Stepping towards prevention of bone loss after stroke: A systematic review of the skeletal effects of physical activity after stroke

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Abstract

Rationale Bone loss after stroke is immediate, pronounced, and contributes to increased fracture risk. People who fracture after stroke experience reduced mobility and increased mortality. Physical activity can maintain or improve bone mineral density and structure in healthy older adults, likely reducing fracture risk. The purpose of this systematic review was to investigate the skeletal effects of physical activity in adults affected by stroke.

Method A search of electronic databases was undertaken. Selection criteria of trials were 1) randomized or pseudo randomized design, 2) physical activity based intervention, 3) participants with history of stroke, and 4) bone related outcome measures. Effect sizes were calculated for outcomes of paretic and non paretic limbs.

Results Three of 349 identified records met the inclusion criteria. Small effect sizes were found in favor of physical activity in adults with chronic stroke (n=95, 40% female, average age 63.8 years,, > one year post stroke). Patients in intervention groups had significantly higher changes in femoral neck bone mineral density, tibial cortical thickness and trabecular bone mineral content of the paretic limb, compared to controls ($p< 0.05$). It is not known whether these benefits reduced fracture risk.

Conclusion There are limited trials investigating the skeletal effect of physical activity for adults post stroke. Given the increased risk of, and poor outcomes following a fracture after stroke, randomized trials are warranted to investigate the benefits of physical activity on bone, post

stroke. Interventions are likely to be beneficial if implemented soon after stroke, when bone loss appears to be rapid and pronounced.

INTRODUCTION

Accelerated bone loss and the development of osteoporosis are well documented sequelea of stroke (9-11), with loss most pronounced in the paretic or paralyzed limbs (12). Loss of BMD of up to 24% in the paretic proximal humerus (13) and 12% in the proximal femur (10) have been observed in patients one year after stroke. The most rapid bone loss occurs within the first six months of stroke (14), followed by slower rates of loss thereafter. The amount of bone lost after stroke appears related to the length of time of immobility (15), severity of impairment (13, 16), disuse of paretic limbs (17), reduction in weight bearing (16), reduced muscle mass (18), muscle weakness (19), and reduced cardio-respiratory fitness (18). In stroke patients who remained non-ambulant for one year after stroke, loses of up to 13% were observed in femoral neck BMD of the paretic limb (15). In contrast, patients who relearned to walk within two months, and patients who could walk from the first week after stroke showed losses of 8% and 3% respectively (15). Up to 73% of stroke survivors report falling within six months of stroke (20), making them particularly vulnerable to fall related injuries, especially fractures. The risk of fracture after stroke is 1.5 to 4 fold compared to age matched controls (21). Fractures after stroke can reduce the ability to regain independent walking, and increase mortality (22), reinforcing the importance of fracture prevention in this vulnerable group.

Physical activity levels are often very low among acute stroke patients (1, 2), not only due to physical impairments directly caused by the stroke, but also due to the general thinking that patients with stroke are too “sick” to participate in activities and exercise (1, 2). Prolonged bed-rest however, leads to rapid loss of bone (3). Reductions in bone mineral density (BMD) at the tibia of up to 3% have been observed in healthy males aged 25.5 (SD 2.9) years after just five

weeks of bed-rest (4). Urinary markers of bone resorption [C-telopeptide (CTX) and N-telopeptide (NTX)] were also elevated by 17.8% (SD 8.3) and 28.7% (SD 14.0) respectively, after one day of bed-rest in a similar group (3).

The normal rate of bone loss in healthy men and women aged over 60 years is approximately 1% per year (6, 7) (8). Peak BMD is reached at approximately 30 years of age (23), after cessation of bone longitudinal growth. Bone adapts its structural and material properties in response to its loading environment, helping to maintain bone strength (24). Loads on bone can be generated by ground reaction forces and muscle activity. Immobility decreases loads and thus contributes to loss of bone mineralization and causes micro-architectural deterioration through increased bone resorption (removal of bone) (23). Conversely, mechanical loading on bone can contribute to maintenance of bone strength by maintaining bone mass, and vigorous high-impact loading may have a small capacity to increase bone mass (23). Some evidence exists that supports the role of physical activity in maintaining or improving BMD in healthy women and men aged over 60 years, in whom bone loss is occurring (25, 26). High-impact loading exercise has a modest, positive, site-specific effect in healthy postmenopausal women, primarily enhancing cortical, rather than trabecular, bone mass and geometry (27). Following a stroke, physical activity can improve mobility, function (28), muscle strength (29) and fitness (30), so it is plausible that skeletal benefits can be achieved with physical activity after stroke.

Given that bone loss and fracture risk post stroke is pronounced, and physical activity in healthy older adults appears to have the potential to slow bone loss, we aimed to review the evidence regarding the skeletal effects of physical activity in stroke affected adults. Separate evaluations

of physical activity after stroke is needed, since the generalizability of results from studies with healthy older adults to individuals with stroke may be limited due to mobility limitations (16), and muscle composition and neuro-vascular changes (31, 32) that occur secondary to stroke. Additionally, there is emerging evidence regarding the hypothalamic control of bone modeling, which may be disrupted after stroke (REF).

