Chapter 8
Osteoporosis in Stroke and Seizure Disorders

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Osteoporosis is recognized as a frequent consequence following cerebrovascular events. Not only is there an increased incidence of fractures primarily in the hip, but there are complications from fractures that lead to increased morbidity and mortality; increased healthcare costs, pain, and discomfort; and increased burden of care on the family members ultimately responsible for stroke patients. The causes of osteoporosis post stroke include preexisting osteoporosis, immobility, medications, and poor balance, leading to reduced weight-bearing activity and reduced maintenance of current bone density. In terms of falls, decreased strength, balance, proprioception, and cognition all play an important role. This chapter will review unique causes of osteoporosis in the stroke population, illustrate both functional and biological risk factors for falls, and discuss approaches to treatment.

The leading cause of disability, stroke is the most common diagnosis among patients admitted to inpatient rehabilitation hospitals and to subacute nursing facilities that offer rehabilitation [1]. In acute rehabilitation facilities, stroke admissions in the United States annually account for the diagnosis of disability and functional deficits more than any other single diagnosis [2]. Remarkably, osteoporosis has received little attention as a consequence of stroke. Early recognition must be given to consideration of premorbid risk factors for osteoporosis, prior to the first stroke. Additionally, evaluation of ongoing factors following the stroke that might increase the risk of falls and efforts to prevent future falls must be undertaken. Should osteoporosis develop in the first year following stroke, when resorption of bone is aggressive and rapid, treatment must be initiated as soon as possible.

Epidemiology of Osteoporosis After Stroke

While osteoporosis is highly prevalent in the elderly, once a stroke has occurred, it is very important to recognize the presence of any preexisting osteoporosis. A Korean study from 2008 describes baseline BMD and fracture presence in patients

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at the time of diagnosis of a new stroke. Kim et al. [3] evaluated 48 patients within the first 30 days of a stroke, specifically looking at bone density in both the total hip, femoral neck, and lumbar spine. Plain x-rays were also obtained for both thoracic and lumbar spine. Results indicated osteoporosis at the total hip in 37.5 %, 39.8 % at the femoral neck, and 31 % at the lumbar spine. Overall 43.8 % of the 48 subjects had established osteoporosis at the onset of the stroke, while 39.6 % were osteopenic. In addition, 25 % had at least one thoracic or lumbar vertebral body (VB) fracture, and 16.7 % had two or more VB fractures.

Moreover, of the 12 individuals in the study that had established fractures, only four were aware of these fractures. Given anticipated further bone loss and functional deficits following stroke, it is imperative that initial screening for BMD and at least a basic thoracolumbar spine image be performed. As described in earlier chapters, osteoporotic compression fractures of the spine are commonly painless and often go undetected. However, if a patient were to fall following a stroke, this type of fracture could result in additional fractures or angulation of the current fracture and potentially compromise to the spinal cord, leading to devastating consequences. Early screening for osteoporosis is essential in building a safe and effective rehabilitation program for these patients.

A number of prior studies have documented the incidence of osteoporosis post stroke. A large cohort study of 78,461 patients in Germany over six years found an increased risk of osteoporotic fractures among stroke subjects without functional deficits relative to healthy controls [4]. Yet it did not find an increase in osteoporosis for patients with functional deficits, above what a comparable non-stroke reference group of subjects with equivalent functional deficits demonstrated. Relative risk of fractures for the stroke patients remaining with good overall function was higher in the lower extremities than upper extremities. In terms of absolute risk, data clearly demonstrate higher fracture rates in nonfunctional patients due to paresis on the affected side, but the unusual increase seen even among those who regained function warrants closer analysis. The reasons the stroke patients had increased risk of fractures even in the absence of functional deficits are unclear. Stroke patients share a number of common medical conditions also seen in patients with established osteoporosis, including higher than desirable alcohol consumptions, smoking, and suboptimal diet with poor calcium intake [5–7]. Studies have demonstrated a possible association of vascular calcifications and vascular cerebral events leading to ischemia, oxidative stress factors, and chronic inflammation [8].

Additional studies have illustrated a relationship between stroke and bone loss at 6–12 months following the stroke. Liu et al. [9] studied 69 men and 35 women with stroke at baseline with a follow-up at seven months post stroke. Their findings indicate a 15.2 % loss in the total arm, 11.6 % BMD decline in the humerus and 15.6 % in the distal radius, 5 % in the total femur, and 7.4 % in the proximal femur. A more common time for follow-up has been 12 months post stroke. Multiple investigations have demonstrated bone loss in the upper extremities (humerus or distal radius) ranging from 12 to 16 % and in the lower extremities (total leg or femoral neck) from 5 to 12 % [10–14]. Bone loss is typically on the side affected by the stroke and more in the upper than lower extremity [15]. Sato observed not

only a decline in the upper more than lower limb bone density on the hemiplegic limb and a greater decline in the upper extremity BMD than lower but also the presence of a decline over the first year after stroke in the unaffected side [16]. This unexpected decrease in BMD may be the result of reduced weight-bearing following hemiplegia; the relative absence of sunlight exposure if going outdoors is less frequent or nonexistent; limited sun exposure due to placement in short- or long-term nursing facilities if functional deficits are substantial; and changes in diet with less calcium or vitamin D if dysphagia is present or if depression leads to anorexia.

