

## REVIEW

# Can early onset bone loss be effectively managed in post-stroke patients? An integrative review of the evidence

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## Abstract

**Background:** bone loss post-stroke can lead to an increased risk of fracture. Fractures compound the effects of a stroke, resulting in greater dependency for the individual and an increased burden for health and social care.

**Objectives:** to identify risk factors for bone loss post-stroke and appraise bone loss or fracture risk reduction interventions. To develop a research agenda that informs the design and development of risk reduction strategies.

**Design:** an integrative review.

**Methods:** the search strategies used in Medline, Embase, AMED and CINAHL from 1966 to July 2006 identified 530 records. Ninety-nine papers with a focus on risk factors or interventions to prevent bone loss or fractures post-stroke were identified. Hand searching and scoping grey literature produced 59 additional papers. Data analysis, including data reduction and data display using matrices, enabled patterns and themes to be derived from differing study designs.

**Results:** risk factors for bone loss post-stroke are reduced mobility, vitamin D deficiency, gender and time since stroke. Early mobilisation post-stroke may reduce bone loss, and so avoid fractures, but evidence is needed. Providing vitamin D supplements and Bisphosphonates in post-stroke patients tends to reduce bone loss, but larger treatment trials are required.

**Conclusions:** the evidence base for bone loss management post-stroke is limited. Large, prospective, multi-centre, longitudinal studies are needed to clarify optimum treatments to reduce post-stroke bone loss, and test the effects on clinical outcomes. A 'skeletal health' checklist to aid implementation of treatments within stroke rehabilitation has been suggested but not yet developed.

**Keywords:** cerebrovascular accident, hemiplegia, fractures, osteoporosis bone density, elderly

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## Introduction

Falls are common after stroke, and motor balance, sensory and visual impairments contribute to risk of falls [1]. A study of community dwelling stroke survivors found that 25 of 55 (45%) reported a fall within 6 months and 12 of 55 (22%) reported a recurrent fall [2]. The risk of falling at least once was more than twice as high for patients

with stroke, when controlled for potential confounders (relative risk 2.2; 95% CI, 1.1–4.3) [3]. Incidence of falls post-stroke was reported as 8.9/1,000 per day, with 25% of falls resulting in injury, 2% of which resulted in hip fractures [4].

Higher fracture rates are reported in stroke than the general population [5] and fractures potentially compound the effects of stroke, increasing dependency, and thus the

burden to the patient, carer, health and social care. The probable risk factors for fractures after a stroke are the high numbers of accidental falls and progressing osteoporosis on the paretic side [6].

Fractures are more likely to occur in those with low bone density. Immobilisation and the lack of weight-bearing activity after stroke may result in bone breakdown exceeding bone formation, thus reducing bone density. Currently, the nature and extent of bone loss post-stroke, or whether interventions can limit it and protect against fracture, is not fully understood.

This integrative review will identify the risk factors for bone loss post-stroke, potential interventions and the research required to inform the design and development of risk reduction strategies.

### Search methods

A search strategy (Appendix 1) was developed to search Medline from 1966 to July 2006, and was adapted to search Embase, Amed and Cinahl (see the supplementary data on the journal website <http://www.ageing.oxfordjournals.org/>). A total of 530 records were retrieved and the abstracts were reviewed. In the absence of an abstract the title was considered. Ninety-nine papers were eligible for inclusion and were searched for secondary references. Hand searching and scoping grey literature produced 59 papers, which were filtered. Reviewing and filtering was performed by two reviewers and differences of opinion were resolved by discussion. Studies were included if the participants were stroke patients and the study focus was risk factors for, or interventions to prevent, bone loss or fracture. The National Clinical Guidelines for Stroke provides a grading for the recommendation of evidence, and this was applied to the intervention studies [7]. This ranges from A (high) to D (low).

### Epidemiology and incidence

There is limited epidemiological data on bone loss in stroke *per se* because bone density is not routinely measured in clinical practice. The most clinically relevant outcome of bone loss after stroke is fragility fracture, i.e. a fracture resulting from a fall. Thus, epidemiological studies that document fracture rates after stroke are important. Bone loss is an additional risk factor for fracture after stroke.

