https://doi.org/10.1016/j.bone.2020.115831

Title Page

Determinants of estimated failure load in the distal radius after stroke: an HR-pQCT study

Authors

[1]Tiev Miller, MSc, [2]Michael T.C. Ying, PhD, [3]Vivian W.Y. Hung, MSc, [1]Charlotte S.L. Tsang, PhD, [1]Huixi Ouyang, MPhil, [1]Raymond C.K. Chung, PhD, [3]Ling Qin, PhD, and [1]Marco Y. C. Pang, PhD

Author affiliations

[1]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

[2]Department of Health Technology and Informatics, The Hong Kong Polytechnic University

[3]Bone Quality and Health Centre, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong

Corresponding author

Marco Pang, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, SAR, Telephone: (852) 2766-7156, Email: marco.pang@polyu.edu.hk

Running Title

Bone quality post-stroke

Keywords

Radius, Stroke, Failure Load, HR-pQCT

Disclosure Page

Disclosure of funding sources

Tiev Miller was funded by a post-graduate research studentship through the department of Rehabilitation Sciences at The Hong Kong Polytechnic University (Grant RL27). This study was substantially supported by a research grant provided to Marco Y. C. Pang by the Research Grants Council (General Research Fund; 151031/18M).

Conflict of interest

The authors have no conflicts of interest to declare.

Data accessibility

The authors agree to deposit all project data on a community-recognized data repository at the time of publication.

Abstract

Bone health is often compromised after stroke and the distal radius is a common site of fragility fractures. The macro- and mircoproperties of bone tissue after stroke and their clinical correlates are understudied. The objectives of the study were to use High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) to investigate the bone properties at the distal radius, and to identify the correlates of estimated failure load for the distal radius in people with chronic stroke. This was a cross-sectional study of 64 stroke patients (age: 60.8±7.7 years, stroke duration: 5.7±3.9 years) and 64 age- and sex-matched controls. Bilateral bone structural, densitometric, geometric and strength parameters of the distal radius were measured using HR-pQCT. The architecture, stiffness and echo intensity of the bilateral biceps brachii muscle and brachial artery blood flow were evaluated using diagnostic ultrasound. Other outcomes included the Fugl-Meyer Motor Assessment (FMA), Motor Activity Log (MAL), and Composite Spasticity Scale (CSS). The results revealed a significant side (paretic vs non-paretic for stroke group, non-dominant vs dominant for controls) by group (stroke vs control) interaction effect for estimated failure load, cortical area, cortical thickness, trabecular number and trabecular separation, and all volumetric density parameters. Post-hoc analysis showed percent side-to-side differences in bone outcomes were greater in the stroke group than the control group, with the exception of trabecular thickness and intracortical porosity. Among the HR-pQCT variables, percent side-to-side difference in trabecular volumetric bone mineral density contributed the most to the percent side-to-side difference in estimated failure load in the stroke group (R^2 change=0.334, β=1.106). Stroke-related impairments (FMA, MAL, CSS) were found to be significant determinants of the percent side-to-side difference in estimated failure load (R^2 change=0.233, β=-0.480). This was the first study to examine bone microstructure post-stroke. We found that the paretic distal radius had compromised bone structural properties

and lower estimated failure load compared to the non-paretic side. Motor impairment was a determinant of estimated bone strength at the distal radius and may be a potential intervention target for improving bone health post-stroke.

Keywords: Radius, Stroke, Failure Load, HR-pQCT

1. Introduction

The economic implications of stroke are large, with long-term and indirect expenditures increasing for stroke-related health care.[1] The musculoskeletal system has been shown to undergo substantial change after stroke,[2] with bone loss prevention often being under prioritized during recovery.[3] Reduced bone mass and altered bone geometry (i.e., reduced cortical area), which compromise bone strength, are among the more serious complications after stroke.[4,5] Along with advanced age and female sex, reduced bone strength is an important factor related to upper limb fragility fractures after stroke.[6] While dual-energy x-ray absorptiometry (DXA) was used in the clinical assessment of total and site-specific areal bone mineral density (aBMD) post-stroke,[7,8] it can only generate bone mass and aBMD measurements due to its planar nature and lacks the ability to assess other bone parameters such as bone geometry and architecture, which are also important determinants of bone strength.[9-11] Other methods that are capable of assessing bone geometry and architecture are needed for studying the bone properties in health and disease.[12] Peripheral quantitative computed tomography (pQCT) can be used to examine compartmentalized volumetric density and geometry of both trabecular and cortical bone at peripheral skeletal sites.[8,13,14] It has also been used in research investigating bone health in specific musculoskeletal conditions such as adolescent idiopathic scoliosis, psoriatic arthritis and hip fracture.[15-17]

Several studies have used pQCT to examine bone properties of the upper limb post-stroke.[5,8,14,18-20] At the distal radius site (i.e., epiphysis), a consistent finding was a lower BMD on the paretic side, with no significant side-to-side difference in total area.[14,18] Previously, it was not possible to evaluate bone microstructure (e.g., cortical porosity, trabecular number, thickness and separation) using the first generation of pQCT scanners due to its relatively low resolution (voxel size: 300-500 μm).[5,14,21] Bone microstructure is another important factor determining bone fragility.[11,22,23] Among large prospective cohort studies, microstructure is consistently shown to be a predictor of fracture risk estimation in other populations.[10,24,25] Thus, examining bone microstructure using high-resolution peripheral quantitative computed tomography (HR-pQCT) (voxel size: 61-82 μm) should be of value in the study of bone health among individuals with stroke. To date, no study has examined bone microstructure in individuals with chronic stroke.

Previous pQCT studies in stroke patients have shown that neuromuscular (i.e., strength, spasticity, paretic arm disuse) and cardiovascular factors (i.e., vascular elasticity, oxygen consumption) have either been moderately associated with or predictive of compressive bone strength index (cBSI) or polar stress-strain index (p-SSI) among stroke patients, which are only surrogate measures of bone strength largely based on bone cross-sectional geometry (e.g., moment of inertia) and cortical/total bone density.[14,18] It is unknown whether these factors are also correlated with the estimated failure load derived from finite element (FE) analysis. When coupled with HR-pQCT, this computer modelling technique can intrinsically account for complex bone structure and provide an estimation of bone strength.[26] A recent systematic review showed muscle mass and strength to be consistently correlated with upper limb bone outcomes (i.e,, bone mineral content, density, bone strength index) in previous DEXA and pQCT studies involving stroke populations.[27] However, the relationship between bone strength and mechanical muscle tissue alterations

(i.e., stiffness) of the paretic upper limb, often ensuing stroke,[28,29] has not been examined and may also be relevant to bone health.

To address the above knowledge gaps identified above, the aims of this study were to investigate the impact of stroke on bone properties (macrostructure, microstructure, geometry, estimated strength) of the distal radius and to examine the association between the estimated failure load and indicators of muscle and physical function during the chronic stage of recovery. The wrist region is the second most frequent site of fragility fractures post-stroke.[6] As changes in peripheral bone sites have been shown to be more pronounced in the upper limb than lower limb following stroke,[19] the distal radius was examined in this study.

2. Methods

2.1 Participants

Individuals with chronic stroke and age- and sex-matched controls without prior stroke history were recruited from the general public, community self-help groups and an existing patient database. Relevant medical history and demographic data were obtained by phone interviews. Recruitment of participants commenced April 11, 2018 and ended February 28, 2019. A total of 67 stroke and 66 control participants were screened prior to data collection which was conducted from June 1, 2018 to March 30, 2019. From the stroke group, one person was excluded due to a congenital bone deformation in the tibia and two others withdrew from the study before all of the assessments were conducted. From the control group, one person was excluded due to a previous Achilles tendon repair surgery and another person was excluded due to an essential tremor. Study approval was granted by the Human Subjects Ethics Sub-committee of the University (reference number HSEARS20171212003 on January 2, 2018) and the Clinical Research Ethics Committee of the hospital (Joint Chinese University of Hong Kong-New Territories East Cluster Clinical

Research Ethics Committee, CREC reference number 2017-711 on April 10, 2018). Informed consent was obtained for all participants prior to data collection. All procedures were conducted in accordance with the Helsinki Declaration for human experiments.

