Changes to volumetric bone mineral density and structure after stroke: a prospective study

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Abstract

Rationale and aim: Stroke survivors experience accelerated bone loss and increased fracture risk, particularly in paretic limbs. Understanding how these changes unfold and their relationship to stroke severity and physical activity could help us develop targeted interventions to prevent or reduce the severity of these outcomes. The primary aim of this study is to investigate the time course and magnitude of changes in bone structure and mineral density within the first year after stroke, and to examine the relationship between these factors and physical activity and motor recovery.

Design: Prospective, observational study of 43 non-diabetic, non-ambulant adults with first ever hemispheric stroke.

Primary outcome: Total volumetric bone mineral density (vBMD) of paretic and non-paretic distal tibiae (4% bone length site) using high-resolution peripheral quantitative computed tomography (HR-pQCT).

Secondary outcomes: Cortical and trabecular vBMD, cortical thickness, total and cross sectional area of distal tibiae and radii of paretic and non-paretic limbs. Total body and regional BMD derived using dual-energy X-ray absorptiometry (DXA), physical activity measured using accelerometry, and motor recovery (Chedoke McMaster Stroke Assessment).

Discussion: Measuring the timing and magnitude of changes to bone structure and volumetric mineral density, from immediately after stroke, and relationships between these changes with physical activity and motor recovery will provide the basis for targeted interventions to skeletal outcomes for stroke survivors.

Introduction

The reduction of bone mineral density (BMD) is accelerated in adults within one year of stroke, predominantly on the hemiparetic side [1]. This exaggerated bone loss partially accounts for an up to seven-fold increase in fracture risk compared with age-matched controls [2-3], with most post-stroke fractures occurring at the hip [4]. Impaired mobility and prolonged immobilisation [5], motor impairment [6], muscle weakness [7], and reduced cardiovascular fitness [8] after stroke are associated with increased rates of bone loss.

Previous research of skeletal change after stroke has predominantly utilised dual energy X-ray absorptiometry (DXA) estimates of areal BMD (grams per square centimetre) as a surrogate measure of bone strength. Authors of longitudinal studies [5, 9-11] have reported greater reduction of BMD in paretic compared to non-paretic upper and lower limbs, particularly for people unable to walk after stroke. Peripheral computed quantitative tomography (pQCT) which can separately examine cortical and trabecular components of three-dimensional bone density and geometry has been utilised more recently in studies of paretic and non-paretic limbs after stroke [9, 12]. Lazoura et al [9] observed a reduction in a group's mean values of trabecular and cortical volumetric BMD between three and 12 months after stroke, however significance levels and confidence intervals of data were not reported. Pang et al [13] observed lower cortical bone areas, cortical bone mineral contents and cortical thicknesses in paretic legs compared to non-paretic legs at the site of 30% of tibia length (primarily cortical bone) in a cross-sectional study of people more than a year post-stroke. Little more is known about the rate of change in cortical and trabecular bone components after stroke, and the relationship between longitudinal bone loss to physical activity has not been explored.

Other common issues following stroke are loss of muscle mass [14], hyperglycemia and impaired insulin and glucose metabolism [15-17]. Acute hyperglycemia predicts increased risk of in-hospital mortality after ischemic stroke in non-diabetic patients and an increased risk of poor functional recovery in non-diabetic stroke survivors [16-17]. Bone loss and changes in insulin and glucose metabolism after stroke share some common risk factors. Indeed, type 2 diabetes is associated with increased fracture risk

[18]. Glucose metabolism after stroke is influenced not only by diabetes (diagnosed or undiagnosed) or an acute physiological 'stress response', but also site of brain lesion [19], muscle loss [14] and intramuscular changes [20]. There is increased awareness that a complex interaction between bone and glucose metabolic processes exist [21] and the role of the brain and neural processes in regulation of bone formation [21-22], however current understanding of this relationship is in its infancy.

