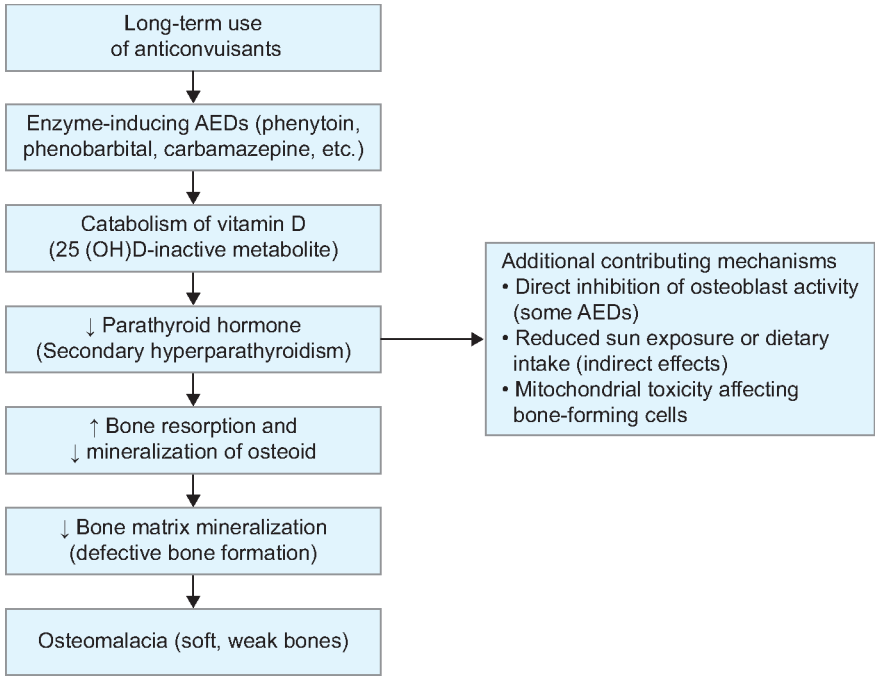

Fig. 1: Pathogenesis of anticonvulsant-induced osteomalacia

vitamins D, calcium, or phosphate. Vitamin D is the central player since it promotes the intestinal absorption of calcium and phosphate and the mineralization of bone. Deficiency states in which calcium absorption is decreased result in hypocalcemia and consequent stimulation of the parathyroid glands to release parathyroid hormone (PTH). PTH in turn causes increased bone resorption as well as phosphate wasting by the kidneys, thereby exacerbating the mineral disorder. Accumulation of unmineralized osteoid with the development of soft and weak bones is characteristic of osteomalacia.[5]

Mechanism of Anticonvulsant-induced Osteomalacia

Osteomalacia is strongly associated with long-term use of enzyme-inducing anticonvulsants such as phenytoin, carbamazepine, and phenobarbital. These drugs induce the hepatic cytochrome P450 enzymes, increasing the hepatic catabolism of vitamin D to inactive metabolites. The lack of active vitamin D reduces intestinal calcium and phosphate absorption, hypocalcemia, secondary hyperparathyroidism, and bone resorption. These changes lead to poorly mineralized bones, which has been called osteomalacia. Another possible direct inhibitory effect by some anticonvulsants may be on osteoblast function. Decreased sun exposure and poor nutrition during chronic therapy further add to the risk of developing bone disease as depicted in Figure 1.[16]

Induction of Hepatic Cytochrome P450 Enzymes

Anticonvulsants such as phenytoin, carbamazepine, phenobarbital, and primidone are the most potent inducers of hepatic cytochrome P450 enzymes and in particular the CYP3A4 isoenzyme. These enzymes are the metabolizers of a large number of substances, including vitamin D. During the induction process, the hydroxylation of vitamin D metabolites into their inactive forms is accelerated. Consequently, there is a marked reduction in the serum levels of 25-hydroxyvitamin D [25(OH)D], the major circulating storage form, and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the active hormone vital for calcium homeostasis. Vitamin D becomes less biologically active in the regulation of calcium and phosphate due to this depletion. This is especially dangerous with chronically sustained anticonvulsant treatment, where the persistent enzyme induction maintains the deficit in vitamin D metabolites, thereby predisposing to subsequent metabolic derangements affecting bone.[17]