For between-group comparisons of bone variables, a priori power analysis to determine the required sample size was done using the GPower 3.1 software (Heinrich Heine Universitat Dusseldorf, Germany).[30] Based on a previous pQCT study by Pang et al.,[14] the side × group interaction effect for the bone strength index of the radius yielded an effect size of f=0.25. Assuming the same effect size, an alpha of 0.05, and a power of 0.8, a minimum of 49 participants per group were required.

For the hierarchical regression analysis in predicting the percent side-to-side difference (%SSD) of estimated failure load among individuals with stroke, a separate power analysis was done using Free Statistics Calculators version 4.0 (https://www.danielsoper.com/statcalc/calculator.aspx?id=16). A previous pQCT study found that various stroke impairment variables (e.g., strength, spasticity) were associated with side-to-side difference in cortical thickness and bone mineral content of the radius (R^2 change = 0.20-0.26, equivalent to effect sizes f^2= 0.25-0.35).[5] Therefore, assuming an effect size of f^2=0.3 attributable to the stroke impairment variables, an alpha of 0.05, and a power of 0.8, a minimum sample size of 61 individuals with chronic stroke would be required to detect a significant effect of 5 impairment variables (e.g., muscle parameters measured by ultrasound, spasticity, etc.), after accounting for the effects of age, sex, post-stroke duration, body mass index (BMI), physical activity level, comorbidities, medications, tobacco, alcohol, calcium and vitamin D supplement usage, and %SSD in cortical perimeter.

After considering the two power analyses above, we aimed to recruit a minimum of 61 individuals with stroke, and 61 control participants.

2.2 Inclusion & exclusion criteria

The inclusion criteria for the stroke group were: (1) history of chronic stroke (onset >6 months), (2) age >18, (3) community-dwelling, (4) able to reach 60° of passive elbow flexion, (5) Abbreviated Mental Test (AMT) score ≥6.[31] The exclusion criteria were: (1) diagnoses of other neurological conditions, (2) significant musculoskeletal conditions (e.g. amputations), (3) metal implants in distal radius, (4) upper extremity fracture within the past 12 months, (5) diagnosis of osteoporosis, (6) severe contractures prohibiting the individual from reaching 60° of passive elbow flexion, (7) other serious illnesses that precluded participation in the study. The control group had the same eligibility criteria with the exception of prior stroke history.

2.3 Measurement procedures

2.3.1 HR-pQCT

Bone imaging was conducted at a bone imaging center in a local hospital. Volumetric bone mineral density (vBMD) and architecture were measured at the distal radius using a three-dimensional HR-pQCT system (XtremeCT II; Scanco Medical AG, Bassersdorf, Switzerland) which simultaneously acquires a stack of 168 parallel CT slices with an isotropic voxel size of 61µm and a matrix size of 2304 × 2304. All standard scans were performed under the following settings: effective energy of 68 kVp, X-ray tube current of 1470 µA, scanning time per site of 1.8 minutes and an effective dose of 5µSv per scan.[26] The same scanner was used for all stroke and control participants throughout the study period. The scan region was fixed at 9.0 mm (distal radius) proximal from the mid-joint line. Length of the scan region spanned 10.2 mm proximally. A fixed rather than relative offset distance (i.e., %-length method) was used.[26] A summary description of all HR-pQCT variables collected is provided in the supplementary appendices (Supplemental Table 1).

Standard analysis of 3D bone parameters was conducted using Image Processing Language software (IPL v5.08b, Scanco Medical AG, Brüttisellen, Switzerland). The forearm, wrist and hand were immobilized prior to placement within the scanner gantry using a formable padded cast provided by the manufacturer in order to standardize anatomical orientation and minimize motion during acquisition. Calibration using a quality control phantom was performed daily to monitor the stability of the density and architectural parameters as suggested by the manufacturer (Scanco Medical AG, User's Guide for XtremeCT II Version 1.2). The deviation of the calibration value was less than 1.5% of the quality control phantom value provided by the manufacturer (Scanco Medical AG, User's Guide for XtremeCT II Version 1.2). To confirm image quality, motion grading guidelines were followed [32]. Scans with a motion grade score between 1-4 would be retained.[26] The second generation scanner (XtremeCT II) has demonstrated excellent reproducibility.[33] In the current study, the root mean squared percent coefficient of variation ($CV\%_{RMS}$) of short term precision for the radius among a cohort of 30 healthy individuals were 0.21-0.94% for geometric measures. The corresponding values for density and microstructural parameters were 0.29-0.95% and 0.52-3.36%, respectively. This scanner has comparatively higher resolution (isotropic voxel size of 61 μm for XtremeCT II) and has demonstrated excellent agreement with the previous-generation scanner for most densitometric measures.[34]

2.3.2 Finite Element Analysis

The finite element (μFE) analysis was performed using the FE-solver provided by the manufacturer (IPL v5.08b, Scanco Medical AG, Brüttisellen, Switzerland). CT images were segmented using a dual-threshold technique and converted into an FE mesh. A voxel-by-voxel conversion approach was used to convert each voxel into a cubic hexahedral finite element for analysis. Material properties chosen were isotropic and elastic. A linear high-

friction compression model was applied with a Young's modulus of 10 GPa and a Poisson's ratio of 0.3 assigned. A compression test was simulated in which a 1000N load in the axial direction was applied at one end (distal-most row of elements) while the other end (proximal-most row of the elements) was fully constrained to simulate a fall from standing height on an outstretched arm.[35] A bone tissue yield strain of 7000 μstrain was chosen based on studies by van Rietbergen et al.[36] and Niebur et al.[37] The failure criterion was set at 2% of bone tissue strained based on the published data from Pistoia et al. [38] The experimental study, using cadaveric arms, was performed in correlating the experimental failure load (using uniaxial-driven mechanical testing machine) and FE analysis (using HR-pQCT images) at different failure criterion (varying from 1%-7% strained). Among the 1-7% failure criteria, the best prediction of bone failure was obtained when it was assumed that 2% of the bone tissue is loaded beyond a yield strain of 7000 μstrain at the onset of fracture. Similar results were also supported by Niebur et al.[37] who reported that 2.5% of the tissue exceeded the tissue yield strain when reaching the apparent compressive yield point. Therefore, we selected a 2% strain at 7000 μstrain. Similar settings have been applied in previous clinical and large, population-based studies to predict fracture risk[17] and determine age-related differences in bone loss.[39]

2.3.3 Ultrasound

To measure various aspects of muscle properties (stiffness, echo intensity, cross-sectional area, blood flow), ultrasound imaging was conducted in a muscle imaging lab of the University. An Aixplorer ultrasound scanner (Aixplorer, SuperSonic Imagine, Aix en-Provence, France) coupled with a linear array probe (4-15 MHz, SuperLinear, 15-4, Vermon, France) was used. For each parameter, the average of 3 measures was used for the analysis. A standoff gel couplant layer of approximately 2mm thickness served as the interface between

the probe and skin surface to minimize probe compression on muscle during measurements. Surface electromyography (sEMG) (Bagnoli EMG system, Delsys Inc, Natick, Massachusetts, USA) was used concomitantly to confirm muscle relaxation. In the event of contracture or spastic response, images were retaken. A low-pass filter <10Hz was applied for wave rectification of all real-time sEMG signal data using LabVIEW software (National Instruments Co., Austin, Texas, USA). A notch filter was also applied at 50, 100 and 150Hz frequencies to preserve sEMG signal integrity and suppress powerline and harmonic noise during image capture. Following skin preparation (i.e., shaving, abrading, sterilization and conductive gel), a sensor (SX230, Biometrics Ltd, Gwent, UK) was placed on the skin surface of the muscle and affixed using a die cut medical grade adhesive tape. A bilateral comparison of muscle parameters is shown in Figure 2.

