A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a peripheral quantitative computed tomography study

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Abstract

Introduction and Hypothesis—Regular skeletal-loading exercise is an effective intervention to improve bone health in older individuals. However, little is known about the bone responses to exercise in people with stroke. Following a stroke, muscle atrophy and bone loss occurs. Diminished areal bone mineral density combined with an increased number of falls substantially enhances the risk for a fragility fracture. We undertook a randomized controlled intervention trial to assess the impact of a 19-week comprehensive exercise program on lower extremity bone health in people with chronic stroke.

Methods—Sixty-three community-dwelling individuals with chronic stroke were randomly allocated to either an intervention group or a control group. The intervention group participated in a 19-week thrice-weekly exercise program consisting of skeletal-loading, aerobic, strengthening and balance exercises. The control group completed a seated upper extremity exercise program. We used peripheral quantitative computed tomography (pQCT) to measure bone geometry and volumetric bone mineral density at the distal 4% and midshaft 50% of the tibia before and after the intervention.

Results—Following the exercise program, the intervention group had significantly more percent gain in trabecular bone content at the 4% site on the paretic side than the control group ($p=0.048$). At the 50% site on the paretic side, the intervention group also had significantly greater percent gain in cortical thickness ($p=0.026$) but not the polar stress strain index (p-SSI) when compared with the control group. However, no significant between-group difference was found in trabecular bone density (4% site) and cortical bone density (50% site) percent gain on the paretic side. No significant changes were observed in any variables on the non-paretic side at the 4% or 50% site.

Conclusions—This study provided some evidence that the 19-week comprehensive exercise program could have a positive impact on bone parameters at the tibia for individuals with chronic stroke. However, a larger randomized controlled trial is required in the future to assess the impact of exercise on lower extremity bone health in the stroke population.

Keywords

Cerebrovascular accident; bone health; physical activity; rehabilitation; peripheral quantitative computed tomography

Introduction

Within the first three years following a stroke, approximately 5% of stroke survivors sustain a hip fracture [1,2]. Impaired balance, muscle weakness and spasticity that occur after a stroke can lead to reduced mobility [3,4] with a risk of disuse of the paretic leg during functional activities [5,6,7]. These impairments can result in muscle atrophy and may compromise bone health [8,9,10] and can contribute to the increased risk for fragility fracture observed in this population [1,2,11].

Areal bone mineral density (BMD, g/cm^2), as measured by dual-energy X-ray absorptiometry (DXA), is consistently lower in the paretic extremity compared with the non-paretic extremity. Specifically, previous cross-sectional studies have shown significant side-to-side differences in BMD at the femoral neck [6,12,13,14,15,16], trochanter [6,13], proximal femur [9], and total femur [9,13]. Prospective observational studies have reported a 12% decrease in proximal femur BMD and a 3% decrease in lean mass of the paretic leg within 1-year after stroke [8,9].

Compromised bone health and increased number of injurious falls contribute to the enhanced risk of fragility fractures in the stroke population compared with aged-matched healthy individuals (i.e. >7 fold) [1]. The majority of fragility fractures occur on the paretic side [16] and lower extremity fractures account for more than 40% of all fractures in the stroke population [2,16]. Mechanical loading is essential to maintain bone mineral [17]. Regular skeletal-loading exercise is an effective intervention to improve bone health in older healthy individuals [18,19,20,21,22]. However, little is known about the response of bone geometry to exercise in people with stroke.

Most previous investigations to evaluate bone health in older adult populations have used DXA to assess bone mass, but the planar nature of this instrument makes it unable to assess bone geometry or to separate cortical from trabecular bone compartments [23,24]. In

contrast, peripheral quantitative computed tomography (pQCT) is capable of analyzing cortical and trabecular bone separately, can evaluate bone geometry and provides an estimate of volumetric BMD (mg/cm^3). To our knowledge, no study has investigated the effect of an exercise intervention on lower extremity bone geometry in a stroke population using pQCT.

We sought to establish the efficacy of physical activity as a treatment strategy to reduce the risk of fragility fractures in people after a stroke. To achieve this, we conducted a randomized controlled trial to examine the effects of a 19-week comprehensive exercise program on bone parameters in a chronic stroke population. The efficacy of the program on physical outcomes such as cardiorespiratory fitness, mobility, balance, and leg muscle strength has been reported elsewhere [25]. Our primary objective was to investigate the effect of the same exercise intervention on the geometry and volumetric BMD of the cortical and trabecular bone compartments using pQCT in people with chronic stroke.

Materials and Methods

Participants

We recruited community-dwelling individuals who were living with the residual effects of a stroke longer than 1 year. The study flow chart is presented in Figure 1. A total of 187 individuals expressed interest in the study. These people were first screened by a telephone interview and had to fulfill entry criteria. The inclusion criteria were: (1) sustained only one stroke, (2) in chronic stage of stroke recovery (i.e. stroke onset $\geq$ 1 year), (3) independent in walking with or without an assistive device, (4) age 50 years or older, (5) living at home (i.e. not institutionalized) (6) a Folstein Mini Mental Status Examination (MMSE) score $\geq$ 22 [26] and able to pedal a stationary cycling ergometer. Exclusion criteria included: (1) coexisting other neurological conditions, (2) significant musculoskeletal conditions that excluded them from exercise training, (3) unstable cardiovascular disease. Seventy-seven individuals fulfilled the entry criteria.