METHODS

A methodology of systematic review was devised, in order to retrieve all available trials which used physical activity as an intervention in stroke patients and included bone related outcomes.

Inclusion and exclusion criteria

Inclusion criteria were participants with a history of stroke of any type and duration. We sought all prospective trials that included physical activity interventions and bone related outcome measures. Physical activity was defined as any volitional body movement, with or without assistance from another person, or device. This included, but was not limited to, walking, standing, weight bearing, active assisted limb movement, muscle strengthening, and fitness training. Any intensity or duration of intervention was included. Outcomes of interest included BMD, bone mineral content (BMC), bone structural properties: total cross sectional area, cortical thickness, bone strength: polar stress strain index (p-SSI) and compression bone strength index (cBSI), fracture risk, and biochemical markers of bone resorption or formation. Adverse events were also noted.

Search strategy

The following electronic databases were searched up to November 2010: Medline, Amed, Ageline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Embase, Physiotherapy Evidence Database (PEDro), PsycINFO, Sport Discus and Web of Knowledge. The search strategy was broad, to ensure the maximum number of appropriate articles were identified. Keywords included 'stroke, neurology, physical activity, exercise, therapy, bone and osteoporosis'. Medical Subject Headings (MESH) and free text terms were used. There was no language restriction on the search. Reference lists of selected papers were hand searched and citation tracking was run on key authors and papers for additional references. Full search terms are available from the corresponding author. The inclusion criteria were applied to titles and abstracts of all identified articles, by the primary author. Full texts of articles were obtained when exclusion was not clearly indicated, and a second author (JB), more experienced in research methodology, was consulted to if it was unclear whether a citation met inclusion criteria.

Assessment of methodological quality and data analysis

All included trials were evaluated for methodological quality using the PEDro scale (33). Higher scores out of 10 indicate better quality. Effect sizes (ES) (Cohen's *d*) of outcomes for paretic and non- paretic limbs were calculated. Pooling of data was planned for studies with comparable outcome measures.

RESULTS

Study Characteristics

A total of 349 citations were identified from the search. The inclusion criteria were not met in 345 citations, predominantly due to the trials not including patients with stroke (n=314) or not reporting bone related outcomes (n= 14) (Figure 1). Two papers (34, 35) included participants from the same trial. Thus three trials of interest were identified and reviewed (34-37). Table 1 shows the main characteristics and PEDro scores of these studies.

RESULTS

All three trials included bone related outcomes, but the intervention program was specifically designed for skeletal benefits in only one study (36). Studies varied in mode and length of physical activity interventions, and are summarized in Table 1. In total, 95 community dwelling people with stroke with an average age of 63.8 years were included. Outcome measures identified were only related to bone mineralization or architecture. No measures of serum or urinary bone markers or fracture risk were reported. Five non-injurious falls during the intervention and one during the control program were reported (34). No other adverse events were reported. The methodological quality of the studies ranged from poor (37) to good (34, 35). The main methodological problems were that therapists and patients were not blind in trials, and outcome assessors were not blind in two trials (36, 37), potentially introducing bias.

Effect sizes were small, but tended to favour physical activity interventions for lower limb programs (Table 2). Statistically significant ($p<0.05$) differences in change scores between

intervention and control groups were observed for: paretic limb femoral neck BMD [0 (95% CI -0.02-0.01) v -0.02 (-0.03 to -0.01)] (35), mid-tibial cortical thickness at the 50% site (mean +/- SD = 0.4 +/- 2.2% v -0.9+/- 1.9 mm) (34, 36), and 66% site (0.1+/- 0.1 v 0.0 +/- 0.1 mm) (36), and distal tibia trabecular BMC (5.6 +/- 6.7 v -0.5 +/- 10.8 mg) (35). Pooling of effect sizes was not possible, as no studies reported data from the same skeletal site.

DISCUSSION

Despite well documented bone loss and increased fracture risk in people with stroke (15, 38), we found few studies investigating the skeletal effect of physical activity in this population. Although this review revealed that physical activity intervention in chronic stroke patients may maintain or improve BMD and cortical thickness at some sites on the paretic limb, effect sizes were small. Of the two trials (34-36) that reported small but significant improvements in bone outcomes with physical activity, only one intervention (36) was designed specifically to reduce bone loss. The positive finding from this trial is promising, as skeletal benefits were observed in an intervention program which included weight bearing and muscle strengthening, but was not initially designed for skeletal outcomes. The clinical relevance of results however, needs consideration. The 'least significant change' is the least amount of change between two measurements required to consider differences to be true with 95% confidence (39), and relates to the error margin of bone scanning equipment. Therefore, if observed differences are less than the least significant change, the validity and clinical significance of results remain uncertain. While promising, these results require confirmation in larger, well designed trials, with primary outcomes that are specifically bone related. The trials included in this review involved subjects with the average age of about 60 years, which is younger than the average age (75) of people

who sustain stroke (REF XX). In addition, with bone loss appearing to occur early after stroke, the full skeletal impact of physical activity is unlikely to be observed in studies of people after one year post-stroke. Studies of bone loss in the acute stage of stroke are required to determine the timing and magnitude of initial bone loss. This information will inform the development of early intervention studies which compare current rehabilitation practices with targeted physical activity interventions aimed at stemming expected early loss of bone after stroke.

