

# Changes in bone density and geometry of the radius in chronic stroke and related factors: A one-year prospective study

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## Abstract

**Objectives:** To describe the changes in bone density and geometry of the radius after chronic stroke and the associated clinical factors. **Methods:** Twenty stroke patients (12 men and 8 women, age=42-78 years, time post-stroke=12-166 months) and 23 control participants (14 men and 9 women, age=53-77 years) were assessed at the time of enrolment and one year later. Peripheral quantitative computed tomography was used to scan the radius epiphysis (4% site) and diaphysis (33% site). Grip strength, spasticity, paretic arm disuse, physical activity, and vascular health were also evaluated. **Results:** During the follow-up period, only the cortical thickness and cortical bone mineral content (BMC) in the paretic radius diaphysis showed a decline that exceeded the least significant change value ( $p=0.002$ ). Paretic arm disuse, lower vascular elasticity and physical activity level at initial assessment were significantly related to more decline in cortical thickness at this site ( $p<0.01$ ). **Conclusions:** The paretic radius diaphysis sustained significant reduction in cortical thickness and cortical BMC over time in chronic stroke, but these changes were less pronounced than those previously reported in sub-acute stroke. Strategies to modify vascular health, disuse, and physical activity may be important in improving upper limb bone health but will need further investigations.

**Keywords:** Cerebrovascular Accident, Muscle, Osteoporosis, Rehabilitation, peripheral Quantitative Computed Tomography

## Introduction

Stroke survivors are highly prone to hemiosteoporosis, which may lead to exaggerated rates of fragility fractures<sup>1,2</sup>. Fractures post-stroke can give rise to detrimental consequences, including prolonged hospital stay, increased disability, and reduced survival rate<sup>3,4</sup>. As over 25% of post-stroke fractures occur in the upper extremity<sup>5</sup>, it is clinically relevant to study bone health in upper extremity skeletal sites among stroke patients.

Previous studies using dual-energy X-ray absorptiometry

(DXA) have reported significant reduction in areal bone mineral density (aBMD) in various skeletal sites on the paretic side following stroke<sup>1,6</sup>. More recent studies have employed peripheral quantitative computed tomography (pQCT) to examine volumetric bone mineral density (BMD) and bone geometry (e.g., total cross-sectional area, cortical bone area, cortical thickness) in chronic stroke patients<sup>8,12</sup>. Studying bone geometry is important because geometric properties of a bone have considerable influence on bone strength<sup>13,14</sup>. For example, in the long bone diaphysis, if the total cross sectional area of the bone segment is enlarged, the bone would become more resistant to externally applied bending forces due to an increase in moment of inertia, although the bone mass and BMD values remain unchanged<sup>13</sup>.

A number of pQCT studies have demonstrated significant side-to-side differences in densitometric and geometric properties of various upper extremity bone sites among chronic stroke survivors<sup>8,11</sup>. However, these studies are cross-sectional in nature and could not demonstrate actual bone changes over time. The side-to-side differences in bone properties reported

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in these studies could be explained by the changes in the paretic limb or non-paretic limb or both.

To date, only Lazoura et al.<sup>12</sup> has used pQCT to examine the longitudinal bone changes in the upper extremity following stroke. Significant decline in BMD measured at the epiphyseal (4% site) and diaphyseal (20% site) regions of the paretic radius was reported within a 9-month follow-up period spanning from 3 months to 12 months after stroke onset (i.e. subacute stage of stroke recovery). However, severity of stroke impairments that are highly relevant to bone health (i.e. muscle weakness, vascular health) and changes in bone geometry were not reported<sup>12</sup>. Additionally, whether bone density and geometry continue to deteriorate during the chronic stage of recovery (after 1 year post-stroke) remains elusive.

In this study, we aimed to examine the longitudinal changes in bone densitometric and geometric parameters of the radius in a group of chronic stroke patients. A comprehensive assessment of various stroke impairment variables was included, enabling us to identify the clinical correlates of bone changes. To strengthen the study design, a healthy control group was also incorporated. The findings may provide some insight into the actual changes in density and geometry of the radius post-stroke and the related clinical factors.

## Methods

### *Study design*

This was a prospective, exploratory study. Each subject was assessed at the time of enrolment and again one year later. The bone imaging was performed by an experienced technician who was blinded to the results of the physical assessment. A rehabilitation therapist, who was not aware of the bone imaging results, conducted all assessments of stroke impairments.

### *Subjects*

The recruitment of subjects took place in Hong Kong, China during the period between January 2009 and March 2010. Sixty five stroke patients, who were all members of a local stroke self-help group and had participated in previous research studies of our team, were invited to participate in the present study. Relevant information (e.g. demographics, medical history) was obtained by means of subject interviews. Each subject had to fulfill the following inclusion criteria: a diagnosis of stroke, onset of stroke for at least one year or more, aged 18 or more, community-dwelling, medically stable, of Chinese origin, and able to respond to simple verbal commands with an Abbreviated Mental Test score of 6 or higher. Exclusion criteria included: recurrent stroke, neurological conditions in addition to stroke, significant musculoskeletal conditions (e.g. amputations), metal implants in the upper extremity, previous fracture of the upper extremity, taking medications for the treatment of osteoporosis before or after stroke, or other serious illnesses which precluded participation in this study (e.g. malignancy).

Healthy control subjects in this study were recruited from an existing database of subjects who had participated in pre-

vious research projects of our team. The same eligibility criteria applied, except that these subjects should not have a history of stroke. Ethics approval of this study was granted by the Hong Kong Polytechnic University. Effort was made to identify control subjects who had demographic characteristics similar to the stroke patients recruited. Informed, written consent was obtained from each subject prior to his/her participation in the study. All procedures were conducted in accordance with the Declaration of Helsinki.