Baseline Characteristics

Participants were instructed to pedal a cycle ergometer (Excaliber; Lode B.V. Medical Technology; Groningen, Netherlands) with a progressive increase in the workload. Those with a heart rate of 60% of age-predicted heart rate maximum were invited to participate in the study. This ensured that participants were able to complete a cardiopulmonary stress test and to meet the cardiovascular demands of the intervention. On a separate day, each enrolled participant underwent a maximal exercise test on the cycle ergometer. During the maximal exercise test, the participant wore a mask and oxygen consumption was measured by a portable metabolic unit (Cosmed K4 b² system; COSMED Srl; Rome, Italy). The participant was required to pedal at 60 revolutions per minute (rpm) and resistance was gradually increased as the test progressed. The individual would continue to pedal the cycle ergometer until he or she was unable to maintain a cycling rate of 60rpm. The peak oxygen consumption rate at the end of the test represented cardiopulmonary fitness.

Sixty-three people fulfilled all entry criteria and participated in the trial. Eligible participants gave informed, written consent to participate in the study. Each participant's physician

confirmed the presence of stroke and the inclusion/exclusion criteria. The study was approved by the local university and hospital ethics review boards. The study was conducted according to the Helsinki Declaration for human experiments [27]. All enrolled participants were classified according to the functional classification level of the American Heart Association Stroke Outcome Classification [28]. Each participant was rated according to their ability to perform basic activities of daily living (BADLs, e.g. bathing, feeding, climbing stairs, dressing) and instrumental activities of daily living (e.g. shopping, handling finances, preparing meals) (Level I: Independent in BADLs and IADLs; Level II: Independent in BADLs but partially dependent in routine IADLs; Level III: dependent in IADLs and less than 3 areas of BADLs; Level IV: dependent in 3 or more areas of BADLs; Level V: dependent in 5 or more areas of BADLs).

Study Design

This was a prospective, single-blind, randomized controlled intervention trial. Participants were stratified by gender to ensure approximately equal numbers of men and women between the intervention and control groups. All participants were randomly assigned to the intervention or control group by drawing ballots marked “I” (intervention) or “C” (control). Thirty-two and 31 individuals were assigned to the intervention and control groups, respectively. The randomization was carried out by an individual who was not involved in any of the outcome assessment procedures. The research personnel who performed the outcome assessments (e.g. physical measures, bone imaging) were blinded to group assignment. Participants were not blinded to group assignment. Participants were instructed not to tell the assessors about the group assignment or the intervention they received.

Intervention

The intervention group participated in an intensive exercise program for 19 weeks (1-hour sessions, 3 sessions per week) in a multi-purpose room of a community hall. The exercise program was designed to enhance lower extremity bone strength in addition to aerobic fitness and balance. The program was comprised of three different exercise stations that provided a variety of weight-bearing activities to load the lower extremities and enhance bone strength. At *Station 1*, participants rotated through three different exercise stations. In the first station, participants were engaged in aerobic exercise training including weight-bearing functional activities such as brisk walking, repeated sit-to-stand, and alternate stepping onto low risers. The duration of aerobic training was initially 10 minutes of continuous exercise, increasing by increments of 5 minutes every week up to 30 minutes of continuous exercise as tolerated. Exercise intensity was set at 40–50% heart rate reserve (HRR) and increased by 10% HRR every 4 weeks, up to 70–80% HRR, as tolerated. The participant wore a heart rate monitor (Polar A3, Polar Electro Inc., Woodbury, NY, USA) and was instructed to exercise within the set target heart rate zone. At *Station 2*, participants completed different static and dynamic balance exercises during weight-bearing, such as standing on a balance disc (33 cm in diameter and 6 cm in height) or a tilting board (40cm in length × 37.5 cm in width × 7.5 cm in height) (Fitter International Inc., Calgary, Canada), tandem walking, walking in different directions, and kicking a ball with either foot. *Station 3* consisted of functional exercises to promote leg loading and improve muscle strength. These included partial squats and toe rises while holding hand weights. As the training program

progressed, the amount of lower extremity loading was increased by increasing the height of the riser, changing from bilateral to unilateral toe rises and reducing arm support. The details of the intervention exercise program are outlined in Table 1. Each participant in the intervention group wore a hip protector (SAFEHIP, Tutex, Denmark) during each session.

The control group completed a seated upper extremity exercise program for the same duration (1-hour sessions, 3 sessions a week for 19 weeks) in the same multi-purpose room at different times of the day. The program consisted of upper extremity muscle strengthening exercises, passive or self-assisted range of motion exercises, and functional training (i.e. picking up objects of various shapes and sizes, playing cards). For participants with less than 20 degrees of active wrist extension, electrical stimulation (Neurotrac Sports, Verity Medical Ltd., Hampshire, England) to the wrist extensor muscles was applied (Frequency: 100Hz; pulse duration: 150µs; ON time: 10 seconds; OFF time: 10 seconds; ramp: 1 second; treatment time: 10–15 minutes). This protocol was based on a pre-set program designed by the manufacturer (Neurotrac Sports, Verity Medical Ltd., Hampshire, England). In individuals with stroke, weakness in wrist extensors is common and often accompanied by spasticity in the wrist and finger flexors. Stimulation to the antagonist muscles (wrist extensors) to the spastic muscles may be beneficial in maintaining wrist extension range of motion. No specific leg skeletal-loading or muscle strengthening exercises were provided to this group. For both intervention and control groups, each exercise session (9–12 participants) was supervised by a physical therapist, an occupational therapist and an exercise instructor. The specific exercises completed in each session were recorded.