In comparing the Liu study performed at an average of 203 days post stroke to the many other studies with one year follow-up, it is clear that, much like spinal cord injury, bone loss on the hemiparetic side following stroke occurs rapidly following the loss of motor function [15, 16]. The precise pathophysiology of bone loss is a function of five factors: (1) partial or complete paralysis, reduced mobility, and reduction in bone loading, (2) endocrine changes promoting bone loss, (3) nutritional causes, (4) older age, and (5) pharmacologic influences [9, 15].

Paralysis, Reduced Mobility, and Bone Load Reduction

The mechanism of rapid bone loss in the paretic side following stroke is a function of the extent of weakness, the duration of time the limb remains weak, and the time for reinitiation of activity in the affected limb. The sooner and more complete the recovery occurs, the less potent the metabolic forces that resorb bone. Following acute reduction of mobility and weight-bearing, osteoclastic upregulation occurs, leading to bone loss. Whereas in the case of fracture there is compensatory upregulation of osteoblastic activity, in patients with immobility, the unloading of bone leads to a decrement of osteoblastic activity and results in cortical thinning [17]. The early initiation of functional activity post stroke and the intensity of treatment actively mobilizing the affected limb have implications not only for osteoporosis prevention but also for facilitating more complete motor recovery [18, 19]. Also, Liu et al. [9] found the loss of bone in the humerus quantified by DXA correlated with increase in bone turnover markers: urinary pyridinoline and deoxypyridinoline.

Endocrine Changes and Nutrition

Reduced sunlight exposure, poor intake of foods with high percentages of vitamin D, and potential post stroke inhibition of PTH secretion may all contribute to osteoporosis. Hypercalcemia due to bone unloading will block and/or reduce PTH secretion, thereby blocking the renal synthesis of $1,25(OH)_2$ vitamin D3. The prevention of the active form of vitamin D from being formed contributes to post stroke

osteoporosis [15]. Sato [20] in his review of factors contributing to osteoporosis in post stroke patients found significant decrements in vitamin D, especially among inpatients relative to outpatients. An older report by Sato and colleagues [21] found that 64 % of outpatients with long-standing stroke had serum vitamin D25-OH concentrations of below 10 ng/ml, in the range of osteomalacia, and 82 % of patients with long-standing stroke admitted to the hospital for other new medical reasons had deficits in this range. In fact, 17 % and 47 %, respectively, actually had levels below 5 ng/ml. In addition, Sato [20] indicated that many patients who are older have less access to outdoor activities following stroke, and others have levels of vitamin D low enough to cause secondary hyperparathyroidism which will favor additional bone resorption.

Vitamin K is critical to the construction of the bone matrix due to its utilization by G1a protein carboxylation. Increased hip fracture rates are seen in stroke patients with reduced G1a protein levels [15]. Sato [20] also found a correlation between serum vitamin K levels and stroke patients in the first year following the onset of paralysis. Their investigation also demonstrated improvement in BMD after supplementation with vitamin K.

Those with stroke as well as TBI and various forms of paraneoplastic syndromes are susceptible to the syndrome of inappropriate antidiuretic hormone (SIADH), the treatment for which is generally fluid restriction but in some cases also salt tablets orally. In this context, observations by Antonios and colleagues [22] that higher salt intake produces increased hydroxyproline excretion are noteworthy. Hydroxyproline is one of several bone breakdown products. It is conceivable that bone breakdown occurs in the context of a high-sodium diet, through alterations of calcium balance in a mechanism involving sodium–calcium exchange.

The Impact of Spasticity

Whereas in SCI, spasticity has been shown to have either a neutral or positive effect on BMD [23], there is clearly a negative effect on the bone after stroke. In a study of radial BMD in 47 partially ambulatory chronic (> one year) stroke patients ages 50 or older, significant side to side differences in BMD were observed. Spasticity, along with chronic disuse and muscle weakness, had an adverse effect on several parameters of bone quality. Based on the Modified Ashworth Scale (MAS), regression analysis demonstrated that spasticity alone accounted for 23.2 % of the variance in bone mineral content and BMD, determined by quantitative CT between the paretic and non-paretic sides. Spasticity was independent of motor weakness and disuse in individual regression models, although a cumulative effect of all three factors was also found [24].

In a study examining hip BMD one year after stroke, no significant correlation of MAS to BMD at the proximal femur was seen between the affected and unaffected limbs of 58 subjects. There was a trend of increasing spasticity corresponding to lower BMD, but the relationship failed to reach statistical significance, in part due

to the relatively preserved ambulatory status of low spasticity scores. Spastic subjects reported a median score of 1 on the MAS scale which ranges from 0 to 4. In this case, neither the lack of ground reaction force due to impaired active or passive range of motion (ROM) from spasms nor the relative preservation of muscle mass from spasms, sufficient to translate to muscle pulling on the bone in a positive manner, would affect BMD [25]. Another study investigated BMD in the distal tibia and found that BMD in this location was negatively associated with spasticity; the higher the spasticity was, the lower the BMD [26].

Spasticity can be classified in terms of "positive" symptoms and "negative" symptoms, which characterize the activity and potency of the upper motor neuron system activity. These terms do not refer to a beneficial (positive) or detrimental (negative) effect on the patient. Rather, both types of symptoms can cause functional problems in stroke patients with spasticity. Table 1 gives the positive and negative symptoms of spasticity.