No study has examined longitudinal changes in pQCT parameters in chronic stroke patients, and the estimation of sample size was based on the results from previous pQCT and DXA studies in stroke patients before 1 year post-stroke. Large effect sizes (Cohen's  $d=0.8-1.0$ ) were reported in these studies<sup>6,12</sup>. Therefore, a large effect size of 0.9 was used to estimate the sample size for this study. Based on analysis using t-test (two-tailed), with an effect size of 0.9, alpha at 5%, power at 80%, and 20% attrition rate, the estimated sample size required would be 26 subjects per group.

Twenty-eight stroke patients and 27 healthy control subjects participated in the study. During the study period, 12 subjects dropped out of the study: 8 from the stroke group and four from the control group. The reasons for the withdrawals are outlined in Figure 1.

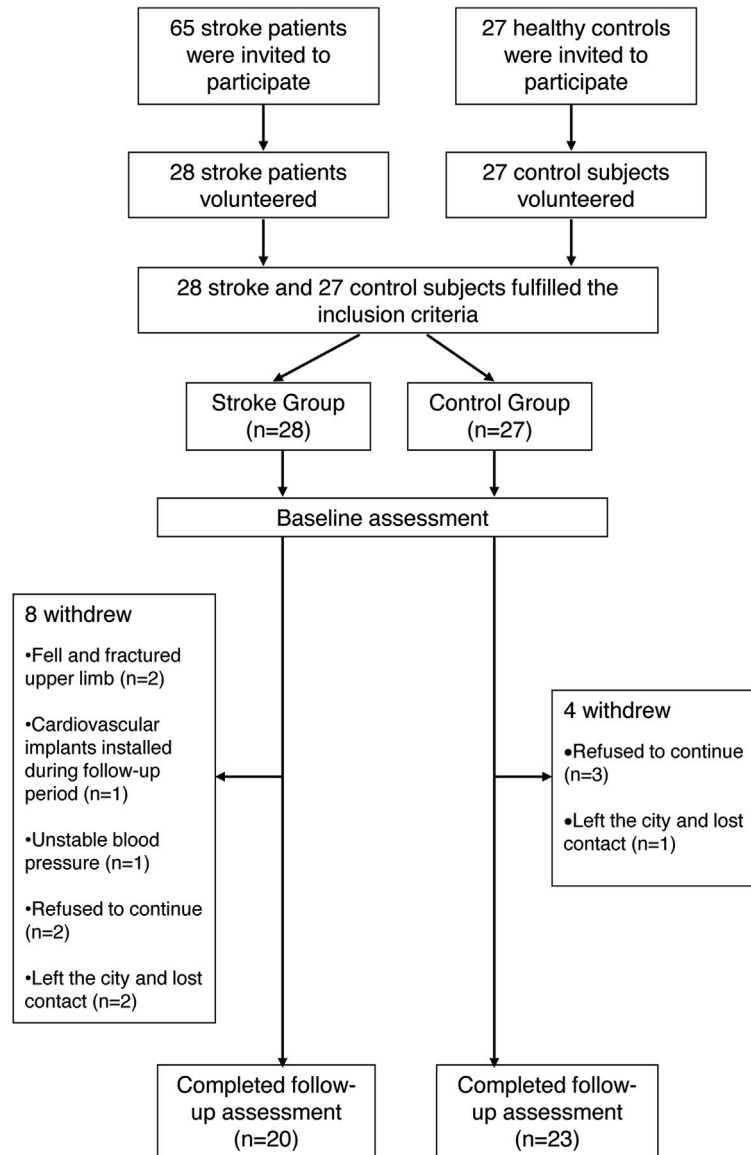
### *Assessment*

#### *Demographics*

Demographic data including age, sex, post-menopausal years, type of stroke, side of paresis, duration after stroke, hand dominance, co-morbid conditions, and medications/supplements were collected through subject interview. The weight (kg) and height (cm) were measured using the Mechanical Beam Scale (Health O Meter, Alsip, IL, USA). Based on this information, the body mass index (BMI) was computed for each individual. The Physical Activity Scale for the Elderly (PASE) was used to measure physical activity level<sup>15</sup>. This questionnaire assessed the amount of participation in physical activities of different intensities in the previous seven days and generated a PASE score, which could range from 0 to 400 or more. The PASE is a valid and reliable instrument for measuring physical activity in the elderly population<sup>15</sup>.

#### *Bone imaging*

All subjects underwent bone imaging of the radius on both sides using Peripheral QCT (Stratec Medizintechnik XCT 3000; software version 6.00B; Pforzheim, Germany)<sup>16</sup>. To minimize the probability of motion artifacts, extra care was taken by the technician to ensure that the tested limb was properly placed in the tray supporting the limb. If necessary, straps were applied to the forearm to further secure the limb in position. A scout view was then obtained, and the anatomical reference line was placed at the cortical end plate of the distal radius. Scans 2.3 mm thick were obtained at two different sites of the radius: (1) radius epiphysis (4% of the total bone length proximal to the reference line, primarily trabecular bone), and (2)



**Figure 1. Study flow chart.** Twenty stroke patients and twenty three control subjects completed both the initial and follow-up assessments.

radius diaphysis (33% of the total bone length proximal to the reference line, primarily cortical bone). Studying both the epiphysis and diaphysis of the radius was important because it can shed light on whether different regions of a bone undergo different changes after stroke. While the radius epiphysis is the most common site of fracture in the upper extremity<sup>5</sup>, studying the diaphyseal regions, where the origins of major muscle groups are located, allowed us to examine the muscle-bone relationship<sup>9</sup>. A voxel size of 400 microns and scan speed of 25 mm/sec were used. These testing protocols were chosen because a relatively fast scanning speed would keep the scanning time short to avoid movement artifacts, as patients after stroke are susceptible to involuntary movements, change in muscle tone, or tremors<sup>8</sup>.

Stratec software version 6.00B (Pforzheim, Germany) was used for image analysis. For analysis of the 4% site of the radius, CALCB Contour Mode 2 and Peel Mode 2 were used, with a density threshold of 169/400 mg/cm<sup>3</sup>. For image analysis of the 33% site of the radius, cortical bone analysis was performed using CORTBD (Mode 1), with a threshold of 710 mg/cm<sup>3</sup>. These thresholds were chosen based on previous studies in patients after stroke<sup>9,10</sup>. All the analyses were performed using customized software (Stratec software, Version 6.00B).