Outcome Measurements

For all participants, we undertook standard measurement of height to the nearest millimeter with a customized wall-mounted stadiometer (Seca Model # 242, Hanover, MD). We assessed body weight with an electronic scale to the nearest 0.1kg. All of the following assessments were performed 1–2 weeks before the commencement of the intervention program and again within 1–2 weeks after the termination of the program.

Peripheral Quantitative Computed Tomography—We excluded participants if they had any metal in the portion of the limb within the imaging field. We also excluded participants who had any obvious tremor or were unable to comfortably position the limb into the XCT gantry opening. We measured participants' bilateral tibiae using peripheral quantitative computed tomography (pQCT; Stratec Medizintechnik XCT 2000; software version 5.50; Pforzheim, Germany). All participants were seated comfortably in a chair adjacent to the pQCT gantry. A custom-built tray designed to support the limb. We obtained a scout view and positioned the anatomical reference line at the distal medial edge of the tibia. We measured tibial length (mm) as recommended by the manufacturer and obtained one 2.5 mm scan at the 4% and another acquired at 50% site of the tibia, bilaterally. This was done to ensure consistency in regional sites. Scan acquisition resulted in an in-plane pixel size of 300 microns and slice thickness of 2.5 mm. All pQCT scans were acquired by the same operator.

At the 4% site, we measured total bone area ($\text{Area}_{\text{total}}$, mm^2), and trabecular area ($\text{Area}_{\text{trab}}$, mm^2), trabecular bone mineral content (BMC_{trab} , mg), and trabecular bone mineral density (BMD_{trab} , mg/cm^3). At the 50% sites, we measured total bone area ($\text{Area}_{\text{total}}$, mm^2), cortical bone area ($\text{Area}_{\text{cort}}$, mm^2), cortical bone mineral content (BMC_{cort} , mg), cortical bone mineral density (BMD_{cort} , mg/cm^3), cortical thickness (mm), and Polar Stress-Strain Index (p-SSI, mm^3).

At all sites, we used XCT v.5.50 software and CALCB Contour (outer edge-detection) Mode 3 and Peel Mode 2 and CORTBD Mode 4. For the 4% site, we used an outer threshold/inner threshold of 169/400 mg/cm^3 . For edge detection and cortical bone analysis at the 50% site, we analyzed all scans using 710/710 mg/cm^3 thresholds. These particular thresholds were chosen based on the experiences drawn from our previous research [29], the default thresholding recommended by the manufacturer and consultation with an independent pQCT technician. The coefficients of variation (CV) for the pQCT scanner at our lab for acquiring images in vivo at the distal tibia were 0.59% and 0.58% for total bone mineral content and total bone mineral density, respectively. At the proximal tibia, the CV for BMD_{cort} and p-SSI were 0.46% and 1.12%, respectively [30].

Physical Activity Level—Habitual physical activity was measured by Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) [31]. It contained 13 items that assessed participation in physical activities of different intensities for the previous 7 days. A metabolic equivalent (MET) value was assigned to each activity and the maximal score was 199.5MET hour/day.

Statistical Analysis—Independent t-tests (for continuous variables) and chi-squares (for categorical variables) were used to compare the baseline variables between the two groups. First, data for men and women were analyzed separately. For each pQCT variable, percent change was obtained by subtracting the post-test value from the pre-test value divided by the pre-test value. The percent change scores were then compared between women and men participants using independent t-tests. Data were pooled if there was no statistically significant difference in percent change scores between men and women. For the pooled data, independent t-tests were used to compare the percent change scores between the intervention and control groups for all pQCT variables. The percent change scores for the two groups were also used to calculate the standardized effect size (SES) for each outcome variable. A SES of 0.2–0.5 was considered as small, 0.5–0.8 as medium, and 0.8 as large [32]. A sensitivity analysis was also performed and participants taking bone resorption inhibitors were excluded. Statistical analyses were performed using SPSS v.13 software (SPSS Inc.) using a significance level of 0.05 (2-tailed).

Results

Sixty-three (21 women) fulfilled all criteria and were enrolled (Figure 1). Thirty-two and 31 individuals were randomly assigned to the intervention and control groups, respectively. During the course of the program, two participants dropped out of the intervention group while one dropped out of the control group. Therefore, thirty participants in each group (a total of 60 participants) completed all baseline and follow-up assessments.