Vitamin D Deficiency and Impaired Calcium Absorption

The role of vitamin D is essential in allowing intestinal absorption of calcium, a mineral important for population-level bone mineralization. By increased metabolism, there is a diminution in the level of active vitamin D, which results in the reduced synthesis of calcium-binding proteins in the intestinal epithelium. In consequence, calcium absorption declines from the gastrointestinal tract, giving rise to hypocalcemia or low serum calcium levels. To compensate for this insufficiency, PTH secretion is stimulated, a condition termed secondary hyperparathyroidism. PTH tries to restore serum calcium at the expense of bone integrity by pulling calcium from the skeleton and promoting its reabsorption in the kidney. The process of pulling calcium from the skeleton dries out the porous city bones and, together with the inadequate mineral supply, weakens bones and increases the propensity of patients for osteomalacia.[18]

Secondary Hyperparathyroidism and Bone Resorption

The hypocalcemia induced by chronic vitamin D deficiency leads to secondary hyperparathyroidism, with PTH increase profoundly impacting bone and mineral metabolism. The enhanced osteoclastic bone resorption caused by PTH promotes the

passage of calcium and phosphate into the blood. PTH also induces phosphaturia by impairing phosphate reabsorption at the renal proximal tubules so that plasma phosphate concentrations diminish. These two minerals are crucial in the formation of hydroxyapatite crystals that endow bone with hardness and strength. Therefore, lowering these two minerals in bones impairs the mineralization process of osteoid tissues, the unmineralized organic matrix produced by osteoblasts. Deficient mineralization becomes apparent on histology as osteoid accumulation and clinically as high osteoid and soft bones. The imbalance between excessive resorption of bones and insufficient mineralization contributes directly to the appearance of osteomalacia in cases undergoing long-term anticonvulsant therapy.[19]

Direct Effects on Bone Cells

Conversely, there may be a direct cellular toxicity exerted by anticonvulsants on bone cells, furthering bone deterioration. Osteoblasts, which form new bone tissue, include inhibited proliferation and diminished capacity in differentiation when exposed to certain anticonvulsants. Thus, inhibition decreases the ability to form and to mineralize the new bone matrix. From the other side, osteoclastic activity might increase, setting the scale to the remedy of bone loss. Such direct cellular impacts compound on the mineral deficit induced by modified Vitamin D metabolism. Although the exact molecular details remain to be probed, it is assumed that an anticonvulsant may interfere with intracellular signaling pathways and gene expression in bone cells, thereby enhancing diminished bone formation and accelerated resorption, culminating in softened and fragile bones.[20]

Additional Contributory Factors

Several other unsuspected common factors observed in patients undergoing long-term anticonvulsant therapy may eventually feed into the risk or even igniting a more severe osteomalacic condition. These include a decrease in exposure to sunlight-whether as a direct consequence of a lifestyle restriction or because of medication-induced photosensitivity, which interferes with vitamin D3 synthesis in the skin from UV-B radiation.

Nutritional deficiencies, such as in calcium, phosphate, or protein, inhibit normal bone mineralization directly. Lastly, some other interacting conditions, such as chronic kidney disease or liver disease, impair the hydroxylations necessary for vitamin D activation, adding onto the deficiency.

Other possible synergistic bone-evolving factors include treatments such as glucocorticoids and chemotherapeutics. Conversely, increased immobility or a dysfunctional movement system decreases mechanical loading on the bones required to stimulate bone density and strength. The smiling of these factors with the idiopathic channel of anticonvulsant vitamin D deficiency and secondary hyperparathyroidism puts forth a multidimensional scheme of pathophysiology culminating in osteomalacia.[21]

Epidemiology

Anticonvulsant-induced osteomalacia is a well-recognized decimen that flees recognition in most instances in patients under chronic AED administration. It is estimated from studies that as much as 50–80% of patients on enzyme-inducing anticonvulsants such as phenytoin, carbamazepine, and phenobarbital may show some signs of vitamin D deficiency and/or alterations in bone metabolism. The prevalence of osteomalacia is another story, being 5–40% in different accounts, depending on the population studied, exposure duration, and how it is being assessed.