In the design of physical activity trials to improve bone in people with stroke, interventions should be based on exercise principles that are likely or proven to provide a skeletal benefit. Improvements to bone strength from interventions result mainly from reduced endosteal bone resorption (removal of bone from the inner surface) relative to controls (40), and perhaps through small amounts of periosteal apposition (addition of bone to the outer surface) that occur throughout ageing (41). The timing of interventions is of importance, when seeking to reduce bone loss. As previously described, reduced loads (for example, from sudden immobilization) on bone induces increased bone resorption. This supports the assertion that mobility training from early after stroke may reduce bone loss after immobilization from stroke {Jorgensen, 2000 #400}. Components of physical activity that can prevent bone loss include loading specific skeletal sites with short bouts of weight bearing movements (42), and strengthening of muscles connected to skeletal sites which are most susceptible to osteoporotic fracture (e.g. hip, wrist, spine) (43). Physical activity programs may need to be individualized for people with stroke, taking into consideration their mobility, function, and risk of falls. Tools are available to assess fracture risk prior to commencement of programs as an aid to maximize participant safety (44) and these too should be considered in trials. Additionally, location of care may contribute to

skeletal outcomes after stroke. Designated stroke units which aim to provide early mobilization have been demonstrated improved patient outcomes. Therefore, early transfer of patients to such units may positively impact on skeletal outcomes, if early mobilization is in fact, able to modulate bone loss. Other modifiable lifestyle habits known to influence bone should also be considered – for example, smoking, diet, and sunlight exposure.

Due to the heightened risk of falls, and the fact that half of the people who have a stroke are aged over 75 (REF XX) and are likely to have pre-existing age related bone loss and other co-morbidities, high impact exercises may not be appropriate for all people with stroke. However, skeletal benefits can be achieved provided the mechanical loads imposed on the skeleton are greater than the habitual load at that skeletal site. For example, any form of upright weight bearing movement imposes a greater load than bed rest. The osteogenic index [OI= peak ground reaction force (GRF) (in body weight) x (number of repetitions per minute + 1)] of a series of weight bearing exercises has been calculated to determine skeletal loading of paretic limbs for people with stroke (45). Walking at the individual's maximal speed and stepping up onto a 6 inch step with the non-paretic leg had the highest OI for people with mild to moderate leg motor impairments, and stepping up had the highest OI for people with more severe impairments (45). Therefore, physical activity which incorporate stepping up and brisk walking, with or without leg muscle strengthening, may be suitable to help minimize bone loss at the lower limbs. Safety measures may include one-to-one supervision, use of safety harnesses and hip protectors, and modification of equipment (e.g, hand and foot straps to maintain limb position).

There are many outcome measures available for studies of the skeletal effect of physical activity. Blood and urine markers can detect differences in bone turnover within days of immobility and thus can be used to investigate short and long term skeletal benefits of interventions aimed at reducing bone loss and fracture risk in stroke patients. Bone strength and fracture risk is largely determined by its structure (46), and can be estimated using quantitative computed tomography (qCT). Changes in bone structure and mass can be observed with qCT, even when dual energy x-ray absorptiometry (DXA) results of two dimensional assessment of BMD are unremarkable (27). However, qCT involves exposure to large doses of radiation. Peripheral qCT (PqCT) can be used at distal skeletal sites (i.e. wrist and ankle). It involves radiation exposure similar to that of DXA, so may be appropriate for large scale use to assess the efficacy of physical activity in reducing bone loss in stroke patients. However, skeletal outcomes cannot be accurately obtained in all patients after stroke, due to impairments such as muscle tremor and spasticity causing involuntary limb movements, which affect the image quality and validity of scans.

The timing of outcome measurement is crucial in the assessment of skeletal changes after stroke. Given that elevated bone resorption appears to be rapid and immediate, measurements of bone metabolic markers from very early after stroke are warranted, and can be easily achieved from serum or urine samples. Bone remodeling takes at least 23 weeks for primary mineralization and potentially 30 months for secondary mineralization to be completed (47), so repeat measurements of bone structure or mineral density may be measured up to this time to determine the efficacy of physical activity interventions on bone.

CONCLUSION

The negative skeletal effect of immobility after stroke appears to be rapid and pronounced, and fracture risk post stroke increases up to four fold. There are limited studies examining the effect of physical activity in maintaining or improving bone density and bone structure on the paretic side in chronic stroke patients, and no long term studies of reduced fracture risk were identified through this review. Quality studies are required to investigate the effect of targeted physical activity interventions to minimize the early and rapid loss of bone mineral and deterioration of bone structure after stroke. The type, quantity and timing of physical activity appropriate for patients early after stroke needs further investigation. If accelerated bone loss in the early post stroke period can be prevented or minimized, fracture risk is reduced, thus reducing the likelihood of fracture related mortality, morbidity and quality of life.

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