Exclusion of unsatisfactory pQCT scans

Two investigators reviewed each pQCT scan independently to ensure scan quality and included/excluded scans by consensus. For inclusion, the participant had to have good-quality scans obtained in both the baseline assessment and the follow-up assessment. For the 4% site, we excluded scans if there was tremor/movement/spasticity ($n=20$), if metal was present within the imaging field ($n=1$) or if participants had extremely low bone density at distal sites which made analysis impossible ($n=3$). Therefore, a total of 24 participants (12 participants in the intervention group and 12 participants in the control group) were excluded from the analysis of the 4% site data. At 50% site, we excluded those scans with obvious image artifacts that were the results of tremor/movement/spasticity ($n=8$ participants' scans, 4 participants in the intervention group and 4 participants in the control group). As a result, the total number of scans from participants included in the analysis was 36 (18 participants per group) for the 4% site and 52 (26 participants per group) for the 50% site.

Comparison of baseline characteristics

Participant characteristics are described in Table 2. In the 4% site sample (18 participants per group), there was no significant difference in demographics, functional capabilities, stroke and other characteristics between the intervention and control groups. The intervention group and control group attended $84\pm13\%$ and $85\pm15\%$ of the sessions, respectively. This difference was not statistically significant (independent t-test, $p=0.805$).

In the 50% site sample (26 participants per group, $n=52$), characteristics of the participants were similar between the intervention and the control groups (Table 2). The intervention group and the control group attended $86\pm13\%$ and $85\pm14\%$ of the sessions, respectively. This difference was not statistically significant (independent t-test, $p=0.921$).

No significant differences were found between participants who were included in data analysis and those who were excluded because of poor scan quality (Table 2).

Changes in outcomes

Separate analyses were conducted for women and men to examine the difference in percent change scores between the two sexes (Table 3). At the 4% site, there was no statistically significant difference between men and women for percent changes of any pQCT parameter. At the 50% site on the non-paretic side, women in the intervention group had a 2.6% decrease in p-SSI compared with men in the intervention group had a 0.5% increase. This difference was statistically significant ($p=0.02$). There were no other significant differences between sexes for percent change. Therefore, the data were pooled for subsequent analysis of treatment effect, with the exception of p-SSI.

Comparison between Groups at the 4% Site

Overall, pQCT changes at the 4% site in both the paretic and non-paretic side showed similar trends (Table 3). On the paretic side, the intervention group had a 5.6% increase in BMC_{trab} compared with a 0.5% decrease in the control group. This difference between groups was statistically significant ($P=0.048$). A similar trend was also found on the non-

paretic side. The intervention group had a 4.4% increase in BMC_{trab} and the control group demonstrated a 0.3% decrease. This difference did not reach statistical significance ($P=0.084$). On the paretic side, BMD_{trab} increased more in the intervention group than the control group but did not reach statistical significance ($p=0.14$).

Comparison between Groups at the 50% Site

At the 50% site (Table 4) on the paretic side, the intervention group had a slight increase in cortical thickness (0.4%) whereas the control group sustained a 0.9% decrease. The between-group difference (1.3%) was statistically significant ($P=0.026$). There was no between-group difference in other pQCT variables at the 50% site on either the paretic or non-paretic side.

A sensitivity analysis was performed to determine whether excluding those who were taking bone resorption inhibitors would affect the results at either the 4% or 50% sites. Two people in each of the intervention and control groups were excluded in this analysis. At the 50% site, there were no evident changes in the results. Percent change in cortical thickness on the paretic side continued to show a significant between-group difference ($p = 0.024$).

Physical Activity

The increase in the amount of physical activity during the course of the trial was similar between intervention and control groups. In the 4% site group, the percent change in physical activity score was not significantly different between intervention and control groups ($p=0.89$) (Table 4). Results were similar for those participants in the 50% site sample ($p = 0.78$) (Table 5).

Standardized effect size calculations

At the 4% site, the SESs for BMC_{trab} (paretic side = 0.68; non-paretic side = 0.59) and BMD_{trab} (paretic side = 0.49; non-paretic side = 0.42) were medium and small, respectively. Given the sample sizes (18 per group) and the SESs described above, the statistical power for the analysis of paretic BMC_{trab} , non-paretic BMC_{trab} , paretic BMD_{trab} and non-paretic BMD_{trab} was 0.51, 0.41, 0.30, and 0.23, respectively. We found a significant between-group difference in paretic BMC_{trab} ($p=0.048$), but not in the other three outcome variables (Table 4). The only significant between-group difference at the 50% site was the paretic cortical thickness percent change score ($p=0.026$) which had a small SES (0.45). Changes in paretic BMC_{cort} showed a small SES (0.35), but failed to reach statistical significance ($p=0.21$).

Adverse events

Five falls (4 participants) occurred in the intervention group, and most falls were low-impact. Three falls occurred while the participant was still holding onto a support while exercising (e.g. partial squats). One fall occurred while the participant was kicking a ball. One fall occurred when the participant was stepping down from 2-inch-thick foam. Both of these participants were being spotted and were able to recover independently immediately after the fall. One fall occurred in the control group while the participant was walking. No injuries were reported. Two participants in the arm group reported soreness in the shoulder

region on the paretic side during the first few weeks of exercise. The symptoms were alleviated after modifying the exercises by reducing the weight lifted.

Discussion

This novel study is the first to use pQCT to report the effect of exercise on bone health for men and women living with the residual effects of stroke. Our comprehensive exercise program was achievable for participants, and we observed an increase in BMC_{trab} at the distal site of the tibia and an increase in cortical thickness at the tibial shaft in those participants who undertook the exercise regime.