2.3.3.1 Muscle stiffness: The shear wave velocity (m/s) of the biceps brachii muscles was measured using a standard musculoskeletal imaging preset in shear wave elastography mode. Shear wave velocity is a measure of shear wave dispersion through tissue. Higher velocities indicate greater tissue stiffness.[40] During image acquisition, participants were placed in a supine position with the shoulder abducted 45° and elbow joint immobilized at 60° of flexion using an external fixation device. Measurement sites were standardized at the lower third of the humerus (approximately 66% of the total length) according to an adapted procedure used by Wu et al.[29] The probe was placed in parallel alignment to the muscle fascicle direction. The region of interest (ROI) was standardized for all measures (1.89 cm^2 area with an approximate depth of 1 cm below the subcutaneous tissue layer). Individual images were captured after a consistent and stable color distribution was observed. All values were generated using a Q-box Trace function (Supersonic Imagine, Aix en-Provence, France) during image processing. Ultrasound elastography has demonstrated moderate reliability in

measuring muscle stiffness and good convergent validity with clinical assessments of post-stroke spasticity and motor impairment.[41]

2.3.3.2 Echo intensity: Muscle echo intensity was measured using B-mode ultrasound. For each measurement, the probe was angled cranially and caudally until maximal echo intensity was observed in the scanning plane. Gray-scale analysis was conducted with an impixel calculation function using a customized program written in Matlab (version R2018a, Mathworks, Natick, Massachusetts, USA). The ROI (1.89 cm^2 area) was the same as each elastogram captured.[28] Gray-scale values were standardized at a gain of 50% for all measures, with darkest and lightest pixels represented by values of 0 and 255, respectively.

2.3.3.3 Muscle cross-sectional area: Muscle cross-sectional area (MCSA) (in cm^2) of the biceps brachii was measured using a panoramic image capture function in B-mode ultrasound at the measurement site previously specified for muscle stiffness measures above. A foam padded adhesive probe support was placed in line with the muscle circumference to reduce probe translation and ensure clarity during image capture. Using the perimeter trace function (Supersonic Imagine, Aix en-Provence, France), a muscle region from the medial to lateral borders was manually selected.

2.3.3.4 Vascular measures: Vascular parameters were also measured as previous work has indicated that the influence of these factors on bone strength are regional and more pronounced in the epiphysis than diaphysis.[42-44] Peak systolic velocity (cm/s) of the brachial artery was measured using pulse wave Doppler ultrasound by initially placing the probe transversely along the medial aspect of the upper arm (measurement site previously stated). The probe was then rotated sagittally and tilted to visualize the artery longitudinally. An

electronic calliper was then placed in the artery center, and the sample volume was standardized at 0.5mm. Angle correction and steering were adjusted to optimize angle-to-flow (≤ 60° insonation). Spectral waveform cycles with 3 consistent readings were used to calculate each measurement trial.

2.4 Functional assessment procedures

Measures of functional and stroke-specific impairments were conducted in a university laboratory. For muscle strength and touch pressure threshold parameters, the average of 3 trials were used for the analysis. Functional assessments were conducted on a separate day prior to ultrasound assessments to minimize the influence of strength testing on muscle, vascular and elastography outcomes. All functional assessments were obtained for both control and stroke groups (i.e., physical activity level, muscle strength) with the exception of spasticity, motor impairment and paretic limb usage. These stroke-specific assessments were only conducted among stroke participants.

2.4.1 Spasticity

The composite spasticity scale (CSS) was used to measure elbow flexor spasticity (score range: 1-16), with higher scores indicating more severe spasticity. The CSS has shown high test-retest reliability in previous studies examining spasticity among stroke patients (ICC=0.97).[45,46]

2.4.2 Upper limb motor impairment

The Fugl-Meyer Motor Assessment (FMA) is a stroke-specific assessment used to evaluate the motor impairment of the paretic arm for reflex, neuromuscular coordination and

volitional movement with and without accompanying synergies (score range: 0-66). FMA has demonstrated high inter-rater reliability (ICC=0.97) in stroke patients.[47]

2.4.3 Paretic limb use

The Motor Activity Log (MAL) questionnaire served as a subjective appraisal of paretic arm usage frequency during 30 functional activities according to the Amount of Use (AOU) scale. Mean scores from the 30-item scale were used for analysis. Among stroke patients, the MAL-AOU scale has shown high internal consistency (Cronbach's α=0.88).[48]

2.4.4 Physical activity level

An adapted version of the 12-item Physical Activity Scale for the Elderly (PASE) was used to evaluate general physical activity level. Scores are calculated by weights and frequency values which correspond to each activity type assessed, with higher scores indicating higher activity level. This version has been previously validated in elderly Chinese populations and has demonstrated good test-retest reliability (ICC=0.81) and fair to moderate association with other clinically relevant measures of function.[49]

2.4.5 Muscle strength

The isometric peak torque (N/m) of elbow flexors was assessed using a dynamometer (Humac Norm Systems, Stoughton, Massachusetts, USA) in 60° of elbow flexion and 45° of shoulder abduction. Measurement error has been shown to be smaller for isometric than isokinetic testing conditions.[50] A 60° angle was used for testing based on evidence suggesting elbow flexion torque is greatest in 56° for healthy individuals[51] and 60° for paretic arms in stroke patients.[52] Wrists were used as the contact interface between participants and the dynamometer handle due to impairments in grip strength or dexterity of

paretic hands. The wrist was held in place by elastic straps. A triangular support cushion was also placed in the lower-axilla region to maintain a 45° angle of shoulder abduction.

2.5 Statistical analysis

The following analyses were performed using SPSS (version 26.0, SPSS Inc., Chicago, Illinois, USA) at a significance level of 0.05 (two-tailed). Independent t, Mann-Whitney U and χ^2 tests were used comparing baseline between-group differences for participant characteristics according to continuous, ordinal and nominal levels of data, respectively. Wilcoxon test was used to compare the motion artefact scores between the two sides in each of the stroke and control groups, and Mann-Whitney U test was used to compare these scores between groups. A linear mixed model was used to examine within and between-groups differences for HR-pQCT, ultrasound and isometric peak torque variables assessed bilaterally [within-subject factor: side (paretic vs non-paretic for stroke group or non-dominant vs dominant for control group), between-subject factor: group (stroke vs control)]. This approach takes correlation between repeated measures into account[53] and is considered robust when the variance in data distribution is either non-gaussian or heteroscedastic.[54] A significant side × group interaction effect generated by the model indicates the side-to-side difference of the variable is group-dependent ($p \leq 0.05$). Following the linear mixed model analysis, post-hoc paired t-tests were used to compare between the two sides. Post-hoc independent t-tests were also used to compare the percent (%) side-to-side difference (%SSD) between the stroke and control groups. A more stringent significance level of 0.017 (Bonferroni's correction: 0.05/3) was used for post-hoc tests to adjust for multiple comparisons. The following formula was used in calculating %SSD:

$$\frac{\text{Non-paretic or Dominant side} - \text{Paretic or Non-dominant side}}{\text{Non-paretic or Dominant side}} \times 100$$

The %SSD is derived from comparing the two sides within the same individual and may provide a more specific assessment of the impact of stroke on bone and muscle properties on the hemiparetic side, while controlling for different cofactors affecting bone metabolism across individuals (i.e. genetic, age, nutrition, and other personal and environmental factors).[44,55] As a standardized score, it also facilitates between-group comparisons. The %SSD has also been used in previous research assessing bone status in the upper limb post-stroke.[5,14]

A subgroup analysis was conducted using dichotomous grouping based on average stroke duration (i.e., below or above 5.8±4.0 years) and using tertiles of comparable subject groupings according to stroke onset chronology (i.e., ≤3 years (n=19), 4-5 years (n=21), and ≥6 years (n=24)). A subgroup analysis was also conducted for dichotomous groups based on the limb most affected by stroke (i.e., dominant side (n=28) or non-dominant side (n=36)). Between-group differences for all bone parameters were assessed with independent t-tests for dichotomous grouping and one-way ANOVA for tertiles.

