Falls, Fractures, and Osteoporosis After Stroke
Time to Think About Protection?

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Background—Osteoporosis is a significant complication of stroke. The clinical course of hemiplegic stroke predisposes patients to disturbed bone physiology. Sudden immobility and unilateral loss of function unload the skeleton at key areas such as the affected hip. This is manifest by an early reduction in bone density at this site. Stroke patients may also have motor, sensory, and visual/perceptual deficits that predispose them to falls. These factors result in an early but sustained increase in hip fractures after stroke.

Summary of Comment—Potential bone loss is often overlooked in stroke treatment. Morbidity and mortality from hip fractures might be reduced by preventing bone loss at an early stage. In the crucial first year after stroke, bone loss seems to be due to accelerated resorption. Bisphosphonates are the drugs of choice in preventing osteoclastic bone resorption, but oral administration soon after stroke may be impractical. Potent new intravenous bisphosphonates have been used in postmenopausal women with osteoporosis with good preliminary results. Effective dosing regimens for osteoporosis have included a single annual or semiannual injection of bisphosphate as well as weekly oral dosing. This article reviews the current literature on osteoporosis and hip fractures after stroke, making a case for a trial of intravenous bisphosphonates early after stroke.

Conclusions—Hip fracture after stroke is an increasingly recognized problem. Measures to prevent bone loss and preserve bone architecture have not been part of stroke management thus far. Because rapid bone loss is a risk factor for fracture, we believe that a randomized, placebo-controlled trial of intravenous bisphosphonates given in the early phase of stroke rehabilitation is indicated. (Stroke. 2002;33:1432-1436.)

Key Words: disphosphonates ▪ immobilization ▪ osteoporosis ▪ stroke

Stroke is a major cause of disability and death.1 Figures from the United Kingdom show that the estimated number of new strokes each year is close to 100 000, with a steep rise with age.2 Additionally, an estimated 60 000 fractures of the hip occur annually in the United Kingdom, also rising steeply with age.3 Patients who survive an acute stroke face numerous early and late complications; of these, hip fracture is perhaps the most serious and disabling. Up to 30% of patients with a fractured neck of femur die within a year of the acute event,4 but survivors face pain, disability, and loss of independence.

Recognition of hip fracture as a consequence of hemiplegia began in the 1950s5 and 1960s6–8 with authors reporting a propensity for fracture on the affected side. Peszczynski5 reported that 23 of 150 hip fracture patients undergoing rehabilitation had a previous stroke. Since then there have been several incidence and prevalence studies.9–14 Mulley and Espley9 (1979) found 57 patients (3.9%) with evidence of previous stroke in a group of 1456 patients with hip fractures admitted to the hospital over 4 years. McClure and Goldsborough11 (1986) found 10 patients (20%) with postmortem evidence of stroke in a group of 50 patients who died with a fractured femoral neck. Chiu et al12 (1992) also performed an analysis of 1430 patients admitted with hip fracture, finding 146 (10.2%) with a history of previous stroke and 82% fracturing the hemiplegic side.

Data from Sweden on fracture incidence have been published. Ramnemark et al13 reported 154 fractures (13.5% [all sites]) in a group of 1139 patients admitted consecutively with acute stroke, followed for a median of 2.9 years; 84% of fractures were caused by falls, and hip fracture was the most common. Hip fracture was 2 to 4 times more likely than in an age-matched reference population. Median time until onset of first fracture was 24 months. Subsequently, Ramnemark and colleagues14 examined outcomes in patients with hip fracture and previous stroke. Results showed that survival and recovery of independent mobility after hip fracture were significantly reduced compared with those who had not had previous stroke.
More recently, Kanis et al\(^\text{15}\) reported a >4-fold increased risk of having a hip fracture in the immediate poststroke period compared with the general Swedish population. There was also a substantial increase in risk of hip fracture during the first year in all ages and in both sexes. The analysis was based on a coded database of all Swedish hospital admissions over 10 years and included all strokes, not necessarily hemiplegic individuals. Nine percent of patients had a fracture after hospital admission with stroke, and 5.2% had a hip fracture (mean follow-up, 2.54 years). Although risk decreased in subsequent years after stroke, it still remained higher than the age-matched population risk.\(^\text{15}\) Finally, in their recent publication, Dennis et al\(^\text{15,16}\) showed an increased rate of hip fracture after stroke in Scotland, although lower in magnitude than the Swedish rates. In a prospective cohort study (2696 stroke patients), the rate of hip fracture was 1.4 times the rate observed in the general population. An analysis of routine discharge data showed a rate of hip fracture 1.7 times the rate in the general population.