Individuals with chronic stroke often sustain impairments in many different areas (i.e. muscle weakness, poor balance, reduced aerobic fitness and mobility) that can contribute to bone loss. Therefore, we designed our exercise protocol to address these multiple impairments while promoting skeletal loading. For example, sit-to-stand, stepping onto risers, and walking were performed at a fast pace to train aerobic fitness and promote dynamic loading simultaneously. Fast-paced activities are important, since dynamic (i.e. high-frequency) loading is more effective in promoting osteogenesis than static loading [17]. As lean mass and muscle strength are related to bone density in the stroke population [10], we also incorporated strengthening exercises in a weight-bearing position (e.g. toe rises) to combine muscle strengthening and skeletal loading.

Since individuals with stroke tend to weight-bear less on the paretic side [6,33], it is important to choose activities that promote loading of the paretic side. For example, when stepping onto risers, the paretic leg is forced to bear the full body weight while the non-paretic leg steps up to the riser. Bohannon and Larkin [34] reported that once the non-paretic leg is in contact with a 17 cm height step, the paretic leg still bears 68% of body weight – much more than when standing on level ground (41% of body weight). Brisk walking is also a good leg-loading activity, as the peak ground reaction force rises above body weight and increases with gait velocity [35]. Overall, our intervention program aimed to promote more weight-bearing on the paretic limb. This focus may partially explain why we observed significant changes in the pQCT parameters on the paretic side only.

Osteogenesis also depends on exercise frequency [17]. According to the osteogenic index calculation proposed by Turner and Robling [17], increasing exercise frequency from 1 day per week to 3 days per week alone would more than double the osteogenic index. However, as this time commitment may be too demanding for the participants, we chose an exercise frequency of three 1-hour sessions per week to optimize bone health and encourage compliance.

We found a significant increase in BMC_{trab} in the intervention group at the 4% site (Table 4). Trabecular bone is thought to remodel faster than cortical bone [36] and may explain why we observed greater changes in trabecular bone. The only other study that observed this response was by Rubin and coworkers; they noted a similar phenomenon with cortical and trabecular bone response in the tibia using vibration in young children with cerebral palsy [37]. In their investigation, vibration had an anabolic effect on trabecular bone but no effect

on cortical bone. We did not find a significant between-group difference in BMD_{trab} percent gain ($p=0.14$), despite the increase in BMC_{trab} . One of the explanations is insufficient power. The number of participants required to detect a significant difference in non-paretic BMC_{trab} , paretic BMD_{trab} , and non-paretic BMD_{trab} would be 94, 134, and 180, respectively. Another plausible explanation relates to technical issues. We used an outer threshold\inner threshold of 169\400 mg/cm^3 to define trabecular bone. The increase in BMC_{trab} in the intervention group could simply be caused by an increase in $Area_{trab}$ as we analyzed BMC in a region of interest (ROI) that may have varied slightly in location. The increase in $Area_{trab}$ may be due to a small shift of the border between trabecular and cortical bone. For example, $Area_{trab}$ increased from 1021 mm^2 to 1058 mm^2 in the intervention group after the 19-week exercise program (Table 4). If a circular diameter is assumed (πr^2), the corresponding radii would be 18.03mm and 18.36mm, respectively. The difference in radius between the two measurements is thus 0.33mm (i.e. 330 microns), which is close to the spatial resolution of the system. Therefore, in addition to lack of statistical power, these technical issues may explain our results at the 4% site.

At the 50% site, we note a significant between-group difference of 1.3% in percent change for cortical thickness on the paretic side. It is of note that the significant change in cortical thickness is not accompanied by a significant change in p-SSI and $Area_{total}$. One explanation is endosteal apposition. However, another possible explanation is related to the aforementioned technical issues. The mean change in cortical thickness on the paretic side was 0.03mm and -0.04mm for the intervention and control group, respectively. These values are below the spatial resolution of the system (300 microns). The lack of change in other cortical parameters in our participants may also be due to the fact that our intervention program was only 5 months in duration and this may not be sufficient to induce changes in cortical bone. In addition, our study may be underpowered to detect a significant difference in the cortical parameters (Table 5). Power analysis showed that a total sample size of 260 and 1398 participants would be required to detect statistical significance in BMC_{cort} and p-SSI on the paretic side, respectively.

To our knowledge, only one study has investigated the effects of exercise intervention on pQCT measurements in the lower extremities and it reported positive results. Liu-Ambrose and coworkers [38] examined the effects of a 25-week agility exercise program on pQCT parameters in older women with low bone mass. The agility training program had no significant effect on BMC_{cort} at the 50% site of tibia but they observed a substantial reduction (1%) in $Area_{cort}$. This resulted in a significant 0.5% increase in BMD_{cort} , compared with a 0.4% loss in BMD_{cort} in the control group. The difference between these findings and our study may be due to the difference in study populations and exercise protocol.

It is possible that other factors such as bone resorption inhibitors, physical activity, and gender may have influenced the results. However, the randomized controlled design minimized the systematic bias due to these potentially confounding factors. The two groups had the same small number of participants who were taking bone resorption inhibitors (4 per group). The sensitivity analysis showed that if these participants were excluded, results did not significantly change. The amount of weekly physical activity (PASIPD) was similar

between groups at baseline and increased similarly during the course of the trial. Intervention and control groups had an approximately equal number of men and women; separate analysis showed no significant difference between the two sexes for any pQCT outcomes, except p-SSI. Therefore, these potentially confounding factors are unlikely to account for the results observed in this study.