Because spasticity can increase falls, decrease ability of the patient to perform transfers, and contribute to osteoporosis by limiting functional activities including ambulation and weight-bearing, treatment should be considered that promotes the above tasks without causing side effects that compromise safety, function, and quality of life. Many pharmacologic agents, including baclofen, benzodiazepines like diazepam and clonazepam, and even alpha-2 agonists such as tizanidine, can cause fatigue, postural instability, unintended weakness, hypotension, confusion, and inattention, all of which may lead to falls [27].

For stroke patients with widespread spasticity in multiple muscles of the upper and lower hemiparetic limbs, system oral medications are appropriate. Baclofen acts on GABA-B receptors but has the adverse effects of moderate hypotension, muscle fatigue, and weakness with increasing activities. It is most suitable for patients with tonic spasticity, characterized by muscle tension that inhibits active and passive range of motion. It can be problematic because a dose high enough to assist with increased tone in one limb may adversely affect the uninvolved limb or a patient's core strength.

Diazepam, a long-acting benzodiazepine, and clonazepam, a benzodiazepine of intermediate duration, are helpful with phasic or episodic spasticity and clonus. Both agents enhance the action of the GABA-A receptor whose action reduces muscle spasms and jerking. These agents often cause sedation, worsen confusion, and may exacerbate depression in patients who already have or are prone to this

Table 1 Positive and negative symptoms of spasticity

Positive symptoms of spasticity	Negative symptoms of spasticity
Exaggerated deep tendon reflexes	Reduced deep tendon reflexes
Rigidity	Flaccidity
Dystonia	Fatigue
Flexor spasms	
Extensor spasms	
Contractures from excessive tone	Contractures from lack of range of motion

condition [28]. They can also increase ataxia leading to potential falls. Because of adverse effects on alertness and mental processing, benzodiazepines are best used at night. Advantages of benzodiazepines include their ability to help promote sleep and generally last the full eight hours of sleep time [29]. Because of the above concerns, slower renal clearance and prolonged half-life of 20–60 hours for clonazepam and 35–100 for diazepam, the use of these medications is particularly problematic in elderly patients [28]. Moreover, regular use of benzodiazepines leads to rebound insomnia [28] and chemical dependency, requiring need for slow taper when discontinued [30].

Tizanidine, a centrally acting alpha-2 adrenergic agonist, has a rapid onset as well as a short half-life of only 2.5 hours, the smallest of all the common oral spasticity agents. Benefits of this agent include its lack of clinical dependency and the absence of abuse potential. However, tizanidine has significant sedative properties, may cause confusions or hallucinations, and even low doses can lead to profound hypotension. Another concern, although uncommon, is elevation of liver enzymes. The doses needed to cause liver damage are generally not tolerable in stroke patients, from the perspective of sedation or blood pressure regulation, so this side effect is rarely observed. Another disadvantage is its contraindication with the use of fluoroquinolone antibiotics, a class of antibacterial agents, often used in hospital settings due to their once or twice a day oral usage and their effectiveness and tolerance.

Finally, dantrolene is a common agent of choice to treat spasticity in stroke patients because it acts peripherally at the level of the calcium channels in muscle spindles and has significantly lower risk of cognitive side effects, but fatigue, muscle weakness, hypotension, and elevated liver enzymes have been reported with daily use. The risk of hepatotoxicity is higher than that seen with other antispasticity agents [27].

Due to the above concerns with oral medications, focal treatment with bracing in conjunction with therapy should be the first approach. Localized injections with botulinum toxin (botox) type A to the muscle or alcohol versus phenol to either the nerve or motor point have the benefit of targeted therapy delivered to the spastic extremity of concern, while avoiding systemic adverse effects that oral antispasticity medications can produce. Injections with alcohol or phenol create neurolysis or soft tissue lysis, thereby blocking transmission of excessive nerve impulses to muscles, but side effects can include painful dysesthesias. One benefit of alcohol or phenol is a longer duration of action, up to six months, and significantly lower cost in comparison to botulinum toxin.

Botulinum toxin (botox) type A causes reversible muscle relaxation when directly injected into the most active region of spastic muscles, best identified under electromyographic (EMG) guidance. While botox A is most commonly used in bicep, elbow, and wrist to facilitate ADLs after stroke, it can also be beneficial from a weight-bearing standpoint in stroke patients with equinovarus of the ankle [27]. If reduction of ankle tone permits weight-bearing and standing, this intervention may significantly affect bone density over time.

Pharmacologic Influences

With the exception of severe hemorrhagic stroke, as part of ongoing stroke prophylaxis from a second event, minimizing future risks of stroke from conditions such as irregular heart rhythms (atrial fibrillation, premature contractions), oral anticoagulants are instituted as soon as practitioners feel the risk of a thrombotic event exceeds the risk of post stroke bleeding. In addition, heparins in subcutaneous form are often given for deep vein thrombosis (DVT) prophylaxis until levels of oral anticoagulants are therapeutic. Heparin inhibits osteoblast differentiation and compromises osteoblast function, resulting in decreased bone formation [31, 32]. In the setting of heparin, osteoprotegerin (OPG) upregulates RANKL that promotes osteoclastic differentiation which, in turn, increases bone resorption. Generally, heparin is used only as a bridge to warfarin following stroke, a duration lasting generally 14–30 days depending on bleeding risk. Most studies demonstrating a relationship of heparin use to bone loss describe longer use in terms of either months or years [33]. In contrast, warfarin is used for long-term protection against future strokes. This medication has been shown to decrease the carboxylation of osteocalcin and compromise the calcium-binding capacity of osteocalcin [31].