For instance, it was found in one cohort study that 20–30% of chronic phenytoin users may develop biochemical or radiological evidence of osteomalacia in 1–5 years of treatment with the drug. Besides this, fracture risk has been calculated to be 2–6 times higher among patients receiving long-term AED treatment than in the general population, especially among older adults and postmenopausal women. Other magnitude factors include less vitamin D supplementation, malnutrition, poor atmospheric conditions for adequate sun exposure, among others. These substantially alarming figures have not been able to spur adequate emphasis on awareness and thus, on regular screening, and come diagnosis and treatment of bone disease in epileptic patients face uncalled-for delays.[22]

Diagnosis

Clinical Evaluation

The diagnosis of anticonvulsant-induced osteomalacia begins with a complete clinical evaluation. There is commonly a past medical history of long-term use of anticonvulsants such as phenytoin, carbamazepine, or phenobarbital. Classically, patients present with diffuse bone pain, typically poorly localized, muscle weakness (predominantly in proximal muscles such as the thighs or shoulders), and impaired walking. Bone tenderness, skeletal deformities such as bowing of long bones, and abnormal gait can be elicited on examination. A careful drug history and review of symptoms will allow the clinician to raise suspicion of osteomalacia in such a patient.

Biochemical Investigations

Laboratory testing is crucial in the diagnosis of osteomalacia. Serum calcium is low or low normal because of reduced absorption by the intestine. Serum phosphate is low because of renal phosphate wasting, either caused by secondary hyperparathyroidism or directly by drug effects. ALP, a marker of bone-forming activity, is elevated due to increased osteoblastic activity that attempts to mineralize osteoid. Vitamin D status is determined by measuring levels of 25-hydroxyvitamin D [25(OH)D], which is usually low due to increased breakdown by anticonvulsant medications. PTH is elevated, marking secondary hyperparathyroidism because of hypocalcemia. Urinary phosphate loss would support this diagnosis.[23,24]

Radiological Evaluation

Radiographic imaging plays an essential role in diagnosing osteomalacia. X-ray films could reveal the characteristic features of Looser's zones or pseudofractures, appearing as transverse radiolucent lines at right angles to the cortex, usually located in the ribs, pelvis, or femoral neck. Other findings would be generalized osteopenia and thinning of the cortex. In the early stage of the disease, the X-rays may show nothing abnormal. Bone densitometry shows decreased bone mineral density but does not differentiate osteomalacia from osteoporosis. Bone scintigraphy can be used to detect areas of increased bone turnover and pseudofractures and hence may reveal more sensitive evidence of the disease.

Histological Diagnosis

Histological confirmation through bone biopsy is required for the definite diagnosis of osteomalacia. Transiliac bone biopsies performed with double tetracycline labeling enable direct study and measurement of the mineralization lag time of the osteoid. An increase in the volume and thickness of unmineralized osteoid occurs, with any further mineral deposition being delayed in osteomalacia. Though invasive, bone biopsy is the gold standard distinction between osteomalacia and other metabolic bone diseases, especially when biochemical and radiological findings are inconclusive.[25,26]

Differential Diagnosis

Apart from osteomalacia, many disorders cause bone pains with or without reduced bone density. The most common differential diagnosis is osteoporosis, which differs from osteomalacia in that the bone tissue mineralization remains normal in osteoporosis and generally does not have the biochemical abnormalities seen in osteomalacia. Renal osteodystrophy due

to chronic kidney disease may also present as osteomalacia, but the biochemical profile and clinical context differ. Other conditions such as hypophosphatasia or some inherited metabolic bone disorders should be considered when there are atypical features.

Role of Monitoring in Anticonvulsant Users

Since osteomalacia is a risk, especially in persons on long-term anticonvulsant therapy, these patients grapple with the monitoring of their medical condition. Occasional monitoring of serum levels of calcium, phosphate, alkaline phosphatase, and vitamin D serves well to catch metabolic abnormalities at an early stage before their clinical manifestations arise. This should be accompanied by a clinical assessment for any complaints of bone pain or muscle weakness. Early detection allows treatment to commence, vitamin D and calcium supplementation being the most suitable means to avert the development of more severe forms of osteomalacia and fractures.[27,28]

Evidence from Clinical Studies and Case Reports

An association with osteomalacia has been reported by various clinical studies and case reports in the scenario of long-term administration of enzyme-inducing anticonvulsants. Discussions revolve around the signs and symptoms, diagnostic hallmarks, and the outcome of treated patients.