We note several limitations in our study. First, this is the first report of using pQCT to investigate tibial bone changes in people after a stroke. We highlight the important descriptive information but we recognize that we were unable to collect pQCT data on all participants. This was either a result of participant movement within the pQCT gantry, limb tremor or spasticity that prevented proper positioning. Second, our participants were all independent ambulators, thus they represent those with a higher level of functioning within the chronic stroke population. Relatively mobile individuals, combined with insufficient statistical power, may explain why there was no statistically significant side-to-side difference in both trabecular (paired t-test, $p=0.061$) and cortical BMD measures ($p=0.665$) in our participants. Although this limits the generalizability of our results, the majority of stroke survivors would regain the ability to ambulate [39]. Third, although our exercise protocol was effective for improving certain pQCT parameters, it is possible that an exercise intervention of longer duration (6–12 months) may be more optimal to load the lower extremities. Fourth, the relationship between pQCT measurements and fracture risk is not known. For example, we do not know how the reported 5.6% increase in BMC_{trab} at the 4% tibial site on the paretic side would translate into a reduction in fracture risk. While we have identified specific bone changes following exercise intervention, the clinical importance of these changes is uncertain. Further study is required to examine the relationship between pQCT parameter changes and fracture risk. Finally, we designed our protocol to improve impairments in multiple systems (i.e. balance, strength, aerobic fitness and bone health), in an attempt to target key risk factors for fragility fractures; a more specific skeletal program that focuses on loading and strengthening lower extremity muscles might induce greater changes in pQCT parameters.

In summary, this 19-week exercise intervention aimed at improving bone health for people living with the residual effects of a stroke shows promise. This is the first study to assess bone with pQCT following a targeted exercise regime for people with living with the residual effects of a stroke. We noted a significant increase in BMC_{trab} at the 4% site and an increase in cortical thickness at the 50% site on the paretic side. Further research with a larger sample size is necessary to investigate the effectiveness of exercise intervention for improving bone health in community-dwelling people after a stroke.

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Figure 1.
Study Flow Chart

Table 1

Exercises provided to the intervention group.

Exercise	Protocol (week 1)	Protocol (week 13)	Progression protocol
Station 1: Cardiopulmonary fitness and mobility	<u>Duration:</u> Two 10-minute bouts of continuous exercise. <u>Intensity:</u> 40%–50% HRR	<u>Duration:</u> 30 minutes of continuous exercise. <u>Intensity:</u> 70%–80% HRR	<u>Duration:</u> Increment of 5 minutes of continuous exercise per week, up to 30 minutes as tolerated <u>Intensity:</u> increment of 10% HRR per 4 weeks, up to 70%–80% HRR, as tolerated.
Sit-stand			
Stepping onto risers			
Brisk walking			
Station 2: Balance	<u>Duration:</u> 10 minutes	<u>Duration:</u> 10 minutes	<u>Progressed by:</u> 1 1. Reducing arm support. 2 2. Increasing speed of movement
Tandem walking			
Weight-shifting in standing			
Other balance activities			
Station 3: Muscle strength	<u>Duration:</u> 10 minutes <u>Repetition:</u> 2 sets of 10	<u>Duration:</u> 10–15 minutes <u>Repetition:</u> 3 sets of 15	<u>Repetition:</u> increased up to 3 sets of 15 as tolerated.
Toe rises			
Partial squats			
Stepping onto risers while holding weights in hands			

The participants in the exercise group rotated through 3 exercise stations. The exercise protocol used at the beginning of the trial (week 1), the maximal exercise intensity used (achieved in week 13 if tolerated) and the rate of progression are listed.