Warfarin reduces stores of vitamin K, important in the maintenance of bone density. In 1998, Sato et al. [34] supplemented chronic stroke patients that did not require warfarin with vitamin K and observed an improvement in bone density. With the creation of newer anticoagulants such as apixiban and Xarelto that do not deplete levels of vitamin K, bone density may be affected to a lesser extent in future years as these newer agents gain acceptance in the medical community and with third-party payers. Few controlled studies exist on the newer anticoagulants, although preliminary reports indicate their effects are less harmful on BMD than many traditional anticoagulants.

Nonpharmacologic Treatment

Reduction of Falls

The majority of acute fractures following stroke occur from falling, primarily to the paretic side. Ramnemark et al. [35] found that among 1,139 patients with stroke within the last three years, 154 fractures were seen in 120 patients, with 84 % occurring from falls. Hip fracture was the most common type of fracture observed. Moreover, the majority of the 154 fractures observed (13.5 % of the sample) happened within 24 months, when the onset of osteoporosis on the affected side has had adequate time to develop. Stroke patients have multiple reasons for falls, apart from established osteopenia or osteoporosis:

- Weakness
- Ataxia or motor planning deficits

- Poor vision or visual neglect of one side
- Impaired cognition
- Agitation or impulsivity
- Urinary incontinence
- Forgetting to use or lack of immediate access to wheelchair, walker, or cane
- Forgetting to wear or inability to reach orthotics needed for gait stability

Prevention of falls in relation to prevention of osteoporosis is intimately linked in a number of nonpharmacologic interventions and is accomplished through physical therapy measures, working on strengthening, balance skills, and anticipatory planning of motor activities and those skills of daily living where falls frequently occur, such as during transfers to and from toilet, while getting dressed, and during bathing.

Apart from direct instruction on these skills, the use of mechanical hip protectors has been advocated as a means of minimizing the impact of a fall in high-risk patients. By this same measure, the use of seizure pads on the ground at the bedside and choosing a low bed rather than one of standard height may be helpful if a confused patient awakens and attempts to get out of bed without assistance. Falling out of bed and attempts to walk at night are common in elderly patients or in those with cognitive deficits who may also be impulsive.

The Role of Exercise

Exercise has been recently adopted as an additional intervention to facilitate osteoporosis rehabilitation in patients with stroke, independent of the role of exercise in treating muscle weakness, pain, spasticity, and balance deficits. Exercise serves a role in not only reducing the incidence of falls but also in maintaining bone health. As Eng et al. point out, because the greatest amount of rapid bone loss occurs in the first six months following stroke, early intervention with exercise therapy is essential [36]. Because the number of falls that also result in a bone fracture is relatively small (approximately 10 % of total falls), large samples are needed for high statistical power, ensuring the accurate evaluation of exercise [36] in reducing fractures. In a study that examined 560 stroke patients, the authors found a 64 % reduction in the risk of hip fractures with a power of 80 % p-value 0.05 % for a structured program of exercise. Eng and colleagues found a number of benefits after a 19-week fitness program with mobility exercises. Known as the "FAME" program, skills such as repeated practice of sit to stand transfers, stepping onto risers, brisk walking, and other tests of walking endurance resulted in improved aerobic capacity, muscle strength, stamina, tolerance to activity, and retention of bone mineral density in the hip. The intervention group lost only 0.7 % of bone mineral density in the femoral neck, whereas the control group lost 2.5 %. This stands in contrast to comparably aged adults without stroke who lose only 0.5–0.9 % per year.

Pharmacologic Treatment

Given the anticipated rapid bone loss in the immediate months following stroke, prevention of increased bone turnover and osteoclastic upregulation can be addressed by the use of oral bisphosphonates. Several studies have examined the use of oral bisphosphonates following stroke. Sato et al. [37] studied subjects who received 2.5 mg of daily risedronate for one year versus placebo, with onset of treatment beginning two days after an acute stroke. The 375 Asian women who were examined showed reduced hip fracture risk and improved BMD. A very similar study was performed in Asian males [38]. Of the 280 subjects examined, ten subjects in the placebo group and only two in the risedronate group experienced a fracture in the 18-month assessment time. The BMD at 18 months post stroke after using 2.5 mg daily risedronate versus placebo was 2.5 % higher in the hip of those receiving the drug but 3.5 % decreased in the placebo patients. Despite the limitations of the use of lower than standard doses of risedronate and potential lack of applicability to other ethnic groups, the study showed good promise for subjects able to take oral medications so soon following stroke. Two studies examined the effects of etidronate which is a less potent oral bisphosphonate, but outcomes in both were limited to BMD improvement in the metacarpal region only and used computer x-ray densitometry rather than the more accepted DXA technology as a tool to assess BMD [15].

Oral bisphosphonates have several disadvantages if used following acute stroke. Because a number of the pills that must be swallowed are large, patients with dysphagia or reflux have difficulty. If patients must have medications crushed, once weekly or monthly bisphosphonates, such as alendronate or ibandronate, must be avoided. A daily form of alendronate still exists but has the same lifestyle requirements of sitting upright 30–60 minutes after ingestion and abstaining from food two hours prior to consumption [17].