Studies focussing on hip fracture in the general population found a proportion of those with previous stroke which ranged from 8 to 38.5% [8, 9] (see Appendix 2; on the journal website <http://www.ageing.oxfordjournals.org/>). Hip fracture was the most frequent fracture reported post-stroke [5, 10] and maybe attributed to pre-stroke bone density or post-stroke bone loss.

The National Swedish Register, in acute stroke shows a 4-fold risk of fracture, with a hip fracture rate of 28.7/1,000 in comparison to 6.2/1,000 in a female general population [11]. Scottish stroke patients less than 69-years of age were reported to have a higher hip fracture rate compared to the general population [10].

Post-stroke, irrespective of age or sex, there is a marked increase in risk of fracture within a year of the event [11]. Fracture risk was 2–4% by 1 year and 15% by 5 years in a Swedish study [5] and 10.6% by 10 years in a Scottish study [10]. On admission to post-stroke rehabilitation, almost 40% of Japanese patients had osteoporosis at the hip [12].

Hip fracture rates post-stroke vary between countries and are reported differently, making comparison between studies difficult. Hip fracture rate has been reported as 17 per 1,000 person-years in Sweden [5], whereas another study has reported an incidence of 1% by 1 year post-stroke in Scotland [10] and 5.2% by 10 years in Sweden [11]. Significantly higher fracture risk is not reported in all longitudinal studies post-stroke. [13].

In addition to geographical variation, many studies reporting fracture risk and fracture rate in stroke patients are retrospective in design, and have limited accuracy in reporting and coding, e.g. failure to verify fractures by x-ray and lack of fracture reporting in the community.

### Risk factors for bone loss post-stroke

An understanding of factors impacting on bone loss from the onset of stroke is needed.

#### Immobility after stroke

Studies measuring bone loss post-stroke have focussed on patients with hemiplegia. We identified 23 cross-sectional and 12 longitudinal studies, 18 of which were from a recent review [14] (Table 1, available online at the journal's website [www.ageing.oxfordjournals.org](http://www.ageing.oxfordjournals.org/)). Bone loss is evidenced by bone mineral density (BMD) which is measured by dual energy x-ray absorptiometry (DEXA) or computer x-ray densitometry (CXD). Bone measurements have been performed at a variety of sites, e.g. spine, hip, thigh, forearm, heel with DEXA [15–17] and at the metacarpal using CXD [18], making comparisons between studies difficult. However, BMD measurements using DEXA at the hip are considered the 'gold standard'. Biochemical markers of bone turnover are another indicator of bone loss.

Results from cross-sectional studies found significant differences in the density of bone on the paretic and non-paretic sides. Bones were reported as less dense on the paretic side in U S, Japanese, Italian, Turkish and Canadian stroke patients [19–23] using DEXA measurements. There was greater bone loss in upper limbs compared to lower limbs and in the paretic compared to the non-paretic side [15, 16, 24, 25].

For the paretic arm, there was a BMD decrease of 3.7% by 1 month [24], 12% by 3 months [16], 9.3% by 4 months [24] and 17.4% by 12 months [25]. By 12 months, there was a 5.8% increase in BMD in the non-paretic arm, likely due to increased compensatory activity [25].

For the paretic lower limbs, there was a BMD decrease up to 1% by 1 month [24], 5% by 3 months [16], 3.7% by 4 months [24] and 12.2% by 12 months [25]. A significant loss of 4% BMD was found in the non-paretic lower limb

by 12 months, although this was less pronounced than in the paretic side [25]. Bone loss appears to begin early after stroke, increase over time and be more pronounced in the upper paretic limb.

Post-stroke, and as seen in the general population, women lose more bone than men [17, 22] and the time from menopause is a significant determinant of this bone loss [21].

When examining the effect of walking on BMD over the first 12 months post-stroke [26, 27], bone loss was 3% in those who walked throughout the first 12 months, 8% in those who walked by 2 months and 13% in those wheelchair-bound [26]. Most bone loss occurred within the first 7 months post-stroke, suggesting early walking has a protective effect against bone loss [27].

Post-stroke studies have limited generalisability as sample sizes are small, and exclusion and inclusion criteria differ. However, bone loss is evident as early as a month post-stroke, and is ongoing at 12 months [25]. Duration of bone loss beyond a year post-stroke has not been explored.