The pQCT variables of interest are shown in Table 1. The compressive bone strength index (CBSI) at the 4% site (total BMD<sup>2</sup> × total area) is thought to be an appropriate estimate of the strength of the bone segment against compressive forces at the distal end of long bones, considering that long bone epi-

Variable	Least significant change value (%)
<b>4% site (radius distal epiphysis)</b>	
Total BMD (mg/cm <sup>3</sup> ) <sup>a</sup>	8.0
Total BMC (mg/mm) <sup>a</sup>	10.5
Trabecular BMD (mg/cm <sup>3</sup> ) <sup>a</sup>	4.9
Total area (mm <sup>2</sup> )	8.4
Compressive bone strength index (CBSI) (g <sup>2</sup> /cm <sup>4</sup> )	14.7
<b>33% site (radius diaphysis)</b>	
Cortical BMC (mg/mm) <sup>a</sup>	1.3
Cortical BMD (mg/cm <sup>3</sup> ) <sup>a</sup>	4.0
Total area (mm <sup>2</sup> )	4.7
Cortical area (mm <sup>2</sup> )	4.0
Cortical thickness (mm)	2.9
Polar stress-strain index (SSI <sub>p</sub> ) (mm <sup>3</sup> )	4.8

<sup>a</sup>BMC = bone mineral content; BMD = volumetric bone mineral density

**Table 1.** Precision error: least significant change value of each pQCT variable.

physis is primarily subjected to axial compression<sup>17</sup>. A human cadaver study has also shown that the CBSI at the 4% tibial site is highly associated with failure load, accounting for 85% of the variance, when tested in axial compression<sup>18</sup>. The CBSI has also been used in previous studies to indicate the strength of long bones at distal sites<sup>10,19</sup>. The CBSI is thus an acceptable noninvasive estimate of bone strength.

At the diaphysis of the radius (33% site), a different bone strength index called the polar stress-strain index (SSI<sub>p</sub>, in mm<sup>3</sup>) was computed automatically by the pQCT system. The SSI<sub>p</sub> is the density-weighted polar section modulus of a given bone cross section and reflects the torsional rigidity of the long bone shaft<sup>19,20</sup>. The SSI<sub>p</sub> rather than the CBSI was used to indicate bone strength at the diaphyseal site because torsional forces are more predominant at this site, compared with the distal epiphyseal site where compressive forces are more predominant. The SSI has been validated as an estimation of bone bending strength<sup>22-24</sup>. For example, SSI measured at the tibial diaphysis has been shown to be strongly associated with bone breaking strength ( $R^2=0.76$ )<sup>18</sup>. The SSI<sub>p</sub> has also been used in other stroke studies<sup>9,12</sup>.

The precision of the pQCT scanner was assessed by measuring 30 healthy subjects twice (28 men and two women, mean age: 72.3±5.1 years), with repositioning after the first scan, according to the recommendations of the International Society for Clinical Densitometry<sup>23</sup>. The 95% confidence least significant change (LSC) value (calculated from  $2.77 \times$  precision error) for each pQCT variable is listed in Table 1. Any change that exceeds the LSC value reflects a change beyond the variation arising from repeated measurements.

#### Stroke-related impairments

**Muscle Strength:** All stroke and control subjects were assessed for maximal hand grip strength using a Jamar dynamometer (Sammons Preston, Mississauga, Ontario, Canada)

according to standard procedures<sup>10</sup>. Subjects were asked to grip the handle of the dynamometer using maximal effort and the maximum force produced (in kg) was registered. A total of three trials were performed on each side. The maximal grip strength values obtained from the three trials were averaged. The average, rather than the highest value, of the three trials was used for subsequent analysis because we considered the former to reflect more accurately the typical performance of the maximal grip strength test, as there was variability of data across trials, albeit small. The data from the three trials revealed that the test-retest reliability of the hand-grip strength was excellent for both the paretic side [intraclass correlation coefficient ( $ICC_{3,1}=0.984$ )] and non-paretic side ( $ICC_{3,1}=0.966$ ).

**Spasticity:** The Modified Ashworth Scale (MAS) was used to assess resistance to passive elbow flexion/extension movements on the paretic side among stroke subjects, with a higher score representing more severe spasticity (0: no increase in muscle tone, 4: affected part rigid in flexion and extension)<sup>24</sup>. The MAS has demonstrated acceptable reliability in evaluating spasticity in stroke patients (Kendall's tau correlation= $0.847$ )<sup>24,25</sup>.

**Disuse:** The amount-of-use scale in the Motor Activity Log (MAL) was used to assess how much the stroke subjects used the affected upper limb in daily functional activities<sup>26</sup>. The MAL consists of 30 functional tasks (e.g. picking up a phone, brushing teeth, putting on shoes). The subjects were asked to indicate how much they used the paretic upper extremity in each task, and the scoring was based on a 6-point scale, with a higher score indicating more active use (e.g., 0: paretic arm not used; 3: used the weaker arm about half as much as before the stroke; 5: used the weaker arm as much as before stroke). The scores for the 30 items were averaged to obtain a mean MAL score. The MAL has high internal consistency (Cronbach's  $\alpha=0.88$ ) and good construct validity, with moderate correlation with the Action Research Arm test score (spearman's  $\rho=0.63$ ) among stroke patients<sup>27</sup>.