**Mechanisms of Fracture After Stroke**

Most fractures after stroke are on the paretic side and are caused by accidental falls.\(^\text{13,16,17}\) Forster and Young\(^\text{17}\) followed 108 patients after stroke with mild to moderate disability and found that 73% had fallen in the 6 months after discharge. Nevitt et al\(^\text{16}\) investigated mechanisms of osteoporotic fracture in older people (>65 years), with 66% of those who sustained a hip fracture falling sideways onto the hip. Stroke patients fall to the side of the paresis,\(^\text{12}\) and the work of Nevitt et al helps us to understand why such “hemiplegia-side” falls commonly result in fracture. In these patients, the 2 major factors that determined whether a fracture occurred after a fall were bone density at the hip and the ability of the ilipsilateral arm to outstretch and cushion the fall. Triceps weakness was an independent risk factor for hip fracture, and in hemiplegic patients it is easy to see why this protective response is lost. Lower limb dysfunction and visual impairment are common after stroke and are important independent risk factors for hip fractures.\(^\text{18}\)

Bone density changes after stroke are reviewed below. In the analysis of Nevitt et al,\(^\text{16}\) there was a 7-fold increase in risk of hip fracture after a fall for a 2 SD decrease in femoral neck bone density. On the basis of our existing knowledge of the risk of falls after stroke (and their outcome), there is a case to be made for the use of mechanical hip protectors in at-risk individuals, a subject that is reviewed below.

**Bone Density Before and After Stroke**

Stroke can occur at any age but particularly affects the elderly, with half of all strokes occurring in people aged >70 years.\(^\text{2}\) Therefore, the population at most risk of stroke is already at risk of osteoporosis and fracture.\(^\text{19}\) Jorgensen et al\(^\text{19}\) have reported the earliest hip bone mineral density (BMD) measurements taken after stroke but before immobilization and hemiplegia have had their profound effects. In their series, female stroke patients had 8% lower BMD than controls when measured soon after the event.

Several studies have reported BMD reduction on the affected side after hemiplegic stroke.\(^\text{20–26}\) BMD is a major determinant of fracture risk.\(^\text{1}\) The relationship of BMD measurements to fracture risk is analogous to that between blood pressure and stroke and is equally strong.\(^\text{27}\) In normal adults, peak bone mass is achieved at approximately age 30 years. Bone density in adults has been estimated to remain constant or to fall at up to 0.5% per year until the menopause.\(^\text{28,29}\) After menopause, bone loss rises to 0.5% to 1.5% per year depending on years since menopause, site of measurement, and measurement technique.\(^\text{29}\)

In the year after an acute stroke, bone loss from the paretic lower femoral neck has been reported as up to 14%.\(^\text{23}\) In another series, at 11.3 weeks (mean) after stroke, there was a 4.6% (mean) reduction in BMD of the paretic hip compared with the unaffected side.\(^\text{24}\) Bone may also be lost from the unaffected side, and the loss is reported to be intermediate between the hemiplegic side and controls.\(^\text{26}\)

Determinants of BMD loss after stroke are numerous. Duration of immobility,\(^\text{21,25}\) severity of hemiplegia,\(^\text{26}\) and time since menopause in women\(^\text{25}\) may be factors. The nature of stroke is of a sudden neurological deficit, followed by varying degrees of recovery and weight-bearing and walking function. Jorgensen and colleagues\(^\text{22}\) have shown that BMD loss at the hip is highest in those who do not bear weight early or relearn to walk within the first 2 months after stroke. Furthermore, their research suggests that the amount of weight borne on the paretic leg is a determinant of bone loss.\(^\text{23}\)

**Bone Physiology After Stroke**

Central to our understanding of hemiplegia-induced bone loss is the pathophysiology of immobility/disuse bone loss. Such mechanisms of bone loss are not well elucidated.\(^\text{30}\)

Several authors have suggested that bone resorption occurs rapidly after stroke, with a later and slower loss of bone in subsequent years.\(^\text{22,31–34}\) “Regional” osteoporosis of a limb occurs rapidly after it is immobilized. More widespread skeletal osteoporosis can occur with prolonged immobilization, but after a stroke the paretic side is markedly affected.