### Vitamin D deficiency

Older people are at high risk of vitamin D deficiency as their skin has a reduced capacity to produce the pre-vitamin D<sub>3</sub> and may be sunlight deprived. Post-stroke patients are at risk of vitamin D deficiency as they are not only likely to be older but also have a lower dietary intake [28], remain indoors and thus be sunlight deprived [29], and immobile. Immobilisation-induced hypercalcaemia disrupts the metabolism of vitamin D in the kidney [30]. A UK study found 77% of post-stroke patients had reduced levels of vitamin D [31] (Table 2). Although 400 IU of vitamin D daily is currently recommended for older people, it has recently been suggested that 800–1,000 IU daily is actually needed to reduce fracture risk [32].

Studies of vitamin D deficiency post-stroke are mainly cross-sectional and in hemiplegic stroke patients. Vitamin D deficiency was associated with bone loss in the paretic hand [33] and in the paretic leg [22]. Levels of vitamin D at baseline were strongly associated with hip fractures by 2 years post-stroke [34].

Cross-sectional studies post-stroke have found lower levels of 25-OHD (from the diet), a necessary precursor to vitamin D in inpatients as compared to outpatients [28], controls [31–33] or age-matched controls [22, 29, 30, 35].

#### *Immobility and vitamin D interaction*

Stroke patients with high deficiency levels of 25-OHD and severe immobility had higher calcium concentrations, while patients with mild deficiency levels of 25-OHD had low calcium concentrations [35]. Surprisingly, BMD was lower in those with a mild deficiency compared to those with a high deficiency, suggesting that a milder vitamin D deficiency may result in greater bone loss than more severe deficiency. However, these effects may be confounded by differing levels of immobility in each group. It is imperative that

any evaluation or treatment of bone loss in stroke patients takes account of vitamin D status, calcium homeostasis and immobility.

In post-stroke patients with hemiplegia, the serum concentration of vitamin D and its precursor, 25-OHD were reduced and serum calcium concentration was higher [29, 30]. The higher serum calcium inhibits parathyroid hormone secretion and thus reduces production of vitamin D in the kidney, a process which is already limited by the reduction of its precursor, 25-OHD.

The majority of the studies examining vitamin D deficiency post-stroke are based on small samples of chronic, elderly, non-Caucasian patients, which limits generalisability to Caucasian populations.

Thus, the main risk factors identified in post-stroke patients exacerbating bone loss are immobility due to hemiplegia; vitamin D deficiency and the disruption of various bone related processes by prolonged immobility. To counteract the problem of bone loss, post-stroke intervention studies have used exercise, vitamin supplementation and Bisphosphonates.

## Interventions to reduce bone loss post-stroke

### Weight-bearing exercise

One randomised controlled trial (RCT) has examined the effect of an exercise programme on bone loss post-stroke.

In patients 5 years post-stroke, a fitness programme maintained hip bone density (measured by DEXA), compared with a placebo group which experienced bone loss at 5-month follow-up, ( $P = 0.04$ ) [36]. The strength of the recommendation [7] of this trial was graded A, as it was an RCT, although this study sample was small ( $n = 60$ ) and was biased towards a younger, male stroke population. Since this review was completed, a further publication using the same sample reports enhanced bone health on the paretic side compared to controls, using peripheral quantitative computed tomography ( $P = 0.048$ ) [37]. This study excluded a large proportion of subjects from the analysis due to the poor scan quality.

Thus, there remains a lack of robust evidence on the effectiveness of general exercise programmes on bone loss post-stroke and the effects of early intervention have not been explored, though walking early post-stroke seems to reduce bone loss [26].

### Vitamin D supplementation

Three RCTs of vitamin D to reduce bone loss post-stroke were identified (Table 3). In chronic stroke patients, BMD on the paretic side was reduced by 2.4% in the vitamin D supplements and calcium group compared to an 8.9% reduction in the placebo group, ( $P = 0.002$ ) [38]. On the non-paretic side BMD increased by 3.5% in the supplements and calcium group and decreased by 6.3% in the placebo group ( $P = 0.018$ ). No hip fractures