	Stroke		Control		p-value (Between-group comparison for those who completed follow-up assessments)
	All subjects (n=28)	Subjects who completed follow-up assessment (n=20)	All subjects (n=27)	Subjects who completed follow-up assessment (n=23)	
<b>Basic demographics</b>					
Age (year)	62.6±9.0 <sup>a</sup>	63.2±8.1	61.1±8.5	62.5±8.1	0.435
Sex (men/women),n	18:10	12:8	16:11	14:9	0.954
Body Mass Index (BMI), kg/m <sup>2</sup>	23.8±2.8	23.6±2.3	24.4±3.1	24.1±3.2	0.559
Number of postmenopausal women	10	8	11	9	0.954
Postmenopausal years (women only)	17.7±9.9	17.6±10.8	13.5±12.4	15.8±12.5	1.000
PASE score <sup>b</sup>	91.1±51.4	93.2±47.7	157.7±66.2	155.6±68.9	<b>&lt;0.001</b>
Hand dominance (left/right), n	0/28	0/20	0/27	0/23	---
<b>Stroke characteristics</b>					
Type of stroke (ischemic/hemorrhagic/unknown), n	17/10/1	10/9/1	NA <sup>b</sup>	NA	---
Side of paresis (left/right), n	10/18	4/16	NA	NA	---
Duration after stroke (month)	45.6±42.8	48.5±46.6	NA	NA	---
<b>Co-morbid conditions</b>					
Hypertension, n	22	17	12	11	<b>&lt;0.001</b>
Diabetes, n	10	6	1	1	<b>&lt;0.001</b>
High cholesterol, n	13	8	1	1	<b>&lt;0.001</b>
Total number of co-morbid conditions, n	1.7±1.0	1.7±1.0	0.6±0.6	0.7±0.1	<b>0.002</b>
<b>Medications/supplements</b>					
Antihypertensive agents, n	17	14	4	3	<b>0.001</b>
Anticoagulants, n	16	13	0	0	<b>&lt;0.001</b>
Anticonvulsive agents, n	0	0	0	0	---
Hypolipidemic agents, n	15	12	0	0	<b>&lt;0.001</b>
Hypoglycemic agents, n	3	2	0	0	---
Antidepressants, n	3	3	0	0	0.099
Vitamin D supplementation, n	2	2	4	3	0.508
Calcium supplementation, n	3	3	4	3	0.834

*p-values in bold are significant at p<0.05*  
<sup>a</sup>Mean±SD unless otherwise indicated  
<sup>b</sup>NA= not applicable; PASE= Physical Activity Scale for the Elderly

**Table 2.** Subject characteristics.

**Vascular health:** The HDI/PulseWave CR-2000 Research CardioVascular Profiling System (HDI Hypertension Diagnostics Inc., Eagan, MN, USA) was used to assess vascular health in both the stroke and control groups<sup>28</sup>. This profiling system is a reliable, valid, non-invasive method to measure arterial compliance<sup>29</sup>, and has been commonly used in research studies<sup>30</sup>. The subjects were first placed in a supine position, and a blood pressure cuff was applied to the upper-arm on the non-paretic side (or dominant side in control subjects). A rigid plastic wrist stabilizer was placed on the wrist on the paretic side (or non-dominant side in control subjects) to minimize movement of the radial artery during the measurement. With the paretic forearm placed in a supinated position, a piezoelectric-based, acoustical sensor was placed over the radial artery adjacent to the styloid process of the radius. The sensor was adjusted so that the highest

relative signal strength was obtained. Blood pressure (BP) was assessed using a linear dynamic deflation method. When the waveform was satisfactory and consistent, the radial arterial blood pressure waveform data acquired over a 30-second period was used for analysis<sup>28</sup>. The data from two trials were averaged to obtain the mean value of the artery elasticity index. A one-minute rest period was provided between trials. The main outcomes generated by the system were a large artery elasticity index ( $C_1$ ; in mL/mmHg × 10) and small artery elasticity index ( $C_2$ ; in mL/mmHg × 100).  $C_1$  is a measure of the elasticity of the aorta and large arteries.  $C_2$ , on the other hand, is a measure of the elasticity of the small arteries<sup>28,31</sup>. The system is reliable in measuring  $C_1$  and  $C_2$  in stroke patients ( $C_1$ : ICC<sub>3,1</sub>= 0.954;  $C_2$ : ICC<sub>3,1</sub>= 0.948) and control subjects ( $C_1$ : ICC<sub>3,1</sub>= 0.911;  $C_2$ : ICC<sub>3,1</sub>= 0.918) with repeated testing<sup>10</sup>.

Variable	Stroke group (n=20)			Control group (n=23)		
	Initial	Follow-up	p-value	Initial	Follow-up	p-value
Physical activity score	93.2±47.7 <sup>a</sup>	94.4±48.8	0.897	155.6±68.9	165.1±72.9	0.338
Grip strength: paretic side (stroke group) or non-dominant side (controls) (kg)	12.6±9.8	12.2±9.4	0.698	26.2±7.1	26.1±7.1	0.503
Grip strength: non-paretic side (stroke group) or dominant side (controls) (kg)	23.7±7.9	23.7±7.1	0.695	28.2±8.7	28.1±8.7	0.322
Motor Activity Log score (out of 5)	3.0±1.7	3.2±1.9	0.222	NA	NA	---
Modified Ashworth Scale of Spasticity (out of 4); median (IQR) <sup>b</sup>	1 (0-1.9)	0 (0-1.5)	0.039	NA	NA	---
Large artery elasticity index (C <sub>1</sub> ) (mL/mmHg × 10)	12.1±3.7	13.2±5.6	0.575	14.9±5.5	15.6±5.8	0.484
Small artery elasticity index (C <sub>2</sub> ) (mL/mmHg × 100)	4.4±2.5	4.1±2.6	0.121	4.5±1.8	4.4±1.8	0.976

<sup>a</sup>Data are mean ± SD unless otherwise indicated  
<sup>b</sup>IQR = interquartile range

**Table 3.** Change in stroke impairment variables.

### Statistical analysis

Statistical Package for Social Sciences version 17.0 (SPSS Inc., Chicago, US) was used. Descriptive statistics were used to analyze the characteristics of the subjects. Normality of data was checked by using Kolmogorov-Smirnov test. As the criteria for parametric statistics (e.g., normality) were not fulfilled, non-parametric tests were used. Baseline characteristics (e.g., demographics, co-morbid conditions, use of medications/supplements) between the stroke patients and controls were compared using Mann-Whitney test (for continuous and ordinal data) and Chi-square test (for nominal data). Wilcoxon signed-rank test was used to compare the pQCT variables and grip strength between the two sides at baseline for each of the stroke and control groups. Wilcoxon signed-rank test was also used to compare the pQCT and stroke impairment variables (maximal grip strength, spasticity, disuse and vascular elasticity indices) and physical activity level between the baseline and follow-up values. A more stringent significance level was used ( $\alpha = 0.025$ ) because pair-wise comparison was made for both the stroke and control groups.