Extended periods of bed rest and inactivity are detrimental to bone, muscle and glucose metabolism [23], and it is well known that hospitalised stroke patients (acute or rehabilitation) spend much of the day resting in bed [24]. Physical activity after stroke may help reduce these detrimental skeletal [25] and metabolic sequelae [26] in people with chronic stroke but we know little about the relationship between physical activity and skeletal changes immediately after stroke. Recent systematic reviews [14, 27] of skeletal [27] and muscular [14] changes after stroke recommended high-quality longitudinal studies be undertaken to measure the timing and magnitude of changes in bone density and body composition and to investigate relationships with glucose metabolism from very early after stroke.

In this present longitudinal study we seek to further understand the acute and prolonged post-stroke changes that occur in vBMD and structure and their relationships with physical activity and motor recovery. We will utilise high resolution pQCT which will provide high resolution, low radiation imaging of bone. Paretic and non-paretic upper and lower limbs will be assessed within two weeks of stroke and at specified times thereafter, and activity monitoring will be undertaken at each time point. It is hypothesised that within six months of stroke, vBMD will decline more in paretic limbs compared to non-paretic limbs. Other pre-specified data will be collected in order to explore relationships between bone, muscle and insulin and glucose metabolism after stroke, to inform future studies.

Methods

Design

This is a single centre, prospective observational study. A pilot study (n=10) was undertaken to determine feasibility and estimate the effect size of tibial vBMD (primary outcome). In the present study, participants will be assessed within two weeks of stroke (T1), one month after T1, then at three, six and 12 months after stroke. The primary outcome is change in difference between paretic and non-paretic tibial vBMD, between baseline and six months.

The study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000123842). Ethics approval was granted by Austin Health and LaTrobe University Human Research Ethics Committees.

Study Population

Adults over the age of 40 years who are admitted to the Austin Hospital stroke unit (Heidelberg, Australia) within one week of hemispheric stroke onset, who are medically stable, unable to ambulate and able to follow simple verbal commands will be eligible. Exclusion criteria are known diabetes, history of stroke or other neurological disease, other conditions significantly limiting function (e.g. limb amputation) or use of medication known to alter bone metabolism (e.g. bisphosphonates).

Pre-specified measures

Demographics (age, gender, marital status, living arrangements, education level, smoking status), stroke characteristics (stroke severity via National Institute of Health Stroke Scale: NIHSS and stroke classification via Oxfordshire Classification), and past medical history including falls and previous bone fractures will be recorded.

Outcomes

Primary outcome

Total vBMD will be measured at the left and right distal tibiae using HR-pQCT (Xtreme CT, Scanco Medical AG, Brüttisellen, Switzerland). Measurements will be at baseline and at six monthly intervals at the standardised site of 4% of bone length measured from the distal end; a region containing both trabecular and cortical bone.

Reliability of this measure, commonly expressed as coefficient of variation (CV), is 1.3% [28]. Volumetric BMD at the distal tibia site discriminates between healthy postmenopausal women with and without hip fractures [29]. Scans cannot be undertaken if metal is within the scanning region. Images will be excluded if movement occurs during scanning.

Secondary outcomes

Trabecular and cortical bone density and structure: vBMD (cortical and trabecular), cortical thickness, and total and cortical cross sectional area will be measured at the left and right distal tibiae (4% site) and distal radii using HR-pQCT. Trabecular number, thickness and separation will be derived. CV for these parameters ranges from 0.7% to 4.4% [28]. Compressive bone strength index (cBSI, g^2/cm^4) will be calculated; cBSI: Total area × total $vBMD^2$ [30].

Areal bone mineral density and body composition: Total body and regional BMD, and lean and fat mass will be determined using DXA (DPX-L, version 1.3z: Lunar Madison, WI), CV = 1 – 1.2% [31]. All scans will be performed by the same technician using the same scanner for consecutive assessments.

Physical activity will be measured using a single-axis accelerometer with switch tilt, sample rate 10Hz (PAL2, positional activity logger 2, Gorman ProMed Pty Ltd, Melbourne, Australia) [32]. PAL2 registers the number of changes in position and the amount of time that participants spend lying down, sitting, standing and walking. There is high agreement between PAL2 recordings and labour intensive "gold standard" behavioural mapping [33]. Physical activity is consistent across days in acute stroke patients [34]. The device will be worn for one day from 8am to 5pm, representing the most active part of the day [35].