Table 2. Vitamin D deficiency

Study	Design	Study focus	No of stroke patients in study ( <i>n</i> = control) [Total]	Time since stroke	Type of measure	Outcome/ mean values ± SD
Levendoglu 2004 [22]	Cross-sectional	Vitamin D and BMD	80 (20 age-matched controls) [Total 100]	>1 mo and <24 mo	25-OHD, vitamin D	Both types of vitamin D lower in patients than controls. BMD of PS lower than controls. Correlation of Z score of PS and vitamin D serums. Patient's 25-OHD, 16.2 ± 13.3, versus controls 34.9 ± 8.1, ng/mL. Patients vitamin D, 31.2 ± 17.6, compared to controls 55.5 ± 4.8, pg/mL.
Sato 1996 [28]	Cross-sectional	Vitamin D deficiency	45 inpatients, 42 outpatients (28 control) [Total 118]	67.2, 28.8 mo, mean	25-OHD blood serum	82% of inpatients were vitamin D deficient and 64% of outpatients, unclear for controls. Inpatients 25-OHD 5.9 ± 4.1, compared to outpatients 9.1 ± 4.9, compared to control 21.6 ± 3.1, ng/mL. Dietary intake of vitamin D below recommended amount in 72% of patients, and 89% considered sunlight deprived.
Sato 1999a [29]	Cross-sectional	Vitamin D status	129 (28 age-matched controls) [Total 157]	55.2 ± 34.8 mo mean.	25-OHD, vitamin D	Sera concentration and BMD lower in patients compared to controls. Patient's 25-OHD, 11.7 ± 5.3, compared to controls 25.2 ± 4.1, ng/mL.
Sato 1999b [30]	Cross-sectional	Renal synthesis of Vitamin D	170 (72 age-matched controls) [Total 242]	15.6 ± 4.8 mo, mean.	Serum biochemical indices	Sera concentration and BMD lower in patients compared to controls. Patient's 25-OHD, 11.6 ± 5.3, controls 21.8 ± 3.2, ng/mL. Patient's vitamin D, 25 ± 12.4, compared to controls 48.7 ± 9.1, pg/mL.
Poole 2006 [31]	Longitudinal	Reduced Vitamin D in stroke	44 (96 controls) [Total 140]	<1 mo	25-OHD serum every 2 mo for 1 yr	77% of patients in the insufficient range (<50 nmol/L) Z scores -1.4 SD units (95% CI, -1.7, -1.1). Reduced vitamin D in majority of patients throughout year and possibly preceding stroke.
Kuno 1998 [33]	Cross-sectional	Vitamin D status	88 (34 controls) [Total 122]	56.2 mo, mean.	25-OHD, vitamin D	Both types of vitamin D lower* in patients compared to controls. Patient's 25-OHD, 11.5 ± 5.4, compared to controls 21.6 ± 3.1, ng/mL. 43% of patients were vitamin D deficient, 56% had insufficient vitamin D.
Sato 2001 [34]	Longitudinal	Vitamin deficiency and fracture rate	88 vitamin-deficient group, 76 insufficient group, 72 sufficient [Total 236]	9.9 ± 7.3; 11.7 ± 9.7; 9.3 ± 8.3 mo, mean.	Fracture rate at 2-yr follow-up	Seven hip fractures in deficient group (≤ 10 ng/mL), one in insufficient <i>P</i> <0.05. The seven hip fracture patients had osteomalacic 25-OHD levels. The deficient group tended to be of a higher age and severely immobilised.

(continued overleaf)

Table 2. (Continued)

Sato 2004 [35]	Cross-sectional	Calcium status in patients with low vitamin D	83 with low vitamin D, 40 'normal', 43 'low'. (80 age-matched controls) [Total 163]	Serum biochemical indices	BMD lower in 'normal' (mildly deficient) group compared to 'low' (very deficient) group.
				59 ± 26 mo	25-OHD levels: normal 4.2 ± 0.6, low group, 1.8 ± 0.9, controls 21.5 ± 3.2, ng/mL.
				20 ± 14 mo	Vitamin D levels: normal 36.7 ± 11.4, low group, 14.2 ± 3.6, controls 50.3 ± 9.2, pg/mL.

Precursor to Vitamin D—(25-OHD)—[25-hydroxyvitamin D] Vitamin D—(1,25-[OH]<sub>2</sub>D)—[1,25-dihydroxyvitamin D].