Intravenous bisphosphonates eliminate the concern for dysphagia as well as compliance. Most are given once or twice annually in a doctor's office so reliability of a patient with cognitive impairments is not a concern. Poole and colleagues [17] examined 27 acute stroke patients within 35 days of the onset of neurological event. Patients received either 4 mg of intravenous zoledronic acid or placebo. On the affected side, the mean BMD in the total hip was changed by 0 % in the group receiving the drug but declined by 5.5 % in the total hip and 8.1 % in the subtrochanteric region in the placebo group. On the unaffected side, those stroke patients who received zoledronic acid improved by 1.0 % but declined by 2.7 % in the placebo group. Interestingly, 72 % of patients in the study experienced a fall in the follow-up time, but no subjects in either group experienced a fracture.

Limited research has been published on outcomes of intravenous bisphosphonates. Careful risk benefit assessment should be done before initiating intravenous bisphosphonates in terms of hydration and renal function, especially in elderly patients [39]. Given the challenges of dysphagia and compliance with oral medications, alternative intravenous or subcutaneous forms of osteoporosis prevention and treatment deserve further study.

Epilepsy and Chronic Seizure Disorders

Patients with neurological conditions inclusive of seizures disorders experience an increased incidence of osteoporosis. Seizures and epilepsy are not synonymous. An epileptic seizure is a transient event caused by abnormal excessive neuronal activity, synchronous in nature. In the United States, epilepsy affects 2.4 million adults (1.8 % of the population aged 18 and older) and 460,000 children (1 % of the population aged 0–17) [40]. It involves multiple recurrent unprovoked seizures, characterized by an ongoing predisposition to generate excessive neuronal activity in the brain, leading to long-term neurobiological, cognitive, psychological, and social consequences [41]. This general definition, developed in 2005 by the International League Against Epilepsy (ILAE) [42], was revised in 2014. To be classified as epileptic, an individual must now meet any one of the following conditions [43, 44]:

1. At least two unprovoked seizures occurring more than 24 hours apart
2. One unprovoked or reflex seizure and a probability of further seizures over the next 10 years, equivalent to the probability of the general recurrence risk (60 %), typically seen after two unprovoked seizures
3. Diagnosis of an epilepsy syndrome: individuals who have had an age-dependent syndrome but are now past the applicable age (generally 16–21 years) or those who have been seizure-free for 10 years and off medications for five years

The new definition effectively classifies epilepsy as a disease rather than a disorder, underlying its serious nature and incorporating the concept of "resolved epilepsy," meaning that although epilepsy may return, the likelihood is small and individuals may consider themselves to be free of the disease.

Individuals who do not meet the pure definition of epilepsy can nonetheless have a seizure condition that contributes to osteoporosis and related metabolic bone diseases such as osteomalacia. Persons with increased intracranial pressure following a large stroke, those with hemorrhagic stroke or other nontraumatic brain dysfunction such as cerebral aneurysms, or those with brain tumors can experience repeated seizures. However, seizures among these groups are most often considered to be provoked and, with few exceptions, do not fall within the accepted definition of epilepsy. Epilepsy in its pure form can begin in childhood, but bone disease may only manifest itself years later. A subsequent chapter of this book will include a section on seizure disorders in that select population and discuss the long-term effects these young adults face.

Epidemiology of Osteoporosis in Seizure Disorders

The development of low BMD and osteoporosis in patients with seizure disorders contributes to the risk of fractures but is only one of many factors leading to fractures in this population. Low BMD in the hip, spine, and other bones in both

hospitalized and ambulatory patients with seizure disorders has been recognized and described in a number of trials. Among patients taking conventional antiepileptic drugs (AEDs) such as carbamazepine (CBZ) and valproate (VPA), Hamed et al. [45] found statistically significant changes in BMD of the lumbar spine and femoral neck among male and female adults with seizure disorders ranging in duration from 6 to 25 years, with more men affected than women. Pack et al. [46] conducted a retrospective cross-sectional study of 141 patients with enzyme-inducing AED use of >3 years. Men and women were analyzed together in this sample given the lack of significant differences in other baseline characteristics. Relative to healthy postmenopausal females under age 50 with presumed osteopenia of 15.3 % and osteoporosis of less than 1 %, those who took AEDs had 40.2 % osteopenia and 10.3 % osteoporosis at the femoral neck, with 32.7 % osteopenia and 13.7 % osteoporosis at the lumbar spine. For patients over age 50, the findings were even more striking. At the femoral neck, 50.9 % of subjects had osteopenia and 22.6 % had osteoporosis, while at the spine, 35.3 % had osteopenia and 25.5 % showed osteoporosis.

Duration of use of AEDs has also been cited as a causal factor for increased loss of BMD [45, 47]. But other trials focusing on valproate illustrate a conflict in outcome data. Whereas Triantafyllou et al. [48] found that valproate monotherapy duration and dosage did not correlate with BMD in patients who had taken the drug for at least two years, a 6-month prospective study by Boluk et al. [47] showed that valproate monotherapy led to significant decreases in BMD. In both trials, patients were from an ambulatory, community-based practice. In addition, ages studied were similar. Because sodium valproate is not among the traditional enzyme-inducing AEDs, it should theoretically be a better option for preserving BMD than some agents, yet multiple investigations have found reduced BMD and increased fracture risk with this nonenzyme-inducing medication.