For pQCT variables that showed a statistically significant change during the follow-up period that exceeded the LSC values established, Spearman's rho coefficient was then used to determine the association of the demographic variables (e.g., age, post-stroke duration, BMI, physical activity, etc.) and stroke impairment variables (e.g., grip strength, spasticity, disuse, vascular health) with the one-year bone changes in the stroke group.

## Results

Twenty stroke patients (12 men) and 23 control subjects (14 men) completed both the initial and follow-up assessments (Table 2). At the time of initial assessment, the mean time since

stroke onset was 49 months (range= 12-166 months). No significant difference in demographic variables was identified between those who completed the follow-up assessments and those who did not ( $p > 0.05$ ), except that the dropouts in the control group were significantly younger [(mean age: 53.0 (SD:6.2)] than their counterparts who completed the follow-up assessment (mean age: 62.5 (SD:8.1)] ( $p = 0.03$ ). All subsequent analyses were performed only on those subjects who had completed both the initial and follow-up assessments.

The stroke group had significantly lower physical activity (i.e., PASE score) than their peers in the control group (Table 2). The stroke group also had a significantly higher proportion of people with cardiovascular comorbidities than the control group, including hypertension, diabetes, and high cholesterol.

### Stroke impairments

Table 3 shows the stroke impairment variables and presents the p-values for the comparisons between baseline and follow-up data only. The p-values for baseline comparisons would only be presented in the text. At initial assessment, the grip strength on the paretic side was significantly lower by 47% than that on the non-paretic side ( $p < 0.001$ ), indicating substantial paresis. In contrast, the side-to-side difference in grip strength in the control group at baseline was much less (7%,  $p = 0.002$ ). During the 1-year follow-up period, physical activity, level, grip strength on both sides, C<sub>1</sub>, and C<sub>2</sub> values demonstrated no significant change over time in both the stroke and control groups ( $p > 0.05$ ). The spasticity and MAL scores also had no significant change over time among stroke patients ( $p > 0.05$ ) (Table 3).

### Comparison of bone properties measured at initial assessment

None of the pQCT scans was affected by movement artifacts. Table 4 shows the pQCT data. Similar to Table 3, Table 4 only displays the p-values for the comparisons between baseline and

Stroke group (n=20)						Control group (n=23)					
Paretic side			Non-paretic side			Non-dominant side			Dominant side		
Initial Mean±SD	Follow up Mean±SD	p-value	Initial Mean±SD	Follow up Mean±SD	p-value	Initial Mean±SD	Follow up Mean±SD	p-value	Initial Mean±SD	Follow up Mean±SD	p-value
<b>4% site</b>											
<i>Total BMC (mg/mm)<sup>a</sup></i>											
88.1±33.8	86.4±31.4	0.341	106.0±30.4	103.6±32.1	0.117	103.6±28.1	102.4±27.0	0.186	104.3±27.1	103.8±27.2	0.369
<i>Total area (mm<sup>2</sup>)</i>											
290.1±44.0	294.3±45.6	0.433	290.1±58.3	284.5±55.8	0.467	299.1±62.8	301.1±62.6	0.808	305.8±69.7	304.3±64.1	0.584
<i>Total BMD (mg/cm<sup>3</sup>)<sup>a</sup></i>											
301.3±102.1	293.7±97.9	<b>0.014</b>	365.7±81.6	361.8±81.9	0.145	348.0±67.1	343.5±70.7	0.346	344.3±63.2	342.2±60.0	0.605
<i>Trabecular BMD (mg/cm<sup>3</sup>)<sup>a</sup></i>											
169.3±47.8	166.1±48.5	0.054	197.0±36.3	194.3±37.3	0.150	200.4±31.6	199.1±31.4	0.260	201.6±34.0	200.1±33.7	0.121
<i>CBSI (g<sup>2</sup>/cm<sup>4</sup>)<sup>a</sup></i>											
0.30±0.19	0.28±0.17	<b>0.013</b>	0.40±0.18	0.39±0.18	0.097	0.37±0.15	0.36±0.15	0.184	0.37±0.13	0.36±0.14	0.439
<b>33% site</b>											
<i>Cortical BMC (mg/mm)<sup>a</sup></i>											
79.4±30.4	77.7±30.7	<b>0.002</b>	91.9±24.6	91.0±25.0	<b>0.012</b>	92.0±21.9	92.0±23.3	0.100	93.5±21.7	92.9±21.6	0.068
<i>Cortical BMD (mg/cm<sup>3</sup>)<sup>a</sup></i>											
1155.5±78.6	1155.1±76.3	0.794	1195.8±50.5	1191.2±51.0	0.140	1189.7±34.3	1182.5±37.8	0.066	1188.2±32.5	1184.4±35.1	0.308
<i>Total area (mm<sup>2</sup>)</i>											
112.4±16.5	113.1±17.1	0.550	114.5±18.6	114.6±18.5	0.641	116.7±29.3	119.2±25.2	0.796	118.6±25.2	119.8±26.4	0.1115
<i>Cortical area (mm<sup>2</sup>)</i>											
67.4±23.2	66.0±23.4	<b>0.003</b>	76.4±19.2	75.9±19.5	0.276	77.2±17.6	77.6±18.9	0.500	78.5±17.4	78.3±17.4	0.480
<i>Cortical thickness (mm)</i>											
2.2±0.8	2.1±0.8	<b>0.002</b>	2.6±0.6	2.5±0.6	0.627	2.5±0.4	2.5±0.5	0.939	2.6±0.4	2.6±0.4	0.374
<i>SSIp (mm<sup>3</sup>)<sup>a</sup></i>											
206.0±66.7	203.8±67.0	0.093	229.5±60.6	226.0±60.4	0.093	249.7±86.8	248.5±87.2	0.738	246.4±83.8	242.7±82.6	0.075