\* Significant.

occurred in the supplements and calcium group ( $n = 30$ ), and 4 of 34 occurred in the placebo group by 6 months ( $P = 0.036$ ). These findings suggest vitamin D and calcium can prevent further bone loss in patients with chronic stroke. Methodological limitations to this study include unclear sample selection procedures, resulting in a skewed younger male sample, reducing generalisability. Furthermore, 24% (20 of 84) dropped out or were withdrawn from the study and were not included in the final analysis.

A non-blinded trial ( $n = 104$ ) compared Ipriflavone with vitamin D<sub>3</sub> or no treatment post-stroke, and showed bone loss in all groups by 12 months [39]. Metacarpal BMD on the paretic side decreased by 1.4% in the ipriflavone group, 3.8% in the vitamin D<sub>3</sub> group and 5.4% in the control group ( $P < 0.001$ , ipriflavone versus vitamin D<sub>3</sub> and control) [39]. These results should be viewed cautiously due to unclear exclusion criteria.

In chronic stroke patients, 12 months of sunlight exposure increased metacarpal BMD by 3.1% compared with sunlight deprived patients who had decreased BMD of 3.3% ( $P < 0.001$ ) [40]. The authors suggest sunlight exposure increases BMD of vitamin D deficient patients by increasing serum levels of 25-OHD. One hip fracture occurred in the sunlight exposed group ( $n = 109$ ) and 6 in the deprived group ( $n = 108$ ), ( $P = 0.042$ ) [40]. This study sample was restricted by exclusion criteria (less than 2 years of hospitalisation), limiting generalisability. There was limited information on frequency of sunlight exposure in the intervention group, hampering replication. Robust evidence of the effectiveness of early use of vitamin D on bone density post-stroke is lacking. Studies are by the same research group and are mainly based on small samples of older Asian, chronic stroke patients, measuring bone density at the metacarpal using CXD. The authors imply that similar patterns of bone loss are occurring at the hip by reporting fracture rates, but this is not evidenced with any measurement at the hip. Furthermore, ethnicity is a risk factor for bone loss, with Asians having a higher risk

compared to Caucasians. The grade of recommendation was B for all these trials as they were well-designed controlled studies.

### Bisphosphonates

Bisphosphonates reduce the rate of bone resorption [41], and their use has been evaluated in five studies, three of which are from the same research group [42–46].

A double-blind RCT ( $n = 98$ ) to evaluate the efficacy of oral Etidronate started at 1 week post-stroke for 1 year reduced bone loss in the paretic side metacarpal compared to placebo ( $P < 0.001$ ) [42]. When started in women later (mean 2.6 months) post-stroke, for a 2-week period bone loss was reduced in the paretic side of the femoral neck compared to controls at 9 months post-stroke ( $P < 0.05$ ) [43]. Bone loss was minimised even in the non-paretic leg of the treatment group compared to the control group of the latter study. These results should be viewed cautiously due to the lack of detail on randomisation and blinding, and absence of a placebo.

A double-blind, placebo-controlled RCT ( $n = 345$ ) evaluating the efficacy of oral Risedronate (started by day 3) in women significantly increased metacarpal BMD by 1.5% compared to controls, at 12 months [44]. Only one hip fracture occurred in the Risedronate group compared to seven in the placebo group, ( $P = 0.036$ ). When started 90 days post-stroke in male patients, BMD increased by 2.5% in the Risedronate group and decreased by 3.5% in the placebo group by 18 months [45]. In the Risedronate group 2 of 140 had a hip fracture and 10 of 140 of the placebo group had hip fracture; whether this difference was significant is not reported. The relative risk of a hip fracture was reported as 0.19 (95% CI 0.04–0.89). Unfortunately, measures were taken in the finger using CXD, not DEXA hip measures, which limits comparisons with other studies. These findings imply that using Risedronate increases BMD and reduces fracture rate.