Pearson's r was also used to examine bivariate correlations between %SSD in estimated failure load of the distal radius and %SSD of other variables. As %SSD calculations were not suitable for stroke-specific outcomes measured only on the paretic side (i.e., CSS, FMA and MAL-AOU), raw values were used to assess their correlation with %SSD in estimated failure load.

For the stroke group, we were interested in determining which aspects of bone (e.g., densitometric, microstructure, cortical vs trabecular, etc.) contributed more to the %SSD in estimated failure load. Failure load was used the dependent variable because it is considered a material parameter accounting for material behavior (yield, post-yield) and loading (magnitude of applied force) required to strain bone tissue beyond a critical limit.[38]

Estimated failure load has been shown to be a better predictor of incident fracture than volumetric density[56] and bone morphometry measures alone.[38] The identification of failure load thresholds suggestive of higher fracture risk has been described in a multicentre prospective study involving large cohorts of elderly men and women.[57] This study showed estimated failure load to be the strongest correlate of incident fracture.[57] Stroke-related impairment and consequent hemiosteoporosis of paretic limbs may also exacerbate proclivity to fracture.[6] Although estimated failure load is essentially a material parameter and not a direct determinant of fracture risk, the amount of bilateral difference in estimated failure load among individuals with stroke, in comparison to that of their counterparts without stroke, may provide a meaningful comparison of hemiparetic bone status which differs from previous estimates of bone strength (e.g., compressive bone strength index, polar stress-strain index).[5,14,18,19]

First, the bone variables were classified into six categories (i.e., cortical area, trabecular area, cortical vBMD, trabecular vBMD, cortical microstructure, trabecular microstructure), in accordance with description in Whittier et al.[26] For categories containing more than one variable (e.g., trabecular microstructure: %SSD trabecular number, %SSD trabecular thickness, %SSD trabecular separation, %SSD trabecular bone volume fraction; and cortical microstructure: %SSD cortical thickness, %SSD cortical perimeter, %SSD intracortical porosity), a principal component analysis was done to transform the data into one variable (factor). Next, the above six variables were entered into a hierarchical regression model to identify their associations with the %SSD in estimated failure load.

Next, a second hierarchical multiple regression analysis was used to identify the associations between the functional and ultrasound variables and %SSD in estimated failure load (dependent variable) for the stroke group, while adjusting for potentially confounding factors (e.g., demographics). Prior to the regression analysis, the demographic data,

functional and ultrasound variables were entered into the principal component analysis to objectively and quantitatively identify the independent variables for the regression model. Factors extracted from the principal component analysis, and also the %SSD in cortical perimeter (to adjust for the potential variation in the location of the scan region), were entered into the model using a hierarchical regression series procedure described in detail by Mancuso et al.[58]

3. Results

3. 1 Participant characteristics

A total of 64 stroke and 64 control participants completed all the assessments. A summary of participant characteristics is provided in Table 1. Scan quality was good for all stroke and control group participants (i.e., motion grade = 1-4). Significant baseline differences between the stroke and control groups were observed for total number of comorbidities and medications. There was also a small but significant difference in AMT score. Otherwise, no significant between-group differences were found for other variables. For the stroke group, the mean scores for the CSS, FMA and MAL-AOU indicated mild spasticity, moderate degree of motor impairment, and minimal perceived usage frequency of the paretic arm, respectively.

3.2 HR-pQCT variables

As the total number of medications and comorbidities per person are physiologically relevant to bone health and showed significant between-group differences, they were used as covariates in the linear mixed model analysis. There was a significant side × group interaction effect for estimated failure load, indicating that the magnitude of the side-to-side difference in this variable was group-dependent, after accounting for the between-group

differences in total medications and comorbidities (Table 2). A significant interaction effect was also observed for all volumetric density parameters, cortical area, cortical thickness, trabecular number, trabecular separation, and trabecular bone volume fraction (Table 2). Post-hoc paired t-tests showed significant differences in cortical area, trabecular area, number and separation, and estimated failure load parameters between the two sides in both the stroke and control groups. In addition, all volumetric density parameters, cortical thickness and trabecular bone volume fraction demonstrated significant side-to-side differences in the stroke group, but not in controls. On the other hand, the cortical perimeter showed a side-to-side difference in the control group, but not the stroke group (Table 2). With the exception of intracortical porosity and trabecular thickness, post-hoc analysis showed a significant difference in %SSD of all bone parameters between the stroke and control groups (Table 2). No significant differences were found in the motion grade scores between sides for the two groups, as well as between groups suggesting that paretic arm spasticity did not affect scan quality (Supplemental Table 2). The HR-pQCT images obtained from a representative stroke patient and an age- and sex-matched control participant are displayed in Figure 1.

3.3 Other variables

For other variables measured bilaterally, a significant side × group interaction effect was observed for echo intensity and isometric strength. A side-to-side comparison of muscle variables measured using ultrasound is provided in Figure 2. All other ultrasound variables showed no significant interaction effects (Table 3). Post-hoc paired t-tests showed significant side-to-side differences for muscle cross sectional area, echo intensity and isometric strength in the stroke group, but not controls (Table 3). Post-hoc independent t-tests also showed a significant between-group difference in %SSD for these variables (Table 3).

3.4 Subgroup analysis

There were no associations between stroke duration and all bone parameters (r=-0.214–0.218, p≤0.893) (Supplemental Table 3). When participants were grouped dichotomously according to below or above average stroke duration, independent t-test showed no significant differences between groups for all bone parameters (p≤0.997) (Supplemental Table 4). For tertile subdivision of comparable group numbers, one-way ANOVA results also showed no significant between-group difference for all bone parameters (F=0.038-1.629, p≤0.886) (Supplemental Table 5). For dichotomous subgroups based on the stroke-affected side (i.e. dominant vs non-dominant), %SSD in trabecular area was significantly greater for those whose stroke-affected side was the dominant side (n=28, p=0.001) while %SSD in cortical area was significantly greater for those whose stroke-affected side was the non-dominant side (n=36, p=0.013). (Supplemental Table 6).

3.5 Correlations, principal component analysis and regression analysis

Regression analysis was used to determine the relative contributions of different bone properties to the %SSD in estimated failure load for the stroke group. Bone variables under the trabecular microstructure (Factor 1) and cortical microstructure (Factor 2) categories were reduced to single factors following the principal component analysis (Supplemental Table 7). These factors, along with other bone parameters, were then entered into a hierarchical regression model (Table 4). Among the bone parameters, %SSD in trabecular vBMD (β=1.106), trabecular microstructure (Factor 1) (β=-0.674), cortical area (β=0.658) and cortical microstructure (Factor 2) (β=-0.318) were significant determinants of %SSD in estimated failure load (F=18.151, p<0.001), and accounted for 33.4%, 4.0%, 12.9% and 3.5% of the total variance, respectively (Table 4).

Bivariate correlations between %SSD of failure load and other variables (e.g., demographic, functional and ultrasound data) for the stroke group are shown in Supplemental Table 8. A separate regression analysis was done to determine the associations between different functional /ultrasound variables and %SSD in estimated failure load for the stroke group, while adjusting for the effects of potentially confounding variables (e.g., demographic data). Using principal component analysis, the data were reduced to 8 factors (Supplemental Table 9). These factors were then used as independent variables for the hierarchical regression model (Table 5). After controlling for %SSD in cortical perimeter, Factor 1 (i.e., FMA, MAL, CSS) (β=0.480) remained independently associated with %SSD of estimated failure load (F=2.827), accounting for 23.3% of the variance (Table 5).

