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Review

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Hip fractures after stroke and their prevention

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Summary

Increased fracture risk is a recognized complication following stroke. Bone loss following a hemiplegic stroke has been proposed as a major risk factor for post-stroke hip fracture, with a recent focus on the development of novel therapeutic measures to prevent bone loss and fractures after stroke. We briefly review the literature on the epidemiology and pathophysiology of bone loss and hip fracture after stroke, and then critically review recent studies on preventive strategies.

Introduction

In the UK, the estimated number of new strokes is close to 100 000 per annum, the incidence rising steeply with increasing age.[1] Although recent data from the Oxford Vascular Study suggested a falling incidence of stroke,[2] current demographic trends mean that the projected total number of incident strokes within the UK population will increase in the future. Increasing death and disability due to stroke is thus very likely. One of the major factors associated with increased death and disability after stroke is an increased incidence of falling in stroke survivors, with resultant hip fractures.

Multiple factors act together in the pathogenesis of hip fracture after stroke, including a tendency to sustain a fall towards the affected side and the development of osteoporosis in the proximal femur, following a hemiplegic stroke.[3] Research efforts have recently focussed on methods of preventing bone loss after stroke, using either established treatments for osteoporosis, such as oral and intravenous bisphosphonates, or novel strategies such as vitamin B_{12} and folate supplementation.

In this review, we outline the epidemiology and pathophysiology of post-stroke hip fractures and critically review emerging preventive strategies and novel therapies.

Search methodology

We performed PubMed searches using the terms 'stroke' or 'hemiplegia' and: (i) osteoporosis (45); (ii) falls (185); (iii) fracture (104). We included randomized controlled trials, systematic reviews, meta-analyses, and Cochrane database entries. 'Epub ahead of print' sections of the relevant specialist journals were also searched.

Bone health and stroke

In both males and females, peak bone mass is usually achieved around the age of 30 years, after which it has been estimated to remain constant or to fall up to 0.5% per year, based on bone mineral density (BMD) assessment.[4,5] In post-menopausal

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women, the observed rate of bone loss rises to 0.5–1.5% per annum, depending on factors such as years since menopause, site of bone density measurement and the measurement technique.[4] In the literature examining bone health after stroke, several studies have reported a marked reduction in BMD on the affected side after hemiplegic stroke.[6–8] Of the sites measured by dual-energy X-ray absorptionmetry (DXA) scanning, the hemiplegic upper limb and proximal femur appear the most vulnerable for localized bone loss after stroke.[8,9] In a prospective study by Jorgensen and colleagues of 40 patients with acute stroke followed for a year, BMD loss in the femoral neck depended on when or if the patient relearned to walk, and the amount of body weight sustained through the paretic leg.[8]

Several potential mechanisms contribute to BMD loss after stroke, although there has been limited research into hemiplegia-induced bone loss at the cellular level.[10] A major factor is immobility, which contributes to generalized bone loss, in turn compounded by region-specific bone loss at sites such as the hemiplegic hip and upper limb. Prospective studies examining biochemical markers of bone turnover in hemiplegic patients suggest an early (within 7 days) increase in bone resorption after stroke.[11] However, a decline in serum biomarkers of bone formation[11] suggests a remodelling imbalance at the Bone Multicellular Unit (BMU) level. Factors such as the duration of hemiplegia,[12] degree of functional recovery,[13] reduced vitamin D status[14,15] and the use of anticoagulants[16] may determine the rate and extent of bone loss after stroke. In a recently reported study of the changes in BMD of the forearms and legs in relation to the duration of hemiplegia-induced immobilization after stroke, Demirbag and colleagues confirmed that BMD was decreased in the hemiplegic extremities relative to the unaffected side. They also found that there was an inverse relationship between duration of hemiplegia and BMD values.[17] In hemiplegic elderly patients with ischaemic stroke, hyperhomocysteinaemia has also been reported to be associated with hip fracture risk.[18] There are several determinants of BMD loss after stroke, as described earlier.