Intravenous Zoledronic acid prevented bone loss at the hip post-stroke compared to placebo over 12 months [46]. A full paper detailing the aforementioned proof-of-concept study using Zoledronic acid has been published since completion of this review [47]. This randomised, double-blind, placebo-controlled clinical trial reports significant

differences in hip BMD on both sides when comparing the use Zoledronic acid to placebo, ( $P < 0.001$ , hemiplegic;  $P = 0.002$ , unaffected). While Zoledronic acid has been shown to diminish bone loss at the hip after stroke, this was a small RCT ( $n = 27$ ) which only included 7% of patients assessed for eligibility (i.e. those considered to be at high

Table 3. Interventions

Study	Design	Study focus	No of stroke patients in study ( $n =$ control) [Total]	Intervention time point	Duration	Type of measure	Skeletal site	Time of follow-up and outcome
Pang 2005 [36]	RCT (single-blind)	Fitness and mobility exercise programme	32 chronic intervention (31 control) [Total 63]	62.4 ± 60 mo; 62.2 ± 43.2 mo, mean	1 h session 3 × per wk. 19 wk	DEXA	Femur	At 5 mo BMD of PS leg maintained in intervention group, decreased by 2.5% in control.
Sato 1997 [38]	RCT	Effect of vitamin D3 or placebo on BMD	30 chronic (34 placebo) [Total 64]. All given calcium	57.6 mo, mean	6 mo	CXD incidence of hip fracture	2nd meta carpal	At 6 mo PS BMD decreased by 2.4% in treatment and 8.9% in placebo ( $P = 0.002$ ) NPS BMD increased by 3.5% in treatment, (placebo decreased by 6.3%) ( $P = 0.018$ ), No fractures in treatment group, four in placebo ( $P = 0.036$ )
Sato 1999a [39]	RCT (not blind)	Effect of Ipriflavone or vitamin D3 or no drug on serum and fracture rate	Chronic 34 Ipriflavone 34 vitamin D3, 35 control [Total 103]	57.6 mo, mean	12 mo	Serum vitamin D. CXD. Incidence of hip fracture	2nd meta carpal	At 12 mo, BMD on the PS decreased by 1.4% in the ipriflavone group, 3.8% in vitamin D3 group, 5.4% in the control group ( $P < 0.001$ , ipriflavone v vitamin D3 and control). Vitamin D serum in Ipriflavone group increased by 139.9%, vitamin D3 increased by 26.9%, control increased by 1.5% ( $P < 0.001$ ); one fracture in control group.
Sato 2003 [40]	Randomised trial	Effect of sunlight on osteoporosis and hypovitaminosis D	129 sunlight exposed 129 sunlight deprived, (64 control) [Total 322]	Unclear; hospitalised 48 mo	12 mo	Vitamin D levels, CXD, hip fracture	2nd meta carpal	At 12 mo BMD increased 3.1% in sunlit group ( $P < 0.001$ ), decreased 3.3% in deprived group, unchanged in control. Fracture incidence, six in deprived (5.6%), one in sunlit (0.9%), ( $P = 0.042$ ).
Sato 2000 [42]	RCT	Oral Etidronate	49 Etidronate, 49 placebo (40 age-matched controls)	1 wk post-stroke	Four cycles of treatment lasting 14 wk	Biochemical markers, CXD	2nd meta carpal	At 13 mo BMD on PS decreased by 2.3% in Etidronate group and 4.8% in placebo. Vitamin D increased by 62.2% in Etidronate group and decreased by 12.4% in placebo; 4% incidence of fracture in placebo.
Ikai 2001 [43]	Longitudinal	Oral Etidronate	41 Etidronate (41 control) [Total 82] All 3 mo rehab programme	2.7 ± 1.4, 2.6 ± 1.2 mo	2 wk admin. period	Activities of daily living, biochemical markers DEXA	Spine and femur	In low activity group, BMD in PS leg at 3 mo reduced by -4% ± 7.2%, with treatment compared to -9.6% ± 5.9% for controls. In NPS leg BMD reduction of 0.8 ± 5.4% with treatment versus -3.7% ± 5.2% for controls. In high activity group, no differences detected.