Epidemiology of Fractures

Sheth [41] has suggested that AED treatment for at least five years places patients age 50 years or older at twice the risk for osteoporotic fractures. Many studies over the last three decades have described increased risks of fracture for those with seizure disorders, but to what extent these medications are the cause of fractures remains controversial. In 2005, Vestergaard [49] conducted one of the most comprehensive evaluations of osteoporosis and fracture risk associated with epilepsy. In his review of 12 studies of BMD, varying markedly in terms of ages studied, exposures to AEDs, and comorbidities, he demonstrated not only a significant decrease in spine as well as hip BMD (based on *Z*-scores of −0.38 and −0.56, respectively) but a heightened fracture risk as well, with the relative risk (RR) of spine fractures at 6.2 and that of hip fractures at 5.3. Most of the investigations examined, both those involving enzyme-inducing AEDs as well as those using nonenzyme AEDs, reported modest reductions in BMD. While the BMD values were lower than those

of age-matched controls, low BMD alone cannot account for the marked elevation in fracture rates. Other factors, both pharmacologic and functional, clearly contributed to increased fall risk which, in turn, increased fracture rates.

A decade after the Vestergaard review, a second meta-analysis [50] reexamined the relationship between use of AEDs and fracture risk, using RR calculations for case-control, cross-sectional, and cohort studies. It encompassed studies that evaluated "any fracture" or isolated hip fractures in adults over age 50; none of the studies chosen considered spine fractures specifically. Relative risk of any osteoporotic fracture for those using AEDs of any subtype was 1.86. The RR of persons using enzyme-inducing AEDs was 1.6, while the RR for those on nonenzyme-inducing AEDs was 1.27; those using AEDs of any subtype demonstrated an RR of 1.9 for isolated hip fractures. The strong association between AEDs and loss of BMD cannot be disputed, and there are further indications that some AEDs may entail greater risks than others.

Pathophysiology

Metabolic and Pharmacological Mechanisms of Altered Bone Biology

Decreased bone mineralization is not a direct outcome of seizures. Rather, it is multifactorial and often occurs as a result of decreased vitamin D levels attributed to the use of antiepileptic drugs (AEDs). The more potent enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin) contribute to increased fracture risk more than do weak enzyme-inducing AEDs (oxcarbazepine and topiramate) or nonenzyme-inducing AEDs (gabapentin, levetiracetam, lamotrigine) [51, 52]. See Table 2 [53, 54].

Vitamin D is essential for calcium absorption and strong bones, and vitamin D deficiency is considered to be another cause of bone loss. Such AEDs as carbamazepine, phenobarbital (PB), and phenytoin (PHT) increase the metabolic rate of the liver, causing a reduction in vitamin D. They act by inducing the P450 enzyme system, precipitating increased hepatic hydroxylation of vitamin D to polar inactive metabolites, and reducing bioavailable vitamin D [55]. The result is secondary hyperparathyroidism, which, in turn, increases bone turnover and lowers bone density, both of which are key factors in the development of osteoporosis. Moreover, interference with vitamin D metabolism leads to osteomalacia, or the abnormal mineralization of bone, which is distinctly different from osteoporosis [56]. Both osteomalacia and osteoporosis are associated with fractures.

At the same time, recent cross-sectional studies of patients taking enzyme-inducing AEDs have found reduction in bone density even in the absence of vitamin D deficiency [57–59]. This finding is consistent with the results reported in the meta-analyses of Vestergaard and of Sheth et al. [49, 57].

Table 2 Fracture risk of common seizure medications

Drug	Liver-inducing AED Nicholas et al. [53]	Effect on fracture risk Jette et al. [54]	Population studied Jette et al. [54]
Carbamazepine	Y	1.81 (1.46–2.23)	Odds ratios and 95 % confidence intervals were calculated for association between current AED use and fractures. Model was adjusted for sociodemographic variables + homecare use + comorbidities and all AEDs simultaneously
Clonazepam	N	1.24 (1.05–1.47)	
Levetiracetam	N	N/A	
Gabapentin	N	1.49 (1.10–2.02)	
Phenobarbital	Y	1.60 (1.16–2.19)	
Phenytoin	Y	1.91 (1.58–2.30)	
Valproate sodium	N	1.10 (0.70–1.72)	

Sources: Adapted from Nicholas et al. [53] and Jette et al. [54]

Alternative mechanisms of bone loss due to use of AEDs also exist, including indirect metabolic effects on other vitamins or calcium. Studies evaluating agents and their actions [41, 60] found that long-term therapy with phenytoin and carbamazepine may lead to low BMD through a direct adverse effect on human osteoblast-like cells. Impaired calcium absorption can occur through either inadequate oral consumption of calcium-rich foods or by a scenario in which there is sufficient calcium intake but the presence of a superimposed wasting syndrome from medications such as proton pump inhibitors. These agents block acid production in the stomach, creating a chemical environment that is not conducive to absorption of calcium in the gut. Kruse and Kracht [61] propose that inhibition of calcitonin secretion may also contribute to bone loss, possibly as a result of the release of dopamine from nerve tracts in the hypothalamus.

Radiographic evidence of osteoporosis illustrates the association with long-term sodium valproate, phenytoin carbamazepine, and phenobarbital treatments [41]. However, although radiographs may demonstrate an end result of osteoporosis, they do not establish a direct cause and effect relationship. For example, among the AEDs noted above, sodium valproate does not induce the hepatic drug metabolizing enzymes of the P450 system, implying that other mechanisms are also involved and relevant for osteoporosis.