Case Reports

- *Goraya et al.* reported three adolescent cases were reported with carbamazepine and phenobarbital-induced osteomalacia. They exhibited the clinical features of bone pain, muscle weakness, and fractures. Radiological evidence showed Looser's zones and decreased bone densities. Biochemical tests evidenced osteomalacia with low serum calcium, low serum phosphorus, and raised alkaline phosphatase.[29]
- *Patil et al.* reported a 29-year-old woman on long-term phenytoin therapy developed osteomalacia characterized by bilateral hip pain and restricted movement. Biochemical investigations revealed vitamin D deficiency, secondary hyperparathyroidism, and elevated alkaline phosphatase levels. The patient's condition improved after discontinuation of phenytoin and initiation of vitamin D supplementation.[30]

Clinical Studies

- *Moro-Alvarez et al.*: In the study of 30 epileptic patients on long-term phenytoin therapy, it was seen that the prevalence of osteopenia was very high (56.6%) and osteoporosis was very low (3.3%). The bone mineral density was significantly decreased in the femur, and elevated bone turnover markers pointed to enhanced bone resorption.[31]
- *Cock* studies the review underscored that decreased bone mineral density culminating in osteomalacia and a greater risk of fractures is the long-term consequence of the enzyme-inducing anticonvulsants, namely, phenytoin, phenobarbital, and carbamazepine. Close monitoring of bone health, the review emphasized, should be conducted in patients treated with these medications.[32]

Management and Prevention

Vitamin D and Calcium Supplementation

Deficient vitamin D status is the core of anticonvulsant osteomalacia; thus, supplementation is critical. Usually, patients receive an initial high dose of vitamin D, followed by maintenance doses that are given on a daily basis to replenish and maintain vitamin D levels. Calcium requirements should also be met through diet or supplements so that calcium is readily available for bone mineralization. Serum levels of vitamin D, calcium, phosphate, and alkaline phosphatase should be monitored regularly to assess the response to therapy and promptly detect untoward effects. Such proper supplementation allows for the enhancement of bone health, alleviation of osteomalacic symptoms, and prevention of fractures.[33]

Review and Adjustment of Anticonvulsant Therapy

Enzyme-inducing anticonvulsants promote the degradation of vitamin D and predispose to osteomalacia. When possible, pharmacists and physicians would do well to place their patients on a nonenzyme-inducing anticonvulsant, such as levetiracetam or lamotrigine, instead of an enzyme inducer with osteomalacia risks. Lessening the dose of the enzyme inducer may also reduce some of its effect on bone metabolism. Doses may therefore be reduced with the risk of seizures balanced against the risk to bone health. This ultimately must be done under strict neurological supervision. Therapy should always remain focused on optimizing both neurological and skeletal outcomes.

Bone Health Monitoring

Bone-related health status has to be regularly monitored for patients on long-term anticonvulsants. Dual-energy X-ray absorptiometry (DEXA) scans look into bone mineral density for the early detection of bone loss. Moreover, blood tests for vitamin D, calcium, phosphates and alkaline phosphatases are performed to follow up on the metabolic status. Thus, if detected early, interventions are possible to prevent fractures and progression to more severe osteomalacia. Depending on risk factors, the period between monitoring varies: duration of therapy, age, and so on.[34,35]

Lifestyle Interventions

Lifestyle changes are important with regard to both the prevention and management of osteomalacia. Weight-bearing and resistance exercises help strengthen bones as well as help with balance, which in turn reduces the risk of a fracture. Moderate exposure to the sun helps in increasing the natural production of vitamin D. Patients should avoid smoking and excess alcohol consumption, as both of these adversely affect the health of the bone. This also helps to complement the medical treatment in strengthening the bones and improving the quality of life.

Management of Established Osteomalacia

In cases of established osteomalacia, aggressive vitamin D and calcium therapy is necessary to reverse bone softening. Physical therapy can direct patients to work on muscle strength and coordination in an attempt to reduce bone pain and falls. Analgesics can provide symptomatic treatment. In osteoporotic cases, other drugs may be considered, such as bisphosphonates. Fractures must be treated at the earliest opportunity (Table 4). Close follow-up is

Table 4: Drugs used to manage osteomalacia

Drug/supplement	*Purpose*	*Typical dosage*
Vitamin D3 (cholecalciferol)	Correct vitamin D deficiency	50,000 IU weekly for 6–8 weeks, then 800–2000 IU daily maintenance
Vitamin D2 (ergocalciferol)	Alternative to vitamin D3	Similar dosing to vitamin D3
Calcium carbonate or citrate	Support bone mineralization	1000–1500 mg elemental calcium daily
Bisphosphonates (e.g., alendronate)	Treat coexisting osteoporosis	70 mg once weekly orally
Analgesics (e.g., NSAIDs)[36]	Manage bone pain	As needed

needed to ensure complete recovery and to prevent relapse.[37]