4. Discussion

Several HR-pQCT variables demonstrated significant interaction effects, indicating that stroke had a substantial impact on bone density, area and microstructure variables. Among these, trabecular vBMD, trabecular microstructure, cortical area and cortical microstructure were significant determinants of %SSD of estimated failure load at the distal radius. Of the various potential clinical correlates, motor function [Factor 1: motor impairment severity (FMA), perceived usage frequency (MAL-AOU) and spasticity (CSS)] emerged as a significant determinant of the %SSD of estimated failure load.

4.1 HR-pQCT variables

The side-to-side differences in volumetric density parameters observed in our study (4.6%-23.1%, p≤0.017) (i.e., lower cortical, trabecular and total vBMD in paretic limbs) are largely consistent with previous pQCT studies in stroke populations.[8,14,19] The detrimental impact of stroke on geometric and structural bone parameters of the radius have also been

reported previously.[5] However, cortical area and thickness measures at the distal radius have been problematic due to thin cortical shells on the paretic side and lower resolution of previous pQCT scanners (i.e., voxel size: 300-500 μm).[5,14,21] In the present study using HR-pQCT (i.e., 61 μm), these parameters were significantly diminished on the paretic side (14.4%-15.1%, $p \leq 0.017$) (Table 2). Cortical area was also a significant determinant of estimated failure load according to our regression results ($\beta=0.658$) (Table 4). In terms of bone microstructure, the %SSD (i.e., paretic side deficit) was more evident for trabecular number (12.3%), trabecular separation (24.3%), trabecular bone volume fraction (21.1%) and cortical thickness (14.4%) in comparison to trabecular thickness (0.89%, $p>0.05$), cortical perimeter (0.04%) and intracortical porosity (8.4%) (Table 2). The results of the regression analysis seem to indicate a stronger relationship between estimated failure load and trabecular microstructure (Factor 1) ($\beta=-0.674$) compared to cortical microstructure (Factor 2) ($\beta=-0.318$) (Table 4). As trabecular vBMD was the largest contributor of estimated failure load ($\beta=1.106$) (Table 4), together, these findings suggest a greater loss of trabecular bone relative to cortical bone.

Significantly lower number and greater average distance between trabeculae may indicate substantial loss of trabeculae on paretic sides and reduced connectivity with greater heterogeneous distribution of trabecular bone. A similar bone loss pattern has been observed when comparing premenopausal and postmenopausal osteopenic or osteoporotic women ($p<0.01$).[11] Greater trabecular bone loss and more heterogeneous distribution of trabeculae in the radius was found among osteopenic women with fractures compared to women without fracture history ($p<0.02$) despite similar spine and hip bone density.[11] Low trabecular number in the radius has also been shown to be highly associated with increased osteoporotic, vertebral and non-vertebral fracture risk (Hazard Ratio=1.46-1.80 per SD, $p \leq 0.01$) in a large prospective trial of elderly men.[59] In recent meta-analyses, trabecular vBMD in particular, as

well as trabecular bone volume fraction, was strongly associated with fracture.[56,60] However, trabecular microstructure alone may lack the sensitivity and specificity to fully distinguish fracture risk.[59] Though not exclusively for the identification of Colles-type fractures of the radius, material bone parameters from μFE analysis have been suggested to be superior to vBMD and microstructure for separating fragility fracture cases from controls at multiple bone sites.[61] The degree to which compromised microstructural properties contribute to fracture risk in individuals with stroke will require future research.

4.2 Spasticity

Spasticity (CSS score) is one of the variables included in Factor 1 (Table 5) that was shown to be a significant determinant of %SSD in estimated failure load in the regression analysis. Previous studies examining the impact of spasticity on bone properties post-stroke have produced mixed results.[5,8,14,42,43,62,63] Paretic upper limb spasticity has been shown to be a weak correlate of cortical bone mineral content (BMC) ($r=0.457$, $p<0.05$) and cortical thickness ($r=0.476$, $p<0.05$) in the distal radius.[5] In studies involving the lower limb, associations between bone strength index and moderate to severe presentations of spasticity have been shown to be either weak in regression models ($\beta=-0.235$, $p=0.028$)[43] or lacking in bivariate correlations (males: $r=-0.167$, females: $r=-0.014$).[63] There were also methodological differences between spasticity measures in our study (i.e., CSS) compared to previous studies (i.e., Modified Ashworth Scale). The Modified Ashworth Scale is only used to evaluate resistance to passive movement whereas the CSS is a more comprehensive multi-component scale for assessing additional neurogenic aspects of spasticity (i.e., tendon jerk and wrist clonus). Future studies investigating the influence of post-stroke spasticity on bone should consider the precision and specificity of the assessments used.

4.3 Upper limb motor recovery

FMA was moderately correlated with %SSD of estimated failure load in the bivariate correlation analysis (r=-0.54, p<0.001) (Supplemental Table 8). Our regression analysis confirmed that FMA contributed to %SSD of estimated failure load. A previous study reported only a weak association between Wolf Motor Function Test scores and %SSD in cortical BMC (r=-0.42, p<0.05), cortical thickness (r=-0.42, p<0.05) and no association with the %SSD in polar stress-strain index p-SSI (r=-0.150) of the radius diaphysis.[5] Another study also showed a moderate association between FMA scores and stress-strain index of the paretic radius midshaft (R=0.62, p=0.04).[20] Whether or not rehabilitation interventions with motor training components can potentially influence bone strength after stroke is difficult to determine based on the inconsistencies in reported associations. However, a study involving a 6-month comprehensive motor exercise program was shown to be effective in increasing trabecular bone content (p=0.048) and cortical bone thickness (p=0.026) of the paretic tibia in chronic stroke patients.[64] A similar program targeting the neuromotor system for the purpose of enhancing bone strength in upper limb sites, awaits further study.

4.4 Perceived paretic upper limb use

MAL score, indicative of perceived paretic arm disuse, is another variable that constitutes Factor 1 which showed a significant association with %SSD in estimated failure load as revealed by the regression analysis. As stated previously, paretic arm motor impairment, of which disuse is a major component, has been shown to yield a weak to moderate correlation with cortical BMC loss in the paretic distal radius (r=-0.42, p<0.05) and reduced polar stress-strain index in the midshaft of the paretic radius (R=0.62, p=0.04).[5,20] The results of the regression suggest that more frequent paretic arm usage during daily

activities may be an important prescriptive element. During acute and subacute stages of stroke recovery, failed attempts to use the paretic arm in daily activities reinforce psychological patterns of disuse often termed the "learned non-use" phenomenon. Constraint-induced movement therapy, which is commonly used to overcome non-use,[48] has not been explored as a potential intervention for improving bone strength. Although physical activity and exercise in general, are well-accepted stimuli for improving bone strength in populations with comparable changes (i.e., post-menopausal women),[65] it may be relatively underutilized for this specific purpose after stroke.[2,27]

4.5 Muscle Strength

Muscle strength, also pertinent to motor function post-stroke, has consistently proven to be a strong correlate and predictor of bone geometry, density and strength of the paretic radius in previous studies.[5,14,62] The lack of correlation between elbow flexion strength and %SSD of estimated failure load observed in our study is perhaps explained by the different muscle groups and joint actions tested. Elbow flexion peak toque was the only measure of paretic arm strength assessed in our study. As the biceps brachii was the main muscle measured during ultrasound assessments, we used elbow flexor strength as our muscle strength measure. Previous research also showed that the degree of strength impairment in elbow flexion (25.6% of normal) was similar to that in more proximal (shoulder abduction; 23.6% of normal) and distal (wrist extension; 25.6% of normal) muscle actions.[5] However, the muscle force stimulus provided by the biceps brachii is limited to the proximal radius and may thus play a minor role in influencing the bone properties of the distal radius. Grip strength may have been a more appropriate measure for our study.