HRR= Heart rate reserve

Table 2

Characteristics of Participants

4% site							50% site		
		Intervention Group	Control Group (n=18)	Excluded participants	Intervention Group	Control Group (n=26)	Excluded participants		
Demographics									
Women (n)		9	6	11	11	10		5	
Age (years): all participants		63.9±7.0	63.7±7.6	68.0±9.8	65.2±8.8	64.7±8.5		69.1±8.0	
Women		62.8±6.	60.3±5.2	64.7±9.6	63.5±6.	64.7±9.6		64.7±9.6	
Men		65.0±7.4	65.3±8.3	64.6±10.	66.3±10.	64.6±8.1		64.6±10.	
Height (cm): all participants		169.1±1	171.9±7.	167.4±1	170.8±1	169.4±9.		163.7±1	
Women		161.4±8.	165.4±6.	162.4±6.	161.0±7.	162.4±6.		162.4±6.	
Men		176.7±4.	175.2±9.	173.8±8.	178.0±5.	173.8±8.		173.8±8.	
Weight (kg): all participants		78.1±17.	77.9±8.1	76.4±17.	78.5±18.	77.2±12.		74.3±13.	
Women		67.3±8.2	75.8±12.	70.2±12.	65.4±9.7	70.2±12.		70.2±12.	
Men		88.9±18.	79.0±5.7	81.5±9.9	88.1±17.	81.5±9.9		81.5±9.9	
BMI (m/kg ²): all		27.2±5.1	26.5±3.5	27.0±4.1	26.7±4.9	26.9±3.8		27.6±3.1	
Women		25.8±3.0	27.7±4.1	26.5±3.6	25.2±3.5	26.5±3.6		26.5±3.6	
Men		28.6±6.5	25.9±3.1	27.6±2.1	27.8±5.6	27.1±4.1		27.6±2.1	
MMSE		27.9±2.5	27.8±1.9	28.1±2.0	27.9±2.3	28.0±2.0		28.0±2.0	
Walking aid (cane/crutch/quad		2/1/0/1	3/0/1/1	6/0/2/3	6/1/0/2	4/0/2/2		1/0/1/1	
PASIPD (MET hr/day)		9.1±9.2	9.1±10.1	9.0±8.1	8.5±8.1	9.9±10.2		8.3±7.7	
Stroke characteristics									
Functional Classification		2/12/4/0	1/12/5/0	1/12/8/3	3/16/7/0	1/15/8/2		0/5/2/1/	
Post-stroke duration (years)		6.1±6.1	4.7±3.5	4.7±3.2	5.6±5.2	5.0±3.3		4.1±4.3	
Paretic side (right) (n)		7	6	7	9	9		2	
Hemorrhagic stroke (n)		12	10	14	11	10		3	
Comorbidities									
Diabetes (n)		2	2	5	4	3		2	
Arthritis (n)		4	3	5	5	5		2	
Depression (n)		3	3	8	5	6		3	
Medications/supplements									

	4% site			50% site		
	Intervention Group	Control Group (n=18)	Excluded participants	Intervention Group	Control Group (n=26)	Excluded participants
Bone resorption inhibitors	2	2	0	2	2	0
Calcium (n)	3	5	3	4	6	1
Multivitamins (n)	4	4	5	7	5	1

The mean value ± standard deviation is presented unless indicated otherwise. n = number of participants.
BMI = body mass index; MET = Metabolic equivalents; MMSE = Mini Mental Status Examination; PASIPD = Physical Activity Scale for Individuals with Physical Disabilities

Table 3

Percent changes in pQCT parameters in men and women.

Measure	Intervention Group				Control Group							
	Paretic side		Non-paretic side		Paretic side		Non-paretic side					
	Women	Men	p		Women	Men	p					
Percent change (4% tibial site)												
Area _{total}	4.1±3.6	0.5±5.	0.11	2.0±4.5	2.5±4.	0.82	-	-1.4±9.6	0.8	-0.3±2.4	-0.9±8.2	0.87
BMC _{trab}	7.3±4.8	3.9±8.	0.30	4.2±6.4	4.6±6.	0.91	-	-	0.9	-0.7±4.6	-	0.90
Area _{trab}	5.5±4.3	2.9±6.	0.33	2.8±5.9	3.8±5.	0.72	-	-	0.8	-0.2±2.6	-	0.99
BMD _{trab}	1.7±1.9	0.9±1.	0.41	1.4±1.2	0.8±2.	0.53	-	0.2±3.4	0.7	-0.5±2.3	0.2±3.5	0.64
Percent change (50% tibial site)												
Area _{total}	-0.7±2.9	0.1±2.	0.41	-1.6±2.5	-	0.43	-	0.4±1.9	0.2	-1.9±4.3	-0.2±2.2	0.19
Area _{cort}	0.4±2.8	0.7±3.	0.80	-0.8±2.9	2.5±4.	0.36	-	-0.3±1.4	0.9	-0.5±3.0	0.3±3.1	0.54
BMC _{cort}	0.4±2.8	0.4±3.	0.98	-1.0±1.5	0.3±1.	0.06	-	-0.4±1.2	0.8	-0.1±2.0	-0.3±2.9	0.84
BMD _{cort}	-0.0±0.6	-	0.51	-0.1±3.5	0.2±1.	0.75	-	-0.1±0.6	0.7	0.5±2.0	-0.5±1.5	0.16
Cortical	0.3±2.0	0.6±2.	0.74	-0.0±0.1	-	0.77	-	-0.9±2.2	0.9	0.9±3.3	0.1±3.5	0.54
p-SSI	0.5±6.1	1.1±5.	0.78	-2.6±1.3	0.5±3.	0.02	0.0±2.	0.4±2.3	0.7	-0.6±3.9	0.5±3.6	0.44

* p<0.05 (independent t-test)

Area_{total} = total area; BMC_{trab} = trabecular bone mineral content; Area_{trab} = trabecular area; BMD_{trab} = trabecular bone mineral density; Area_{cort} = cortical area; BMC_{cort} = cortical bone mineral content; BMD_{cort} = cortical bone mineral density; p-SSI = Polar Stress-Strain Index