Motor impairment: the Chedoke McMaster Stroke Assessment will be used to evaluate the severity of motor impairment in stroke affected upper and lower limbs [36].

Exploratory measures

To allow for future exploration of links between bone formation and glucose metabolism the following additional measures will be included:

Fasting blood samples will be taken before 9am, and will be batch analysed:

1. *Glucose metabolism:* fasting glucose and insulin concentrations will be measured. Insulin sensitivity will be calculated using the homeostasis model assessment (HOMA) index [37]. Two hour 75 gram oral glucose tolerance test (OGTT) will be performed to observe changes in glucose metabolism over time. Glycated haemoglobin (HbA_{1c}) will be measured to identify the average plasma glucose concentration during the preceding three months. Plasma glucose level will be measured using a hexokinase assay on the Roche Cobas 702. Insulin will be measured by electrochemiluniscence immunoassay (ECLIA) on the Roche Cobas 602. HbA1C will be measured by immunoassay on the Roche Integra 800.

2. *Bone formation and resorption markers* will be measured to observe changes in bone turnover. Formation markers: Osteocalcin, N-terminal propeptide of type 1 procollagen (PINP); and resorption marker: serum C terminal telopeptide of types 1 collagen (CTX) will be determined by electrochemiluminenescence immunoassay (Elecsys 1010 Analytics, Roche Diagnostics, Germany, intra- and inter-assay CV 3–8%) [38].

Sample size

The pilot phase of this study (n=10) was used to estimate effect size. Assuming one sample, 2-tailed test with criterion for significance of p=0.05, and using the difference in six-month change between paretic and non-paretic limbs in distal tibia vBMD [paretic limb = -1.43%, SD 1.92, non-paretic limb = -0.45%, SD 1.37; effect size 0.59], a sample size of 25 participants will provide 80% power to detect a significant effect if present. Adjusting for expected mortality of 30% within the first year of stroke [39], 33 participants are required. Data from the pilot phase will be pooled with results of the present study, thus reporting a total sample size of 43.

Statistical analysis

Comparison of change in paretic and non-paretic limbs will be assessed using a one sample t-test, subject to the validity distribution assumptions, to compare difference in change over time between paretic and non-paretic limb total tibia vBMD. Multilevel analysis with patient as a level will be undertaken to model change over time in primary and secondary outcomes using random effects generalised least squares regression and/ or generalised estimating equations. Additionally, the relationships between primary outcomes and covariates (i.e. physical activity, motor recovery, muscle mass) will be assessed using linear regression, adjusting for gender, age and initial stroke severity. Participants act as their own control between paretic and non-paretic limbs, those with missing data will be excluded from analysis. This will not affect internal validity, but will affect generalisability of results. Statistical analysis will be performed using Stata statistical software. A significance level of 0.05 will be set for all statistical tests.

Summary

Bone fracture is a common and serious sequelae following stroke. High resolution pQCT will be utilised for the first time in this study to prospectively examine changes in vBMD and bone structure of tibiae and radii from within two weeks of stroke. Relationships to physical activity and motor recovery will be investigated. Total body and regional muscle mass derived from DXA, indices of insulin and glucose metabolism and blood markers of bone turnover will be assessed concomitantly in order to inform future studies. Knowledge of interactions between these factors from early after stroke will provide scientific evidence to develop specific and targeted rehabilitation programs, in order to improve quality of life and health outcomes of stroke survivors.

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Table 1: Time points of participant assessment

Outcome Measure	Baseline*	1 month	3 month	6 month	12 month
HR-PqCT	✓	x	x	✓	✓
DXA	✓	✓	✓	✓	✓
Activity monitoring	✓	✓	✓	✓	✓
OGTT	✓	x	x	✓	✓
Fasting glucose, insulin & bone turnover markers	✓	✓	✓	✓	✓
HbA1c	✓	x	✓	✓	✓
Physical assessment	✓	✓	✓	✓	✓

*Within two weeks of stroke; DXA = dual energy X-ray absorptiometry; HbA1c= glycated haemoglobin; HR-pQCT = high resolution peripheral computed tomography; OGTT = two hour oral glucose tolerance test