4.6 Limitations

In this study, the standard μFE analysis with the same linear elastic modulus assignment was used for all participants. This approach has also been used previously for comparing bone parameters between clinical populations and controls.[23] Other studies have also used non-linear approaches (i.e., models using asymmetric strain criteria) with higher and lower modulus values for cortical and trabecular bone elements, respectively.[66-68] The elastic modulus of cortical and trabecular tissues has been shown to differ based on modulus direction.[69] There is some support for the concomitant use of both linear and non-linear μFE analysis for estimating bone strength in comparing the moduli of homogeneous tissue and scaled CT-attenuation models.[66] Although more computationally intensive, non-linear FE analysis may offer a more direct estimate of bone mechanical strength properties given that cortical and trabecular bone exhibit differing post-yield behaviours.[70] Therefore, when anticipating potentially lower volumetric bone density of the paretic side,[8,14,18,19] particularly for cortical bone,[14,18] the use of a non-linear and/or density-dependent modulus in the FE analysis of bone strength properties among stroke groups may warrant future investigation.

Limb length differences between subjects and groups is also a potential confounding element associated with the fixed offset distance scanning protocol used in this study.[26] Although several studies to date have used a fixed offset approach to standardize measures,[15-17,23-25,59] it may be important to consider the limitations associated with both fixed and relative offset methods based on factors influencing limb length for a given subject sample.[26] For example, the fixed offset distance method may result in variation in the location of scanned region between the two sides, particularly when there was a limb length difference. On the other hand, the relative method entails accurate limb length measurement prior to scanning, and assumes proportionality between limb length and bone regions of the epiphysis, metaphysis and diaphysis.[26] Nevertheless, the use of the fixed offset method

should have minimal impact on our overall conclusion, because there was no significant difference in height between the two groups and %SSD in cortical perimeter was used as a covariate in the regression analysis.

This study was unable to demonstrate an association between stroke duration and bone properties. All stroke group participants were in the chronic stages of recovery. There is some evidence that trabecular bone loss in the paretic tibia is continuous but also tends to plateau approximately 2 years following the initial stroke.[21] It is unknown if a similar pattern of loss is evident for the radius. Additionally, participants from the stroke and control groups were only recruited through a non-probability sampling method and results can only be generalizable to individuals who share similar clinical presentations to our sample. Finally, because this study was cross-sectional in nature, it cannot demonstrate temporal changes in bone parameters nor prove a causal relationship between stroke-related impairment and distal radius fracture. The relationship between estimated failure load and incident fracture in stroke patients will require further investigation.

4.7 Conclusion

This study showed that bone density, macrostructure and microstructure of the paretic distal radius were compromised in chronic stroke patients. There was a substantially lower estimated failure load for the paretic compared to the non-paretic side, which was mainly explained by the compromised trabecular vBMD, trabecular microstructure, cortical area and cortical microstructure on the paretic side. Stroke-related motor impairment was the only emergent clinical determinant of the %SSD in estimated failure load in the stroke group. The relevance of these factors for improving bone strength after stroke will require further study.

Acknowledgements

Each author contributed in the following capacities. Study design: MP, MY, LQ and TM. Data collection: TM, MY, VH, CT, HO, and LQ. Data analysis: MP, RC and TM. Data interpretation: MP, RC, and TM. Manuscript drafting: MP, MY, LQ, VH, RC, and TM. Manuscript content revision: MP, RC and TM. Final manuscript approval: MP, MY, LQ, VH, CT, HO, RC, and TM. MP takes responsibility for the integrity of the data analysis. The authors would also like to thank all of the study participants and to acknowledge Carol Wing Yee Choy, Sik Cheung Siu, Chi Hin Li, Pui Hang Chan, Ngai Lam Yu, Tat Wai Lai, Wai Cheong Wong, Virginia Lok Tung Lau, Steven Kang Long Peng, Fei Xue Li, Yi Xuan Duan, Qi Ao, and Meizhen Huang for their support and technical assistance with regards to participant recruitment, protocol refinement, and data collection during the course of this project.

References

1. Demaerschalk BM, Hwang H-M, Leung G. US cost burden of ischemic stroke: a systematic literature review. The American journal of managed care. 2010/07// 2010;16(7):525-33.
2. Eng JJ. Balance, falls, and bone health: Role of exercise in reducing fracture risk after stroke. The Journal of Rehabilitation Research and Development. 2008;45(2):297-314.
3. Poole KES, Reeve J, Warburton EA. Falls, fractures, and osteoporosis after stroke. Time to think about protection? Stroke. 2002;33(5):1432-6.
4. Beaupre GS, Lew HL. Bone-Density Changes After Stroke. Am J Phys Med Rehabil. 2006;85(5):464-72.
5. Pang MY, Ashe MC, Eng JJ. Muscle weakness, spasticity and disuse contribute to demineralization and geometric changes in the radius following chronic stroke. Osteoporos Int. Sep 2007;18(9):1243-52. Epub 2007/04/03.
6. Dennis MS, Lo KM, McDowall M, West T. Fractures After Stroke. Frequency, Types, and Associations. 2002;33(3):728-34.
7. Ramnemark A, Nyberg L, Lorentzon R, Englund U, Gustafson Y. Progressive Hemiosteoporosis on the Paretic Side and Increased Bone Mineral Density in the Nonparetic Arm the First Year after Severe Stroke. Osteoporos Int. 1999/03/01 1999;9(3):269-75.
8. Lazoura O, Groumas N, Antoniadou E, Papadaki PJ, Papadimitriou A, Thriskos P, et al. Bone mineral density alterations in upper and lower extremities 12 months after stroke measured by peripheral quantitative computed tomography and DXA. J Clin Densitom. Oct-Dec 2008;11(4):511-7. Epub 2008/07/22.
9. Langsetmo L, Peters KW, Burghardt AJ, Ensrud KE, Fink HA, Cawthon PM, et al. Volumetric Bone Mineral Density and Failure Load of Distal Limbs Predict Incident Clinical Fracture Independent of FRAX and Clinical Risk Factors Among Older Men. J Bone Miner Res. 2018;33(7):1302-11.
10. Biver E, Durosier-Izart C, Chevalley T, van Rietbergen B, Rizzoli R, Ferrari S. Evaluation of Radius Microstructure and Areal Bone Mineral Density Improves Fracture Prediction in Postmenopausal Women. J Bone Miner Res. Feb 2018;33(2):328-37. Epub 2017/09/30.
11. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab. Dec 2005;90(12):6508-15. Epub 2005/09/29.
12. Souzanchi MF, Palacio-Mancheno P, Borisov YA, Cardoso L, Cowin SC. Microarchitecture and bone quality in the human calcaneus: local variations of fabric anisotropy. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2012;27(12):2562-72.
13. Sievänen H, Koskue V, Rauhio A, Kannus P, Heinonen A, Vuori I. Peripheral Quantitative Computed Tomography in Human Long Bones: Evaluation of In Vitro and In Vivo Precision. J Bone Miner Res. 1998;13(5):871-82.
14. Pang MY, Cheng AQ, Warburton DE, Jones AY. Relative impact of neuromuscular and cardiovascular factors on bone strength index of the hemiparetic distal radius epiphysis among individuals with chronic stroke. Osteoporos Int. Sep 2012;23(9):2369-79. Epub 2012/02/09.