The calcitropic response of the bone structure to hemiplegia has been investigated by Sato,\(^\text{32}\) but research into hemiplegia-induced bone loss at a cellular level is limited. Much more data exist for other “unloading” states, including “bed-rest” immobility and spinal cord injury. After stroke, bed-rest immobility with generalized skeletal unloading occurs initially, but this may be coupled with profound local unloading of affected limbs due to neurological injury. Research into bed-rest volunteers indicates that an early (within 7 days) increase in osteoclast-mediated bone resorption and subsequent decreased osteoblast-mediated bone formation occurs.\(^\text{35–37}\)

The effect of localized limb paralysis is much harder to quantify. Resorptive hypercalcemia from an increase in bone resorption seems to occur in spinal cord injury (paraplegia)\(^\text{38,39}\) and may be implicated in early bone loss after stroke (hemiplegia).\(^\text{31,32,34,40}\) Histological studies on iliac crest bone from paraplegic patients suggest an early increase in osteoclastic resorption surfaces and early depression of osteoblas-
tic bone formation with cortical thinning. After spinal cord injury, a new steady state may develop, with reduced bone turnover. Later in the course of stroke, factors such as the degree of functional recovery, duration of hemiplegia, reduced vitamin D, and anticoagulation with warfarin may contribute to ongoing bone loss. The most appropriate target for preventive therapy is the profound increase in bone turnover and osteoclastic bone resorption that occurs soon after the stroke. Bisphosphonates are appropriate drugs for this purpose because they selectively target osteoclasts and their precursors.

**Oral Bisphosphonates After Stroke**

Bisphosphonates inhibit osteoclast-mediated bone resorption. Indirect evidence for the application of oral bisphosphonates after stroke comes from their effectiveness in paraplegia, where bone resorption is increased. Studies have also shown that bisphosphonates are an effective countermeasure (even better than exercise) in preventing loss of BMD at the femoral neck during simple bed rest. Two studies have been published reporting a beneficial effect of etidronate, an oral bisphosphonate, on bone loss when administered after acute stroke. In a double-blind, randomized, placebo-controlled trial involving 98 patients, the BMD loss on the affected side (finger measurements only) was reduced to a mean reduction of 2.3% at 1 year, with year-long treatment, compared with 4.8% loss in the placebo group. In the study of Ikai et al., an interim report at 3 months suggests that the patients with a low activities of daily living (ADL) score had significantly more bone loss on the hemiplegic side (femoral neck) than those in a high-ADL group. Administration of etidronate was not randomized, nor was there a placebo arm to this study. However, an age-matched control group was followed, and at 3 months, the loss of BMD was reduced in the low-ADL group on etidronate compared with the control low-ADL group. Unfortunately, no trial has been sufficiently powered to have fracture rates as an outcome measure.

Oral bisphosphonates have many disadvantages compared with intravenous preparations after stroke. Early administration of an effective compound to prevent bone resorption is needed after stroke because bone resorption would occur at an early point. Dysphagia or drowsiness after acute stroke may mean that those at most risk cannot receive therapy. Additionally, oral drugs such as etidronate are poorly absorbed from the gastrointestinal tract, and patients must avoid food for at least 2 hours before and after swallowing. For the other oral bisphosphonates commonly used in osteoporosis, patients must remain upright, standing, or sitting for 30 minutes before and after swallowing. Such drugs may be hazardous to esophageal mucosa (even when administered via the nasogastric route) and are therefore not recommended in the presence of swallowing difficulties or an inability to sit or stand up straight. These factors make it difficult to generally recommend oral bisphosphonates after stroke.

**Intravenous Bisphosphonates After Stroke**

Is there a role for intravenous bisphosphonates in the prevention of bone loss after stroke? Intravenous bisphosphonates are used with great effect as inhibitors of bone resorption, eg, in Paget’s disease of bone, metastatic and osteolytic bone disease, and tumor-induced hypercalcemia. The hallmark of such diseases is an increase in osteoclast activity. No published work exists for stroke, but after spinal cord injury, intermittent intravenous pamidronate attenuates bone loss.