Patient Education and Follow-up

Patient education is a necessity for the proper management and prevention of osteomalacia. Patients should be able to list the possibility of bone disease with anticonvulsants, which can relate to symptoms such as bone pain and muscle weakness, and understand that they should adhere strictly to vitamin D and calcium supplementation. Emphasis should also be placed on follow-up visits for biochemical monitoring and bone density testing. Patient education thus enables them to take part fully in their care, which leads to earlier detection and better outcomes.

Role of Healthcare Professionals

Pharmacists are considered precious antedotes to prevent and manage adverse effects of anticonvulsant-induced osteomalacia. Initially, they inform the patient about the potential adverse bone-related effects of long-term antiepileptic treatment. They counsel patients to maintain adequate dietary calcium and vitamin D, engage in safe mud-washing sun exposure, and encourage physical activity to promote bone health. The pharmacist ensures that if supplementation is prescribed, the patient adheres to it; otherwise, in cases of deficiency, they may advise on OTC supplementation.

Early patient education can reduce the development of osteomalacia, especially in susceptible groups such as the elderly, women, and those on enzyme-inducing anticonvulsants.

In addition to education, pharmaceutical and medicinal monitoring and review by a pharmacist and other medical professionals are very important and should always be maintained. They can identify the need for periodic screening of bone health parameters, including serum calcium, vitamin D, and PTH. Once at-risk patients are identified, they can collaborate with physicians to change or modify treatment, e.g., replacing older enzyme-inducing anticonvulsants (such as phenytoin, phenobarbital) with newer ones that have minimal effects on bone metabolism. Regular review of medications will also allow for the recognition of polypharmacy alongside reducing any unnecessary exposure to drugs known for high osteomalacia potential.[38]

Future Perspectives and Research Directions

Progress in understanding about anticonvulsant-induced osteomalacia has been made; however, there are still gaps in concert with its pathophysiology, early diagnosis, and treatment. Research should be directed to the identification of the exact molecular pathways of a particular antiepileptic drug interfering with bone metabolism, especially in genetically susceptible subjects. Large-scale and long-term observational studies are needed to verify the cumulative effects of older and newer anticonvulsants on bone health in various populations. Detection and validation of early biomarkers of bone demineralization caused by AEDs would increase the efficiency of their screening and, therefore, preventive actions.

Furthermore, it is crucial to develop clinical guidelines to monitor bone health as a routine practice in patients who are on long-term anticonvulsant therapy. Work on the development of personalized medicine techniques, such as pharmacogenomic-based systems that can predict the susceptibility of an individual patient toward osteomalacia, should go hand-in-hand. Another priority toward integration would be to place clinical pharmacists within epilepsy care teams, thus providing comprehensive medication management, supplementation when needed, and patient education–interventions that will lead to a reduction in the incidence of this preventable complication.[39]

Conclusion

Anticonvulsant-induced osteomalacia is a clinically important but frequently overlooked consequence of long-term AED therapy. Enzyme-inducing AEDs such as phenytoin, carbamazepine, and phenobarbital interfere with bone metabolism by speeding up the degradation of active vitamin D metabolites through induction of hepatic cytochrome P450 enzymes. This leads to decreased calcium absorption through the intestine, secondary hyperparathyroidism, and poor bone mineralization culminating in osteomalacia. On the clinical side, this manifestation is manifested by diffuse bone pain, muscle weakness, and fragility toward fractures in patients who have not been supplemented adequately with calcium as well as vitamin D.

Evidence from clinical studies and case reports backs the association of long-term therapy with anticonvulsants and reduction in bone mineral density or osteomalacia. Hence, bone health evaluation is infrequently done as a routine in patients on chronic AED therapy. Preventive measures of early screening, vitamin D and calcium supplementation, and repeated bone mineral density measurements should be strongly advocated, especially in the high-risk groups. If at all possible, the nonenzyme-inducing types of AEDs should be used. Hence, the multidisciplinary team approach of neurologists, clinical pharmacists, and primary care providers is important for early diagnosis, prevention, and optimal treatment of the more awkward anticonvulsant-induced osteomalacia.

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