15. Cheuk KY, Hu Y, Tam EMS, Shi L, Yu FWP, Hung VWY, et al. Bone measurements at multiple skeletal sites in adolescent idiopathic scoliosis-an in vivo correlation study using DXA, HR-pQCT and QCT. Arch Osteoporos. Jun 27 2019;14(1):70. Epub 2019/06/30.
16. Wu D, Griffith JF, Lam SHM, Wong PCH, Shi L, Li EK, et al. Progressive structural bone changes and their relationship with treatment in patients with psoriatic arthritis: a longitudinal HR-pQCT study. Arthritis Res Ther. Dec 4 2019;21(1):265. Epub 2019/12/06.
17. Zhu TY, Hung VW, Cheung WH, Cheng JC, Qin L, Leung KS. Value of Measuring Bone Microarchitecture in Fracture Discrimination in Older Women with Recent Hip Fracture: A Case-control Study with HR-pQCT. Sci Rep. Sep 27 2016;6:34185. Epub 2016/09/28.
18. Pang M, Zhang M, Li L, Jones A. Changes in bone density and geometry of the radius in chronic stroke and related factors: A one-year prospective study. J Musculoskelet Neuronal Interact. 2013;13(1):77-88.
19. Talla R, Galea M, Lythgo N, Eser T, Talla P, Angeli P, et al. Contralateral comparison of bone geometry, BMD and muscle function in the lower leg and forearm after stroke. Journal of Musculoskeletal Neuronal Interactions. 2011;11(4):306-13.
20. Ashe MC, Fehling P, Eng JJ, Khan KM, McKay HA. Bone geometric response to chronic disuse following stroke: a pQCT study. Journal of Musculoskeletal and Neuronal Interactions. 2006;6(3):226.
21. Lam FM, Bui M, Yang FZ, Pang MY. Chronic effects of stroke on hip bone density and tibial morphology: a longitudinal study. Osteoporos Int. Feb 2016;27(2):591-603. Epub 2015/09/04.
22. Liu XS, Stein EM, Zhou B, Zhang CA, Nickolas TL, Cohen A, et al. Individual trabecula segmentation (ITS)-based morphological analyses and microfinite element analysis of HR-pQCT images discriminate postmenopausal fragility fractures independent of DXA measurements. J Bone Miner Res. Feb 2012;27(2):263-72. Epub 2011/11/11.
23. Patsch JM, Burghardt AJ, Yap SP, Baum T, Schwartz AV, Joseph GB, et al. Increased cortical porosity in type 2 diabetic postmenopausal women with fragility fractures. J Bone Miner Res. Feb 2013;28(2):313-24. Epub 2012/09/20.
24. Burt LA, Manske SL, Hanley DA, Boyd SK. Lower Bone Density, Impaired Microarchitecture, and Strength Predict Future Fragility Fracture in Postmenopausal Women: 5-Year Follow-up of the Calgary CaMos Cohort. J Bone Miner Res. Apr 2018;33(4):589-97. Epub 2018/01/25.
25. Sornay-Rendu E, Boutroy S, Duboeuf F, Chapurlat RD. Bone Microarchitecture Assessed by HR-pQCT as Predictor of Fracture Risk in Postmenopausal Women: The OFELY Study. J Bone Miner Res. Jun 2017;32(6):1243-51. Epub 2017/03/10.
26. Whittier DE, Boyd SK, Burghardt AJ, Paccou J, Ghasem-Zadeh A, Chapurlat R, et al. Guidelines for the assessment of bone density and microarchitecture in vivo using high-resolution peripheral quantitative computed tomography. Osteoporos Int. May 26 2020. Epub 2020/05/28.
27. Yang FZ, Jehu DAM, Ouyang H, Lam FMH, Pang MYC. The impact of stroke on bone properties and muscle-bone relationship: a systematic review and meta-analysis. Osteoporos Int. 2020/02/01 2020;31(2):211-24.

28. Lee SS, Spear S, Rymer WZ. Quantifying changes in material properties of stroke-impaired muscle. Clin Biomech (Bristol, Avon). Mar 2015;30(3):269-75. Epub 2015/02/02.
29. Wu CH, Ho YC, Hsiao MY, Chen WS, Wang TG. Evaluation of Post-Stroke Spastic Muscle Stiffness Using Shear Wave Ultrasound Elastography. Ultrasound Med Biol. 2017;43(6):1105-11.
30. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. journal article May 01 2007;39(2):175-91.
31. Lam SC, Wong Y-y, Woo J. Reliability and validity of the abbreviated mental test (Hong Kong version) in residential care homes. J Am Geriatr Soc. 2010;58(11):2255-7.
32. Sode M, Burghardt AJ, Pialat J-B, Link TM, Majumdar S. Quantitative characterization of subject motion in HR-pQCT images of the distal radius and tibia. Bone. 2011/06/01/ 2011;48(6):1291-7.
33. Chiba K, Okazaki N, Kurogi A, Isobe Y, Yonekura A, Tomita M, et al. Precision of Second-Generation High-Resolution Peripheral Quantitative Computed Tomography: Intra- and Intertester Reproducibilities and Factors Involved in the Reproducibility of Cortical Porosity. J Clin Densitom. 2018/04/01/ 2018;21(2):295-302.
34. Agarwal S, Rosete F, Zhang C, McMahon DJ, Guo XE, Shane E, et al. In vivo assessment of bone structure and estimated bone strength by first- and second-generation HR-pQCT. Osteoporos Int. Oct 2016;27(10):2955-66. Epub 2016/05/09.
35. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD. Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. J Bone Miner Res. Mar 2008;23(3):392-9. Epub 2007/11/14.
36. Rietbergen vB, Pistoia W, Ulrich D, Huiskes HWJ, Rüegsegger P. Prediction of trabecular bone failure parameters using a tissue failure criterion and muFE analysis. Journal of Computer Simulation and Modelling in Medicine. 2000 2000;1(2):98 - 101.
37. Niebur GL, Feldstein MJ, Yuen JC, Chen TJ, Keaveny TM. High-resolution finite element models with tissue strength asymmetry accurately predict failure of trabecular bone. J Biomech. 2000/12/01/ 2000;33(12):1575-83.
38. Pistoia W, van Rietbergen B, Lochmüller EM, Lill CA, Eckstein F, Rüegsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. Bone. 2002/06/01/ 2002;30(6):842-8.
39. Hung VW, Zhu TY, Cheung WH, Fong TN, Yu FW, Hung LK, et al. Age-related differences in volumetric bone mineral density, microarchitecture, and bone strength of distal radius and tibia in Chinese women: a high-resolution pQCT reference database study. Osteoporos Int. Jun 2015;26(6):1691-703. Epub 2015/01/30.
40. Sigrist RMS, Liau J, Kaffas AE, Chammas MC, Willmann JK. Ultrasound Elastography: Review of Techniques and Clinical Applications. Theranostics. 2017;7(5):1303-29. Epub 2017/04/25.
41. Miller T, Ying M, Sau Lan Tsang C, Huang M, Pang MYC. Reliability and Validity of Ultrasound Elastography for Evaluating Muscle Stiffness in Neurological Populations: A Systematic Review and Meta-Analysis. Phys Ther. 2020.