New third-generation bisphosphonates are being tested in postmenopausal osteoporosis. Zoledronic acid is the most potent intravenous bisphosphonate tested thus far. Administration times for the third-generation bisphosphonates are reduced so that the drugs can now be given over minutes rather than hours. In a small study, the use of a single annual injection of bisphosphonate in postmenopausal osteoporosis was associated with an effect on bone density similar to that achieved by 1 year of oral bisphosphonates. The trial was not powerful enough to show differences in fracture incidence but was a randomized, placebo-controlled trial of intravenous bisphosphonate administered at intervals of 3 months, 6 months, or once annually in 351 women.

It seems plausible that a role exists for intravenous bisphosphonates in the early prevention of bone resorption after stroke. There are favorable efficacy, safety, and tolerability data from the use of such drugs in tumor-induced hypercalcemia. Although the third-generation intravenous bisphosphonates have at least 1 clear advantage over pamidronate in their ease of administration, there is currently more experience with pamidronate, especially in anticancer therapy and Paget’s disease. The main reason why bisphosphonates might not work in this situation would be if the mechanical loading experienced by the stroke patient during a fall was higher than expected from similar falls in other elderly subjects because of more impaired protective reflexes. If all falling stroke patients experienced mechanical overloading that was considerably over the threshold for a fracture, even an effective bisphosphonate might not strengthen the femur sufficiently to prevent a significant proportion of fractures.

**Other Potential Interventions**

**Mechanical Hip Protectors**

Mechanical hip protectors are recommended in elderly patients who are at high risk for hip fracture (eg, falls, impaired balance, or mobility). The most recent Cochrane review of trials from Scandinavia, Japan, Australia, and the United Kingdom reported an occurrence of hip fractures of 2.2% in those assigned hip protectors versus 6.2% of those not. A recent large trial of hip-protecting underwear in nursing homes and the community by Kannus and colleagues showed a 54% lower rate of hip fracture in those assigned to hip protectors than those not. The authors estimated that the rate of hip fracture per fall was 84% lower when the protectors were being worn. Many patients have refused to use the devices, and compliance has been poor in those who were assigned them in some studies. However, enough evidence exists to recommend the use of hip protectors in at-risk patients immediately after mobilization following stroke because such patients are clearly at risk. The best level of protection against hip fracture in stroke patients with a
high risk of bone mineral loss and falls might be a combination of hip protectors and intravenous bisphosphonates.

**Vitamin D Insufficiency**

Moderate vitamin D insufficiency that leads to a moderate degree of secondary hyperparathyroidism may contribute to “type II” osteoporosis, leading to hip fractures in men and women aged >70 years. Reduced sun exposure and reduced dietary intake of vitamin D are common in both inpatients and outpatients after stroke. In practical terms, long-standing stroke patients should in most cases be given vitamin D3 (cholecalciferol) and calcium reduced hip fractures by 43% compared with placebo.

However, deficiency of the active form of vitamin D \([1,25(OH)_{2}D]\) may also play a role in stroke-induced bone loss. 1,25(OH)\(_{2}\)D is produced by hydroxylation of its precursor 25(OH)D in the kidney. Deficiency of 1,25(OH)\(_{2}\)D in immobilized stroke patients may not only be caused by substrate (cholecalciferol) deficiency but also by subclinical hypercalcemia. Sato et al proposed that hypercalcemia (from immobilization) could inhibit parathyroid hormone secretion and therefore production of 1,25(OH)\(_{2}\)D, resulting in decreased BMD. A small trial by the same group tested the effect of 1,25(OH)\(_{2}\)D treatment versus placebo after stroke (64 patients; mean, 4.8 years after stroke). BMD loss was of smaller magnitude in the active vitamin D\(_{3}\)-treated group, and significantly fewer hip fractures occurred. Adequately powered trials in larger number of patients are required before active vitamin D\(_{3}\) metaboty therapy after stroke is recommended.

**Conclusions**

Stroke is now a well-recognized risk factor for hip fracture. Preventing the development of hemiosteoporosis should be a priority in the management of patients with stroke. This article has reviewed current methods of fracture prevention and has highlighted the potential of intravenous bisphosphonates for the prevention of early stroke-associated bone loss. Because of the scale of the problem and because it is not clear which patients (if any) should receive bisphosphonates after stroke, a randomized, controlled trial of an intravenous bisphosphonate versus placebo after acute stroke is required. A study showing effectiveness in preserving BMD should be followed, if possible, by an additional study with sufficient power to show differences in fracture rates. The second- and third-generation bisphosphonates are potent, efficacious, easy to administer, and generally well tolerated. If given soon after stroke, such drugs could well have a role in preventing hip fractures.

**References**


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