(continued overleaf)

Table 3. (Continued)

Study	Design	Study focus	No of stroke patients in study (n = control) [Total]	Intervention time point	Duration	Type of measure	Skeletal site	Time of follow-up and outcome
Sato 2005 [44]	RCT	Oral Risedronate (women)	187 Risedronate (187 placebo) [Total 374]	Day 3	Daily dose for 12 mo	CXD. Hip fracture rate	2nd Meta carpal	At 12 mo Risedronate group, one hip fracture, versus seven in placebo. BMD increased 1.5% in Risedronate, decreased by 4.9% in placebo. Bone resorption marker decreased by 53.4% in Risedronate group and increased by 35.8% in placebo.
Sato 2005 [45]	RCT	Oral Risedronate (men)	140 Risedronate, 140 placebo [Total 280]; no vitamin D or calcium supplements.	3 mo post-stroke	Daily dose for 18 mo	CXD. Hip fracture rate	2nd Meta carpal	BMD increased by 2.5% in Risedronate group and decreased by 3.5% in placebo. At 18 mo 2 of 140 in Risedronate had hip fracture versus 10 of 140 in placebo.
Poole 2004* [46]	RCT	Intravenous Zoledronic acid	16 Zoledronic acid or placebo; details unclear; vitamin D and calcium supplements for all	≤ 1mo; measures at 6, 12 mo	Single dose	DEXA	Total hip region	No decrease in BMD at 12 mo in Zoledronic acid group. At 12 mo, greater reduction in BMD in both hips of placebo compared to Zoledronic group. Mean decrease of 10.2% in PS hip with placebo, and 6% in NPS hip.

RCT, randomised controlled trial.

\* Abstract only—no full paper published.

risk of bone loss and hip fracture). Furthermore, there were baseline differences between groups, which may partly explain the differences in BMD. Therefore, this study would require replication in a larger sample before efficacy could be established.

The grade of recommendation in all trials assessing Bisphosphonate use was an A, as these trials were RCTs.

The identified trials which used vitamin D supplementation and Bisphosphonates to reduce the loss of BMD in stroke patients were preliminary studies. To verify that these treatments lead to a reduction in hip fractures in an acute stroke population, these interventions would require further testing in adequately powered RCTs.

### Current guidelines

Guidelines for osteoporosis diagnosis and management do not include guidance for stroke-related osteoporosis [48, 49]. Guidelines for hip fracture prevention and management do not refer to post-stroke bone loss [50]. Preventing bone loss post-stroke is not recognised as a priority, and is not reflected in any national guidelines [51]. The standards within the National Service Framework for Older People provides general osteoporosis risk assessment and treatment details, but they are not stroke-specific; neither do the National Clinical Guidelines for Stroke contain specific guidance for osteoporosis assessment or treatment [7, 52]. Scottish

guidelines for stroke management do not refer to bone loss [53]. The latest draft guidelines by National Institute for Health and Clinical Excellence do include stroke as a risk factor for fracture [54].

Expert recommendations in the United States include an assessment of ‘skeletal health’ and the factors that affect bone quality as standard components in stroke management [14]. A correction of calcium and vitamin deficiency is suggested as the first step in any strategy to reduce bone loss and should be implemented prior to other drugs [55].

The gaps in knowledge for prevention of bone loss in the post-stroke population contribute to our research agenda.

### Implications for research

Longitudinal, prospective population-based studies are needed to measure hip fracture rate and BMD change over time in post-stroke patients. Interventions using vitamin supplementation, Bisphosphonates and weight-bearing activity early after stroke require development and testing to find the optimum levels to reduce bone loss and fracture incidence.

### Conclusion

In conclusion, the review has identified evidence that reduced mobility, vitamin D deficiency and gender may be risk

factors for bone loss post-stroke. There is a limited evidence base for prevention of bone loss post-stroke, but early mobilisation after stroke, sufficient levels of vitamin D and Bisphosphonates may be a promising way forward. A comprehensive research programme is required to address the gaps in knowledge highlighted within the research agenda. Recognition of the bone loss problem in stroke-specific guidelines would enhance the implementation of the research agenda.

### Key points

- Bone loss occurs rapidly post-stroke mediated by immobility, vitamin D deficiency and gender.
- Fracture rates are higher post-stroke compared to the general population.
- The rate and magnitude of bone loss post-stroke is unclear.
- Limited evidence supports the use of early mobilisation, vitamin supplementation and Bisphosphonates to reduce bone loss post-stroke.
- Strategies to reduce bone loss post-stroke are not evident in guidelines.

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### Conflicts of interest

None.

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### Supplementary data

Supplementary data for this article are available online at <http://ageing.oxfordjournals.org>.

### References

(The list of references supporting this review has meant that only key references are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website <http://www.ageing.oxfordjournals.org/as> Appendix 3.)

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