In addition to stroke-induced bone loss, stroke patients are highly likely to have pre-existing osteoporosis[19] by virtue of their age, and common risk factors for osteoporosis and cerebrovascular disease. Indeed, 40% of stroke patients admitted to a rehabilitation unit in Japan (meantime from onset 38.9 days) had established osteoporosis.[20] Moreover, BMD loss after stroke may be more severe in people with pre-existing osteoporosis.[19]

Epidemiology of fragility hip fractures following stroke

Stroke incidence increases with increasing age. This, in combination with age-associated bone loss, means that the patients with stroke are vulnerable to osteoporotic fractures. Increased fracture risk is a recognized complication following stroke, particularly in hemiplegic stroke. Over 80% of hip fractures after a stroke occur on the hemiparetic side.[21,22] There have been case reports of an increased propensity to fracture on the affected side of the stroke since the 1950s,[10] followed by further studies examining the incidence and prevalence of hip fracture after stroke, and mortality outcomes following the hip fracture.[3,9,23] Although other low trauma fractures occur following stroke, the present review focuses on hip fractures, since not only are they the predominant type of fracture (compared to other fractures such as wrist and vertebral fractures), but they are the most devastating in terms of morbidity and mortality. In one prospective study of 1139 stroke patients from Sweden, upper limb fractures were considerably less common than hip fractures (3.7% vs. 6.1%),[23] whereas in another study of 2696 patients from Scotland, the incidence for both types of fracture was close to 1%.[24]

Hip fractures occur early after stroke, with the greatest risk within the first year after the stroke. Kanis and colleagues[25] studied more than 16 million hospitalizations identified over 10 years using hospital databases in Sweden. They reported that at all ages and in both sexes, there was a marked increase in risk of any fracture and hip fracture within the first year compared with that of the general population. The excess risk, however, was most marked in the first year after stroke, and declined thereafter. The fracture risk remained higher than that seen in the general population, except in those aged $\geqslant$80 years, in both sexes.[25] Although approximately one in five hip fractures after stroke occur on the unaffected side,[21,22] more work is required to better understand fracture risk on the non-hemiplegic side after stroke.

Strategies to prevent hip fractures following stroke

The two major risk factors associated with increased hip fracture risk after stroke are BMD loss and tendency to fall to the affected side. Strategies aimed at preventing post-stroke fragility fractures have focussed around these two major issues: prevention of bone loss and fall prevention.

Fall risk after stroke

A key aspect of fracture risk in stroke patients is their propensity to fall. Injurious falls to the hemiplegic side are receiving more attention in cohort studies. Numerous factors have emerged as predictors of falls among stroke patients. These include general factors such as older age,[26,27] male sex,[28] intercurrent infections;[26,29] factors specific to the stroke such as stroke severity,[26,29] right hemispheric stroke,[26] widespread white matter lesions,[30] previous strokes,[30,31] presence of hemi-neglect,[31] post-stroke seizures[32] and various motor and mental dysfunctions;[32–35] and increased use of drugs, including analgesics, sedatives and antihypertensives.[28,34] Additionally, Lamb *et al.*[36] highlighted a >7-fold increased risk of falling whilst dressing unaided in stroke patients.

The role of hip protectors in prevention of fall-related hip fractures

The risk of hip fracture increases 30-fold if there is direct impact on the hip,[37] and hip protectors can act as shock absorbers.[38] Willig and colleagues reported that people with hemiplegic stroke had significantly higher fracture risks in their case-control study (123 consecutive hip fracture patients vs. 132 individuals who sustained soft tissue injuries from falling, in a prospective study of falling).[39] The authors highlighted the potential benefit of targeted use of hip protectors in post-stroke hip fracture prevention. The recently updated Cochrane Systematic Review (2005) included 15 trials, one of which was a study of compliance:[40] 11 of the trials were done in institutional settings, and the pooled data showed marginally significant reductions in hip fracture incidence (RR 0.77, 95%CI 0.62–0.97). Statistical heterogeneity was significant among these 11 trials. In the three randomized trials in the same review conducted in community-dwelling participants ($n=5135$), the pooled data showed no benefit of hip protectors in preventing hip fractures (RR 1.16, 95%CI 0.85–1.59). The reviewers therefore cast some doubt on the effectiveness of hip protectors in reducing the incidence of hip fractures in older people. Moreover, although hip protector trials were performed in the high-risk institutionalized (including people with prior stroke) there were no condition-specific data, such as the number of people with history of stroke, stroke duration or stroke severity.