*p*-values in bold are significant at  $p < 0.025$ ; <sup>a</sup>BMC=bone mineral content; BMD=volumetric bone mineral density; CBSI=compressive bone strength index; SSIp=polar stress-strain index

**Table 4.** Change in pQCT variables at the radius distal epiphysis (4% site) and diaphysis (33% site).

follow-up data only, but not those for baseline comparisons. At initial assessment, total BMC, total BMD, and CBSI at the 4% site were significantly lower on the paretic side than on the non-paretic side ( $p < 0.001$ ) in the stroke group by 18.0%, 18.8%, and 31.3% respectively. At the 33% site, the paretic side demonstrated significantly lower value in cortical area ( $p = 0.001$ ), cortical BMC ( $p = 0.001$ ), cortical BMD ( $p = 0.001$ ), cortical thickness ( $p = 0.003$ ), and SSIp ( $p < 0.001$ ) than the non-paretic side, by 13.5%, 16.0%, 3.4%, 15.0%, and 11.4% respectively. The total area at both the 4% and 33% sites showed no significant side-to-side difference in the stroke group ( $p > 0.10$ ). In contrast, among the control participants, none of the pQCT variables demonstrated any significant side-to-side difference in both skeletal sites ( $p > 0.10$ ).

#### Bone changes in radius epiphysis and related factors

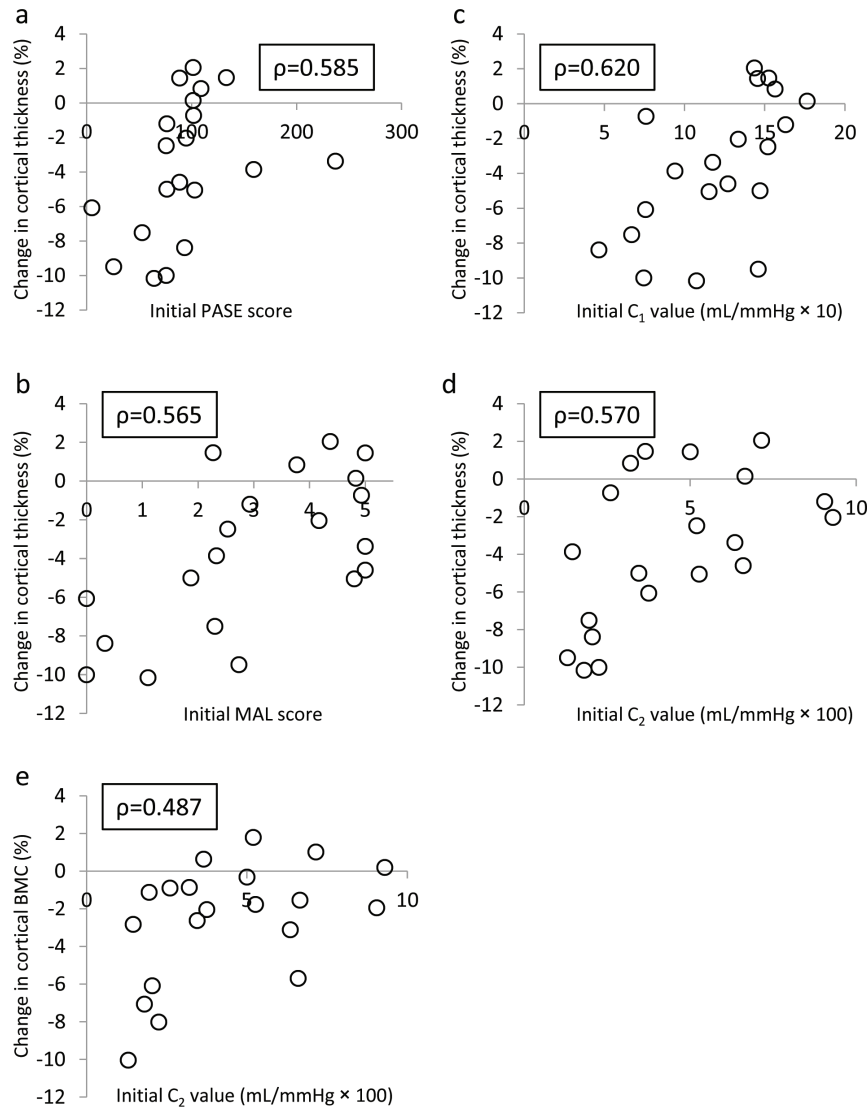
In the stroke group, the distal radius epiphysis on the paretic side showed a significant reduction in total BMD and CBSI, by 2.5% and 6.7% respectively (Table 4). These changes, however, were below the LSC values of our pQCT scanner (Table 1). The non-paretic side of the stroke group, and both the dominant and non-dominant side of the control group showed no significant

change in any of the pQCT variables measured at the radius epiphysis. As none of the pQCT parameters showed changes that exceeded the LSC value, no further correlation analysis was done to examine the association of the changes in pQCT variables with demographic factors (age, post-stroke duration, BMI, physical activity) and stroke impairment variables (spasticity, grip strength, vascular health, disuse).

#### Bone changes in radius diaphysis and related factors

The radius diaphysis on the paretic side sustained a statistically significant reduction in cortical BMC, cortical area, and cortical thickness by 2.1%, 2.1%, and 3.2%, respectively (Table 4). The non-paretic side also sustained a significant reduction in total BMC by 1.0%. However, only the changes in cortical BMC and cortical thickness on the paretic side exceeded the LSC values (Table 1). In the control group, none of the pQCT variables demonstrated any significant change on either side during the follow-up period.