Table 4

Pooled results for participants in whom the 4% tibial pQCT scans were acquired

Measure	Intervention Group (n=18)			Control Group (n=18)			P* (baseline difference)	P† (between-group difference in %)
	Pre-test	Post-test	%	Pre-test	Post-test	%		
Paretic side								
Area _{total} (mm ²)	1194.7±23	1215.9±	2.3±4.7	1256.8±135.	1245.9±18	-1.1±7.9	0.34	0.12
BMC _{trab} (mg)	220.9±57.	231.9±5	5.6±6.7	230.0±39.5	230.5±52.	-0.5±10.8	0.58	0.048 [‡]
Area _{trab} (mm ²)	1021.1±21	1058.3±	4.2±5.6	1084.0±161.	1080.7±19	-0.8±8.9	0.32	0.05
BMD _{trab}	217.1±36.	219.8±3	1.3±1.9	214.7±36.9	214.8±36.	0.1±2.9	0.85	0.14
Non-paretic side								
Area _{total} (mm ²)	1191.8±20	1219.1±	2.2±4.5	1248.0±136.	1236.5±13	-0.7±6.8	0.34	0.14
BMC _{trab} (mg)	226.2±50.	236.5±5	4.4±6.2	230.0±43.4	229.4±48.	-0.3±9.3	0.81	0.08
Area _{trab} (mm ²)	1025.9±18	1059.6±	3.3±5.5	1054.9±183.	1046.8±17	-0.2±9.0	0.64	0.17
BMD _{trab}	220.9±32.	223.4±3	1.1±2.0	221.5±39.4	222.1±43.	-0.0±3.1	0.96	0.21
Reported physical activity								
PASIPD (MET	9.1±9.2	17.8±12.	229.3±35	9.1±10.1	20.6±20.6	212.8±331	0.98	0.89

* Comparison of baseline measures between two groups (independent t-test).

† Comparison of percent change scores between two groups (independent t-test).

‡ p<0.05 (independent t-test)

Area_{total} = total area; BMC_{trab} = trabecular bone mineral content; Area_{trab} = trabecular area; BMD_{trab} = trabecular bone mineral density; PASIPD = Physical Activity Scale for Individuals with Physical Disabilities; MET= metabolic equivalents

Table 5

Pooled results for participants in whom the 50% tibial pQCT scans were acquired.

Measure	Intervention Group (n=26)			Control Group (n=26)			P* (baseline difference)	P† (between-group difference in %)
	Pre-test	Post-test	%	Pre-test	Post-test	%		
Paretic side								
Area _{total} (mm ²)	467.0±89.9	465.9±90.3	-0.3±2.6	468.2±89.7	469.0±90.3	0.2±1.6	0.96	0.49
Area _{cort} (mm ²)	307.5±74.2	309.2±75.2	0.6±2.9	306.3±55.7	305.3±54.9	-0.3±1.4	0.95	0.17
BMC _{cort} (mg)	352.2±86.4	353.5±87.6	0.4±2.9	354.4±66.0	352.9±65.3	-0.4±1.4	0.92	0.21
BMD _{cort} (mg/cm ³)	1143.3±37.9	1141.1±37.9	-0.2±1.0	1156.3±31.8	1154.9±29.9	-0.1±0.7	0.19	0.73
Cortical thickness	5.48±1.07	5.51±1.09	0.4±2.2	5.46±0.95	5.42±0.95	-0.9±1.9	0.95	0.026 [‡]
p-SSI (mm ³);	1404.4±355.	1407.81±34	0.5±6.1	1517.2±199.	1517.0±195.	0.0±2.4	0.39	0.83
p-SSI (mm ³); Men	2364.9±310.	2389.3±317.	1.1±5.1	2294.6±446.	2300.6±436.	0.4±2.3	0.62	0.60
Non-paretic side								
Area _{total} (mm ²)	468.5±87.3	463.3±86.4	-1.0±2.7	474.6±93.6	469.8±89.2	-0.8±3.2	0.81	0.77
Area _{cort} (mm ²)	311.8±74.4	310.5±73.3	-0.32.6	309.8±56.4	309.5±56.2	-0.0±3.1	0.91	0.77
BMC _{cort} (mg)	357.2±86.8	356.6±86.9	-0.2±1.8	357.4±65.0	356.6±65.2	-1.9±2.5	1.00	0.92
BMD _{cort} (mg/cm ³)	1143.0±39.5	1144.1±52.9	0.1±2.5	1154.1±39.8	1152.3±30.7	-0.1±1.8	0.32	0.75
Cortical thickness	5.57±1.08	5.55±1.06	-0.2±1.8	5.48±0.91	5.50±0.94	0.4±3.3	0.75	0.41
p-SSI (mm ³);	1466.2±433.	1429.0±426.	-2.6±1.3	1554.5±252.	1539.6±217.	-0.6±3.9	0.58	0.13
p-SSI (mm ³); Men	2320.1±312.	2326.8±278.	0.5±3.9	2278.6±412.	2287.8±402.	0.5±3.6	0.76	1.00
Reported physical activity								
PASIPD (MET)	8.5±8.1	14.8±11.7	168.7±3	9.9±10.2	18.6±18.0	193.6±323	0.58	0.78

^{*} Comparison of baseline measures between two groups (independent t-test).

[†] Comparison of percent change scores between two groups (independent t-test).

[‡] p<0.05 (independent t-test)

Area_{total} = total area; Area_{cort} = cortical area; BMC_{cort} = cortical bone mineral content; BMD_{cort} = cortical bone mineral density; p-SSI = Polar Stress-Strain Index; PASIPD = Physical Activity Scale for Individuals with Physical Disabilities; MET= metabolic equivalents