Cameron and colleagues reported that hip protectors improved falls 'self-efficacy': an individual's belief in his or her capability to complete an activity.[41] Targeted use of hip protectors also appeared cost-effective in a hypothetical cost-benefit analysis by Honkanen *et al.* in the US,[42] which estimated that Medicare could save 136 million dollars in the first year of a hip-protector reimbursement programme in US nursing homes. There appears to be a need for well-designed randomized controlled trials in stroke patients in various settings.

The major issue with regard to the use of hip protectors is compliance. Clinical trials in institutional settings have suggested that the attitude, education and motivation of staff, the contact person and the size of the nursing homes all influence user compliance.[43,44]

Improving muscle strength and cardiorespiratory fitness

There is emerging evidence that exercise regimens can improve bone health in chronic stroke. In a recent study, Pang *et al.*[45] found beneficial effects on tibial bone architecture (using peripheral QCT) as a result of a 19-week exercise intervention. Further work is necessary to evaluate early physiotherapy and exercise interventions in acute stroke patients. In an earlier study, the same investigators enrolled 58 patients with stroke of >1 year duration. The authors found relationships between ambulatory capacity ($r=0.33$), muscle strength ($r=0.39$) and physical fitness ($r=0.57$) and the proximal femoral BMD of the paretic leg. Under multivariate analysis, lean mass in the paretic leg was a major predictor of the proximal femoral BMD in the paretic leg, and physical fitness as measured by VO_2max was a significant predictor of both BMD and lean muscle mass in the paretic leg.[46] They also reported a randomized controlled trial of a community-based fitness and mobility exercise program for older adults who had stroke for$\geqslant$1 year ($n=63$, aged $\geqslant$50 years), in which the intervention group ($n=32$) not only had significant gains in cardiorespiratory fitness, mobility and muscle strength in the paretic leg, but also maintained femoral neck BMD in the paretic leg, compared to controls ($n=31$). There was a significant decline of paretic leg BMD over 19 weeks in the controls.[47]

Calcium and vitamin D

In a recent case-control study (89 cases vs. 36 controls), when calcium metabolism was assessed 1 week after a hemiplegic stroke, patients' serum concentrations of ionized calcium and ICTP (pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen, a bone resorption marker) were higher than those of controls, and correlated

inversely with activity as rated by the Barthel Index. Parathyroid hormone levels were also low, and hypovitaminosis D was common in patients.[11] Our studies have identified hypovitaminosis D in the majority of patients with acute stroke throughout the year,[48] a significant factor in musculoskeletal health during stroke recovery. A recently reported randomized controlled trial examined 96 elderly women with post-stroke hemiplegia who had deficient levels of vitamin D at baseline. The authors reported that daily vitamin D (1000 IU of ergocalciferol) supplementation over 2 years was associated with an increase in the relative number and size of type II muscle fibres, and improved muscle strength, compared to placebo. Treatment with low-dose vitamin D also accounted for a 59% (28%–81%) reduction in falls, and while hip fractures occurred in 4/48 in the placebo group, there were no fractures in the treatment group (log-rank $p = 0.049$).[49] The dose, timing and efficacy of vitamin D and/or calcium supplementation following stroke is an area requiring further, large clinical trials before definitive recommendations can be made to guide clinical practice. However, ensuring that stroke patients are vitamin-D-replete during stroke rehabilitation is a reasonable aim, given the available research to date.