As the change in cortical thickness and cortical BMC on the paretic side exceeded the LSC values, correlation analysis was done to examine which demographic or clinical factors were associated with these changes. The results revealed that changes



**Figure 2. Scatter plots showing the relationship between 1-year change in pQCT parameters at the 33% radius site on the paretic side and other factors measured at initial assessment.** The vertical axis denotes the amount of bone change during the follow-up period. A negative value indicates a lower value at follow-up compared with initial measurement. Each dot represents the data from a single stroke patient. The results showed that decline in cortical thickness in the paretic radius diaphysis during the follow-up period was significantly related to physical activity score as measured by the Physical Activity Scale for the Elderly (PASE) (a), Motor Activity Log score (MAL) (b), large artery elasticity index (C<sub>1</sub>) (c), and small artery elasticity index (C<sub>2</sub>) (d) measured at the initial assessment. The 1-year change in cortical bone mineral content (BMC) was also significantly correlated with C<sub>2</sub> measured initially (e).

in cortical thickness and cortical BMC were not significantly associated with age, post-stroke duration, BMI, MAL and grip strength at the initial assessment. On the other hand, lower physical activity level ( $\rho=0.585$ ,  $p=0.007$ ), MAL score ( $\rho=0.565$ ,  $p=0.009$ ), C<sub>1</sub> ( $\rho=0.620$ ,  $p=0.004$ ) and C<sub>2</sub> ( $\rho=0.570$ ,  $p=0.009$ ) initially were significantly associated with more decline in cortical thickness at the end of the follow-up period (Figure 2a-d). Additionally, the 1-year change in cortical BMC was significantly correlated with C<sub>2</sub> at the initial assessment ( $\rho=0.487$ ,  $p=0.029$ ) (Figure 2e). There was a tendency for a relationship between the changes in cortical BMC and initial C<sub>1</sub>

values, but it did not quite reach statistical significance ( $\rho=0.414$ ,  $p=0.070$ ).

## Discussion

This study showed that the diaphyseal site of the paretic radius underwent unfavorable bone changes among chronic stroke patients, despite no significant change in various stroke impairment variables overall. The extent of bone changes was modest, compared with that reported among subacute stroke patients in previous studies. We also found that disuse, vascu-

lar health and physical activity measured at initial assessment were significantly related to change in cortical thickness of the radius diaphysis during the follow-up period, suggesting the potential of improving upper limb bone health in chronic stroke patients through modification of these clinical factors.

#### *Changes in radius distal epiphysis*

In the radius epiphysis, a statistically significant decline in CBSI (2.5%) was reported, which was contributed mainly by the reduction in total BMD. These changes, however, were below the least significant change (LSC) values established, suggesting that the changes were within the variation related to precision error of the scanner. Only one longitudinal study has used pQCT to examine changes in BMD at the radius distal epiphysis<sup>12</sup>. In their 9-month follow-up period (from three to 12 months post-stroke), Lazoura et al. found a significant reduction in trabecular BMD in both the paretic (14.0%) and non-paretic (6.8%) radius distal epiphyses<sup>12</sup>. Possible explanations for the discrepancy in results may be attributable to the differences in subject characteristics. Their subjects were more acute (baseline assessment conducted at three months post-stroke) than ours (initial assessment done at 48.5 months post-stroke, on average). Taken together, the results indicated that the degree of bone changes at the radius distal epiphysis in the chronic phase was more modest than in the subacute phase.

#### *Changes in radius diaphysis*

In contrast, at the the 33% site of the radius on the paretic side, both cortical BMC and cortical thickness showed a decline during the 1-year follow-up period that exceeded the LSC values. The different results obtained at the 4% and 33% sites thus reveal that different regions of a bone may show distinct changes after stroke.

The results obtained in the paretic radius diaphysis denote a progressive reduction in bone mass, with thinning of the cortical shell and preservation of the total area, suggesting possible endosteal resorption. Although endosteal resorption after stroke was speculated in a previous study by Pang et al.<sup>9</sup>, the cross-sectional nature of the study could not determine whether the side-to-side differences in pQCT variables were due to actual bone alterations on the paretic side or the non-paretic side or both. This study provides the first piece of evidence of endosteal resorption in the paretic radius diaphysis in chronic stroke. Despite the apparent endosteal resorption, SSIp showed no significant decline over time, probably due to the fact that the extent of change was modest. The relative maintenance of the total area and cortical BMD during the follow-up period may have also helped stabilize the SSIp. It should be acknowledged that majority of, but not all, stroke patients sustained a reduction in cortical thickness and cortical BMC during the follow-up period (Figure 2). The presence/degree of endosteal resorption may be related to certain clinical factors, which will be discussed below.

Nevertheless, our finding is in contrast with Lazoura et al.<sup>12</sup>, which showed that at the 20% hemiparetic radius site, the cortical BMD (2.6-4.0%) and SSIp (7.0%-7.4%) were signifi-

cantly reduced during a follow-up period from 3 to 9 months post-stroke. The difference in subject characteristics (subacute Vs chronic) may partly explain the less impressive bone changes in our subjects. There was no documentation in their study of the details on the recovery of upper extremity function. It is unknown whether the paretic upper extremity function in their subjects was more impaired than ours that may contribute to the difference in results. Additionally, Lazoura et al.<sup>12</sup> did not provide any information on bone geometric changes. It is uncertain whether the more substantial reduction in SSIp was also related to alterations in bone geometry. Finally, the measurement site was different. The 20% site of the radius was used in their study, while a more proximal site (the 33% site) was used in the current study.