A number of common metabolic causes of osteoporosis in patients with chronic seizure disorders are outlined below [62]:

- The use of enzyme-inducing AEDs causing accelerated hepatic vitamin D metabolism
- Lowered calcitonin levels due to use of AEDs
- Inhibition of calcium absorption by other medications
- Poor intake of calcium from diet
- Poor absorption of calcium due to simultaneous use of H+ inhibitors or H2 blockers
- Poor intake of vitamin D from diet

- Altered vitamin K metabolism from medications
- Reduced IGF-binding protein 1 or 3 from hormonal changes
- Reduced sunlight levels due institutionalization
- Reduced levels of estrogen, testosterone, or sex hormone-binding globulin from endocrine changes

In terms of diagnosing osteoporosis in epilepsy, BMD assessment with dual photon x-ray absorptiometry (DXA) remains the gold standard. However, markers of bone remodeling have emerged as valuable tools to assess the rate of bone formation and resorption and to help clinicians intervene in a timely manner to predict fracture risk and ideally prevent fractures. As described in earlier chapters of this book, the ligand of receptor activator of nuclear factor kappa (RANKL) is elevated in settings of heightened osteoclastic activity. RANKL stimulates RANK located on the surface of osteoclasts to further their promotion and differentiation. Osteoprotegerin (OPG) is a decoy protein for RANK such that RANK accepts OPG's binding, rather than that of RANKL. In the latter scenario, osteoclastic activation does not occur because RANKL could not bind to RANK to form the unit required to stimulate action of bone resorbing cells [63].

In the Hamed et al. study [45], significant differences were observed between patients with epilepsy or ongoing seizure disorders and control subjects: markers of bone formation (OPG) and nutrients that work to promote bone formation (serum calcium and serum vitamin D25-OH) were lower in patients with seizure disorders, whereas markers involved in bone resorption including RANKL and RANKL/OPG ratios were elevated Moreover, findings showed no relation between DXA scores and the type of AED used but did show an association between BMD and serum vitamin D25-OH levels, OPG levels, RANKL levels, duration of AED use (of any type), and total duration of illness. Relative to controls, patients with seizures had significantly lower BMD at the femoral neck and in lumbar spine between L2-4.

Nonpharmacologic Causes of Osteoporosis and Fractures

Aside from pharmacologic agents, patients with a recent or long-term history of seizures may be at risk for osteoporosis. Disuse resulting from mobility limitations and decreased weight-bearing through long bones can lead to decreased bone mineralization. Poor nutrition may also be contributory to overall BMD. Lower socioeconomic status may be related to nutrition and has been linked to more emergency room visits, poor adherence to medications, and the use of less expensive medications rather than the agent prescribed for optimal seizure control [64]. Moreover, those with compromised funding may be forced to take generic equivalents of seizure medications, which are among the few classes of pharmaceuticals in which prescription brand and generic options differ substantially in quality and effectiveness. Because medications ultimately issued may be less effective at preventing

seizures and because even appropriate agents may be taken inconsistently, seizures are less well controlled and patients may have breakthrough symptoms, leading to falls. Sudden losses of balance often result in unexpected falls, which may be severe enough to cause fractures, pain, or additional injury due to the osteoporotic fragility of bones.

In patients with epilepsy or other conditions leading to frequent seizures, factors associated with duration of muscle disuse and reduced weight-bearing activity become relevant. Patients with seizures have elevated risks of fractures due to forceful muscle contractions on the skeleton during convulsions. In this scenario, sudden increased loading of the spine or an extremity can trigger joint dislocation, particularly if the onset of seizure is sudden. The dislocation would cause balance loss and falls. A second reason for fracture is the general lack of awareness during the immediate seizure or postictal state, characterized by decreased responsiveness, delayed reaction times, and confusion. During this time, ambulatory patients may experience a loss of balance and increased fatigue. Finally, falls in chronic seizure patients can occur if repeated parenchymal damage and chemical alterations occur from accumulating seizure events.

Pharmacologic Treatment

Bisphosphonates

Only a limited number of investigations have explored osteoporosis drug treatment to prevent further bone loss in patients using long-term antiepileptic agents. Lazzari et al. [65] looked at the effect of risedronate versus placebo treatment in 80 male veterans who had taken one of several AEDs—carbamazepine, phenytoin, phenobarbital, or sodium valproate—for a minimum of two years. Imaging with DXA was performed at 1- and 2-year follow-up times for both groups, who simultaneously received calcium and vitamin D supplementation. At year one, a significant increase in BMD by 3.5 % was evident in the risedronate subjects compared with a nonsignificant decrease in bilateral proximal femoral BMD in placebo subjects. For the spine, again there was a significant BMD increase of 5.2 % in the risedronate subjects with no effective change in the placebo group. Findings were similar for outcomes at year two, except by this time, the total body BMD in placebo subjects demonstrated a significant decline.

At the end of the study, significant improvement in BMD at any of the evaluated sites was evident in the placebo group, a finding that may be attributable to calcium and vitamin D supplementation. However, the percentages of bone gain were far better in the risedronate group with a significant increase in BMD observed in 70 % of these patients, particularly at L1–4, where the increase significantly exceeded that of the placebo group. Moreover, the risedronate subjects had no occurrence of fracture, as opposed to five fractures in the placebo group.