Bisphosphonates

In a 12-month, randomized, double-blind placebo-controlled trial of elderly women, involving 187 patients who received daily risedronate of 2.5 mg and 187 patients who received placebo, one patient in the treatment group sustained hip fracture, compared to seven controls (OR 7.0, $p = 0.036$). There was also a significant difference ($p < 0.0001$) in BMD between the two groups, with better BMD in the treatment group (1.5% increase from the baseline) and worse BMD in the placebo group (4.9% decrease). Urinary deoxypyridinoline (a bone resorption marker) levels also followed the same pattern.[49] Similar results were reported by the same investigators in men aged 65 years and over.[51] The authors did not provide details of the severity of stroke in their RCT patients at the time of publication.[52] The Barthel index scores provided subsequently suggested that the study population was of patients with very mild stroke in whom oral bisphosphonate therapy could be tolerated. Clearly, oral bisphosphonate therapy is contraindicated in stroke patients with residual dysphagia, but may have an important role to play in those with normal swallowing who are able to remain upright. Perhaps unexpectedly (due to the estimated rate of hip fractures after stroke in northern Europe), Sato and colleagues have published significant hip fracture endpoints not only in both their relatively small RCTs of daily oral risedronate therapy, but also in an RCT of mecobalamin/folate supplementation and a small RCT of ergocalciferol. The epidemiology of hip fractures after stroke in Japan is not yet available, but since there are considerable differences in hip fracture rates after stroke between centres such as Scandinavia and the UK, information from Japan would be a welcome addition, particularly in view of global differences in osteoporosis prevalence.

An alternative approach to oral bisphosphonates is the administration of potent intravenous bisphosphonates such as zoledronate or pamidronate in the acute phase of stroke. The rationale for such a strategy is that stroke patients can be targeted in the acute stroke unit as in-patients, are covered during the most rapid phase of bone loss and can be protected even in the event of dysphagia. The results of an RCT comparing a single dose of zoledronate with placebo have confirmed that zoledronate 4 mg completely prevented bone loss at the hemiplegic hip, compared to a substantial decrease in BMD with placebo.[53] All patients had vitamin D assessment and replacement prior to the zoledronate/placebo infusion. However, intravenous bisphosphonates should be used with caution in those with dehydration, renal impairment or vitamin D deficiency. The authors of the zoledronate paper recommended regular assessment of renal function and hydration status in stroke patients selected for intravenous bisphosphonate treatment, even in those without established renal impairment. More work examining the role of intravenous bisphosphonates after stroke is required to establish their efficacy in fracture prevention.

Mecobalamin (B_{12}) and folates

There is evidence of an inverse association between homocysteine level and hip fracture risk[54,55] as well as stroke risk.[56] A double-blind, randomized controlled study of >600 Japanese older adults aged $\geqslant 65$ years with a 2-year follow-up was recently published. Patients were assigned either to treatment with mecobalamin and folate or double placebos. At study completion ($n = 559$), there was a statistically significant difference in hip fractures (10 vs. 43 per 1000 patient-years in treatment and placebo groups, respectively) ($p < 0.002$). The number needed to treat was 14 (95%CI 9–28).[57] The incidence of hip fracture in patients with stroke was 1.75–4.65% per year, compared to 8.6% in the placebo group, over 2 years.[57] The precise biological explanation for these results remains elusive.

However, the beneficial effects on the cardiovascular system of lowering homocysteine levels have been questioned recently.[58] There has also been recent concern over the role of folate in cancer aetiology.[59,60]

Long-term strategy

Prevention of falls, both during stroke rehabilitation and afterwards, is clearly of major importance in preventing hip fractures. However, few studies have evaluated the efficacy of falls interventions (in any study population, including stroke) in fracture pathogenesis. Such studies are urgently needed.

The future

Accumulating evidence suggests that intervention strategies are feasible and also associated with reductions in risk of post-stroke hip fractures. However, due to the modest event rate of hip fractures after stroke, well-designed randomized, controlled trials to test these strategies specifically in stroke patients may need to enrol large numbers of patients.[24] Intravenous zoledronate has recently been shown to be effective in preventing loss of hip BMD after acute stroke, while overcoming compliance, adherence and swallowing difficulties, but more work is needed to confirm that this approach will reduce hip fractures. For the moment, a pragmatic strategy for a stroke unit might be to consider non-pharmacological measures such as adequate sunlight exposure, early physiotherapy and pharmacological measures such as vitamin D and calcium supplementation for hemiplegic patients, and also to develop effective technologies for prevention of falls during the acute hospital stay.

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