#### *Related factors and clinical implications*

A previous cross-sectional study in chronic stroke has identified a significant association of MAL score with cortical BMC at the 30% site<sup>9</sup>. This is the first pQCT study that demonstrates a relationship between disuse and bone changes among stroke patients in a longitudinal study. As the radius is a non-weightbearing bone, the mechanical loading mainly comes from muscle forces. Our results indicated that the amount of habitual use (reflected by MAL score), rather than grip strength, was significantly related to bone changes over time. The grip strength test provides information on the ability to generate grip force, and does not indicate whether the individual would actually engage in daily activities that would mechanically stimulate the bone tissue in the region. The reduced mechanical loading due to chronic disuse, in contrast, would have negative impact on integrity of bone tissue. It has been demonstrated that people with the non-dominant upper limb affected by stroke tend to have more severe impairment (i.e. more muscle weakness, pain and stiffness) and disuse than those whose affected side is the dominant side<sup>33</sup>. It may be because these patients may be less inclined to use the impaired non-dominant arm in daily tasks, as they are not accustomed to using it for these activities prior to stroke. We were unable to examine whether interaction between side of paresis and hand dominance has any effect on bone changes, as only four patients have the non-dominant side affected by paresis.

Our results also showed that better vascular health initially was related to less reduction in cortical thickness and cortical BMC during the 1-year follow-up period. While physical activity may partially explain the relationship between vascular health and bone health, increasing evidence suggests that cardiovascular health is independently associated with bone health in various populations<sup>34</sup>. For example, in a sample of healthy middle-aged women, Farhat et al.<sup>35</sup> showed that more compromised spinal BMD was associated with more advanced aortic calcification independent of common risk factors (e.g., age, physical activity, weight) between osteoporosis and cardiovascular disease. The pathophysiological mechanisms underlying the association are not entirely clear but it was suggested that cytokines, oxidized lipids, homocysteine may be involved<sup>34,36,37</sup>.

Apart from the significant relationship between change in cortical BMC and  $C_2$ , cortical thickness was the only pQCT variable that demonstrated significant results in our correlation analysis. Specifically, less reduction in cortical thickness in the paretic radius diaphysis was associated with higher physical activity level, better vascular health and more active use of the affected arm at the initial assessment. Based on the these relationships identified, one important clinical implication is that increasing cortical thickness may be obtained by targeting the modifiable clinical factors of sedentary lifestyle, poor vascular health and disuse of the affected limb. Increasing cortical thickness play has important implications for enhancing bone strength and reducing fracture risk. In a human cadaver study, Kontulainen et al.<sup>18</sup> showed that at the tibial diaphysis (50% site), cortical thickness ( $R^2=0.68$ ) was highly related to bone failure moment in bending test. Szulc et al.<sup>38</sup> showed that decrease in cortical thickness of the femoral neck was predictive of hip fractures in elderly women. Among postmenopausal women, it was also shown that cortical thickness of the radius was an important determinant of forearm/wrist fracture<sup>39</sup>.

Exercise intervention may be a viable way to influence vascular health, paretic arm disuse and overall physical activity level. Resistance training or impact aerobic exercise has long been used as a method to improve bone outcomes in postmenopausal women and older adults with compromised bone mass<sup>40-43</sup>. Only two studies have examined the effect of muscle strengthening or aerobic exercises on pQCT variables in stroke patients. In a randomized controlled trial, Pang et al.<sup>44</sup> showed that a combination of leg strengthening and aerobic activities can significantly enhance not only aerobic fitness and leg muscle strength, but also trabecular BMC at the tibial distal epiphysis and cortical thickness at the tibial diaphysis on the paretic side among chronic stroke patients. In a non-randomized controlled study, an aerobic treadmill training program was found to be effective in enhancing endurance, paretic leg muscle strength, physical activity level, and cortical thickness in the paretic tibial diaphysis<sup>45</sup>. Moreover, it was found that the change in cortical thickness was positively associated with that in paretic leg muscle strength and physical activity level<sup>45</sup>. Whether exercise interventions designed to improve vascular health and counteract disuse can induce positive effects on upper limb bone outcomes among individuals with stroke is unknown. Research in this important area is very much needed.

### Limitations

The stroke patients were recruited from a community stroke patient self-help group, which held regular activities and meetings for community-dwelling stroke survivors. The stroke patients in our study may therefore be in better health and physically active than other stroke patients living in the community. Nevertheless, our sample did contain stroke patients with various degrees of disability and should thus enable us to examine the association of changes in bone outcomes with severity of stroke impairments.

The time at which the first assessment was done was at least one year post-stroke and varied across the subjects. The time

period during which most substantial bone changes occur might have been missed. However, bone changes in sub-acute stages have been examined in a previous study<sup>12</sup>. Our main aim was to examine bone changes in chronic stroke patients, who are highly susceptible to physical deconditioning. The chronic stroke group also makes up the majority of the stroke population in the community.

Only two measurements were performed. It is thus impossible to determine whether bone changes are linear after the first year post-stroke. Nevertheless, we found no significant relationship between post-stroke duration and change in any of the pQCT parameters. It may indicate that among chronic stroke patients, other factors (e.g., disuse, vascular health) are more important determinants of bone changes rather than time since stroke onset.

We estimated the sample size based on previous studies in subacute stroke, which may result in underestimation, as the extent of bone changes in chronic stroke turned out to be less, as shown in this study. The drop-out rate was also greater than expected. These factors may reduce the statistical power and make it more difficult to find significant results. Additionally, the reduced statistical power did not allow us to perform subgroup analysis (e.g., gender, hand dominance).

Finally, we focused on the associations of neuromuscular and cardiovascular factors with bone changes in this study. The possible influence of dietary factors and sunshine exposure, for example, was not evaluated. Future research with a larger sample size is required to investigate the effects of these different factors on bone changes in the chronic stroke population using multivariate analysis.

## Conclusion

In this prospective study, there is evidence of endosteal resorption in the paretic radius diaphysis after chronic stroke, but the magnitude of bone changes was less when compared with that previously reported in sub-acute stroke patients. Higher physical activity level, better vascular health and more active use of the paretic arm were related to better preservation of cortical thickness in the paretic radius diaphysis among chronic stroke patients during the follow-up period.

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