Calcium and Vitamin D

Trials involving treatment with vitamin D and calcium in the absence of other medications directed at bone loss (bisphosphonates, denosumab, SERMs, or other agents) have produced mixed results. In the Lazzarri et al. study, 65 % of the placebo group had significant improvement in BMD at one site or another in the setting of supplemental vitamin D and calcium [65]. Other studies have found a similar positive correlation [66]. Yet in a large trial involving 3,303 veterans with prolonged seizure disorders, Espinosa and colleagues [67] found that supplementation failed to affect fracture prevalence. Meier and Kraenzlin advise that patients on enzyme-inducing AEDs receive 2,000–4,000 international units (IU) supplemental vitamin D daily and those taking nonenzyme-inducing AEDs take 1,000–2,000 IU daily [55]. For the individual patient, there may be a benefit and rarely is there a disadvantage to such supplementation [68]. Drezner further advises that at the time patients are started on any AED, they simultaneously begin supplemental vitamin D, with doses starting as high as 2,000 IU in patients who are on multiple AEDs, institutionalized, or have limited outdoor activity. In patients with established osteoporosis by BMD, doses may need to be as high as 4,000 IU daily [69].

In all cases, serum calcium and PTH levels should be followed to monitor for secondary hyperparathyroidism. Supplemental calcium should not be given without careful monitoring of serum electrolytes (calcium and phosphorous), vitamin D25-OH levels, and PTH. If the vitamin D deficiency and bone biopsy suggest osteomalacia, doses of supplemental vitamin D may need to be between 5,000 and 15,000 IU daily for 3–4 weeks, during which time calcium and phosphorous levels must be closely followed. It often takes more than a month for serum levels to normalize and all such patients should be monitored by an endocrinologist or rheumatologist with specialized training in this area [68].

Nonpharmacologic Treatment

Any patient who has been on long-standing AEDs for clinical management should undergo basic screening for osteoporosis including serum vitamin D25-OH level, calcium, and PTH. If significantly abnormal serum levels in any of the above measures are identified, ongoing outpatient care with a bone specialist at the time of discharge from acute care or inpatient rehabilitation should be initiated. Patients who meet clinical definitions of epilepsy or who have neurological conditions such as hemorrhagic stroke or brain tumors with edema, leading to ongoing risk for seizures, may require AEDs chronically. Consequently, an intervention plan should be created taking into account the ongoing presence of medications that will further compromise osteoporosis. Coordinating this plan with the patient's neurologist is also strongly advised.

Dedicated training of balance and gait stability are potential avenues of optimization in the effort to decrease falls. Reinforcement of skills learned in inpatient

rehabilitation or at a skilled nursing facility can be carried out short term with a home therapist in the weeks following a patient's transition home. However, this form of individualized therapy is limited, and after 30–60 days, patients are left with a home exercise regimen. Ongoing balance and endurance activities must be emphasized and, if possible, supervised by family or caregivers to ensure these skills are maintained. Loss of function in terms of balance and strength due to lack of practice and failure to repeat safe transfers and proper gait technique translates to an increased fall risk to these patients.

Surgical techniques to control seizures are rapidly advancing in the effort to provide better disease control and reduce the need for medications that may be intermittently rather than consistently effective, cause undesirable side effects, and burden families and patients with high cost. Nowell and colleagues describe several new approaches to improving traditional surgery outcomes [70]. Surgical outcomes for seizure control have been limited by suboptimal imaging for planning procedures. Better imaging of the epileptogenic zone will enable surgeons to more completely ablate an area of seizure focus. A better contoured brain map of seizure probability can help advise surgeons of the risk benefit ratio in attempting to ablate areas closer to essential brain function. A newer imaging modality in the form of 3D magnetic resonance technology may assist clinicians to identify unique differences from patient to patient which may not be as visible in two-dimensional films.

As an alternative to conventional brain surgery for neuroablation of seizures, two types of electrical stimulation, vagus nerve stimulation and deep brain stimulation, have been initiated in both the United States and Canada. These procedures are considered in patients that have seizures in a site of non-resectable brain tissue and for patients in whom conventional antiseizure medications fail to control symptoms or cause such severe side effects that the medications are intolerable [71]. While the procedures are costly and not without risk, they may be beneficial for seizure reduction and quality of life. If deep brain stimulation or vagal nerve stimulation permits the discontinuation of seizure medications that damage the bone, a benefit of improved BMD and reduced fracture risk may be seen over time.

Future Directions

Ultimately, the challenge of metabolic bone disease in patients with seizure disorders including traditional epilepsy will depend on the duration of treatment, agents chosen, and commitment of the whole treatment team to include continued bone health as a focus of the long-term care plan. Too often, patients and practitioners are overwhelmed with management of immediate medical concerns, and in the case of seizure patients, funds and resources are directed largely at pharmacologic treatment and testing for the seizure condition itself. Medications for seizures are enormously expensive with potentially significant out-of-pocket costs. Funds for other potentially expensive medications to maintain bone health and testing to diagnose early osteoporosis, including laboratory studies and DXA imaging, are limited or

nonexistent. Moreover, initiating discussions about a future health problem may not be well received or even recalled during a time when other medical issues are more pressing. Adopting bone health as a strategy of prevention when patients are first put on AEDs, initiating prevention doses of vitamin D at that time, and optimizing their physical functioning and mobility from the onset of diagnosis may be the best approach to preserving bone health in patients with epilepsy and related seizure disorders.

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