42. Yang FZ, Pang MY. Influence of chronic stroke impairments on bone strength index of the tibial distal epiphysis and diaphysis. Osteoporos Int. Feb 2015;26(2):469-80. Epub 2014/09/06.
43. Pang MY, Ashe MC, Eng JJ. Compromised bone strength index in the hemiparetic distal tibia epiphysis among chronic stroke patients: the association with cardiovascular function, muscle atrophy, mobility, and spasticity. Osteoporos Int. Jun 2010;21(6):997-1007. Epub 2009/11/03.
44. Pang MY, Eng JJ, McKay HA, Dawson AS. Reduced hip bone mineral density is related to physical fitness and leg lean mass in ambulatory individuals with chronic stroke. Osteoporos Int. Dec 2005;16(12):1769-79. Epub 2005/05/20.
45. Ng SS, Hui-Chan CW. The timed up & go test: its reliability and association with lower-limb impairments and locomotor capacities in people with chronic stroke. Arch Phys Med Rehabil. Aug 2005;86(8):1641-7. Epub 2005/08/09.
46. Ng SS, Hui-Chan CW. Contribution of ankle dorsiflexor strength to walking endurance in people with spastic hemiplegia after stroke. Arch Phys Med Rehabil. Jun 2012;93(6):1046-51. Epub 2012/03/24.
47. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. Phys Ther. 1993;73(7):447-54.
48. van der Lee JH, Beckerman H, Knol DL, de Vet HC, Bouter LM. Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients. Stroke. Jun 2004;35(6):1410-4. Epub 2004/04/17.
49. Ngai SP, Cheung RT, Lam PL, Chiu JK, Fung EY. Validation and reliability of the Physical Activity Scale for the Elderly in Chinese population. J Rehabil Med. May 2012;44(5):462-5. Epub 2012/05/03.
50. Ekstrand E, Lexell J, Brogardh C. Isometric and isokinetic muscle strength in the upper extremity can be reliably measured in persons with chronic stroke. J Rehabil Med. Sep 2015;47(8):706-13. Epub 2015/07/17.
51. Yang J, Lee J, Lee B, Kim S, Shin D, Lee Y, et al. The Effects of Elbow Joint Angle Changes on Elbow Flexor and Extensor Muscle Strength and Activation. Journal of Physical Therapy Science. 2014;26(7):1079-82.
52. Ada L. Stroke patients have selective muscle weakness in shortened range. Brain. 2003;126(3):724-31.
53. Laird NM, Ware JH. Random-Effects Models for Longitudinal Data. Biometrics. 1982;38(4):963-74.
54. Jacqmin-Gadda H, Sibillot S, Proust C, Molina J-M, Thiébaut R. Robustness of the linear mixed model to misspecified error distribution. Computational Statistics & Data Analysis. 2007/06/15/ 2007;51(10):5142-54.
55. del Puente A, Pappone N, Mandes MG, Mantova D, Scarpa R, Oriente P. Determinants of bone mineral density in immobilization: A study on hemiplegic patients. Osteoporos Int. 1996/01/01 1996;6(1):50-4.
56. Mikolajewicz N, Bishop N, Burghardt AJ, Folkestad L, Hall A, Kozloff KM, et al. HR-pQCT Measures of Bone Microarchitecture Predict Fracture: Systematic Review and Meta-Analysis. J Bone Miner Res. Oct 23 2019. Epub 2019/10/24.
57. Samelson EJ, Broe KE, Xu H, Yang L, Boyd S, Biver E, et al. Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a

prospective study. The Lancet Diabetes & Endocrinology. 2019/01/01/ 2019;7(1):34-43.
58. Mancuso ME, Johnson JE, Ahmed SS, Butler TA, Troy KL. Distal radius microstructure and finite element bone strain are related to site-specific mechanical loading and areal bone mineral density in premenopausal women. Bone Reports. 2018/06/01/ 2018;8:187-94.
59. Szulc P, Boutroy S, Chapurlat R. Prediction of Fractures in Men Using Bone Microarchitectural Parameters Assessed by High-Resolution Peripheral Quantitative Computed Tomography-The Prospective STRAMBO Study. J Bone Miner Res. Aug 2018;33(8):1470-9. Epub 2018/04/26.
60. Wong AK. A comparison of peripheral imaging technologies for bone and muscle quantification: a technical review of image acquisition. J Musculoskelet Neuronal Interact. 2016;16(4):265-82.
61. van Rietbergen B, Ito K. A survey of micro-finite element analysis for clinical assessment of bone strength: The first decade. J Biomech. 2015/03/18/ 2015;48(5):832-41.
62. Pang MY, Eng JJ. Muscle strength is a determinant of bone mineral content in the hemiparetic upper extremity: implications for stroke rehabilitation. Bone. Jul 2005;37(1):103-11. Epub 2005/05/05.
63. Pang MY, Ashe MC, Eng JJ. Tibial bone geometry in chronic stroke patients: influence of sex, cardiovascular health, and muscle mass. J Bone Miner Res. Jul 2008;23(7):1023-30. Epub 2008/02/28.
64. Pang MYC, Ashe MC, Eng JJ, McKay HA, Dawson AS. A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a peripheral quantitative computed tomography study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2006;17(11):1615-25. Epub 2006/07/29.
65. Mohammad Rahimi GR, Smart NA, Liang MTC, Bijeh N, Albanaqi AL, Fathi M, et al. The Impact of Different Modes of Exercise Training on Bone Mineral Density in Older Postmenopausal Women: A Systematic Review and Meta-analysis Research. Calcif Tissue Int. 2020/06/01 2020;106(6):577-90.
66. Macneil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. Bone. Jun 2008;42(6):1203-13. Epub 2008/03/25.
67. Vilayphiou N, Boutroy S, Sornay-Rendu E, Van Rietbergen B, Munoz F, Delmas PD, et al. Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in postmenopausal women. Bone. Apr 2010;46(4):1030-7. Epub 2010/01/02.
68. Zhu TY, Griffith JF, Qin L, Hung VW, Fong TN, Au SK, et al. Structure and strength of the distal radius in female patients with rheumatoid arthritis: a case-control study. J Bone Miner Res. Apr 2013;28(4):794-806. Epub 2012/10/24.
69. Turner CH, Rho J, Takano Y, Tsui TY, Pharr GM. The elastic properties of trabecular and cortical bone tissues are similar: results from two microscopic measurement techniques. J Biomech. 1999/04/01/ 1999;32(4):437-41.
70. Verhulp E, Van Rietbergen B, Muller R, Huiskes R. Micro-finite element simulation of trabecular-bone post-yield behaviour--effects of material model, element size and

type. Comput Methods Biomech Biomed Engin. Aug 2008;11(4):389-95. Epub 2008/06/24.

Table 1. Participant characteristics

		Stroke (n=64)	Control (n=64)	p
Demographics	Sex (men/women), n	38/26	39/25	0.858
	Age, years	60.8 ± 7.7	59.4 ± 7.8	0.306
	Menopause (women), years	12.4 ± 13.1	11.5 ± 9.9	0.787
	Hand dominance (Left/Right/Equivalent), n	1/62/1	2/62/0	0.319
	Height (cm)	161.1 ± 8.4	164.0 ± 8.9	0.058
	Weight (kg)	62.7 ± 8.9	63.1 ± 9.9	0.814
	Body mass index (kg/m^2)	24.3 ± 3.1	23.4± 2.8	0.081
	AMT (out of 10)	9.3 ± 1.1	9.9 ± 0.4	**<0.001**
	PASE	114.7 ± 87.4	142.2 ± 79.4	0.065
Stroke Characteristics	Paretic Side (Left/Right), n	36/28	-	-
	Paretic Side (Non-Dominant/Dominant), n	36/28	-	-
	Type of Stroke (Ischemic/Hemorrhagic), n	41/23	-	-
	Stroke duration, years	5.8 ± 4.0	-	-
	CSS-Total (1-16)	8.6 ± 2.5	-	-
	FMA-UE (0-66)	35.9 ± 18.9	-	-
	MAL-AOU (0-5)	1.3 ± 1.3	-	-
Comorbidity	Total number of comorbidities per person	1.3 ± 1.3	0.6 ± 0.9	**<0.001**
	Hypertension, n	37	22	**0.006**
	Hyperlipidemia, n	21	4	**<0.001**
	Cardiac arrhythmia, n	1	0	0.315
	Diabetes mellitus, n	14	8	0.150
	Ischemic heart disease, n	1	0	0.315
Medications	Total number of medications per person	4.5 ± 3.1	0.9 ± 1.2	**<0.001**
	Antihypertensive agents, n	42	16	**<0.001**
	Hypolipidemic agents, n	41	10	**<0.001**
	Hypoglycemic agents, n	10	6	0.259
	Anticoagulants, n	23	3	**<0.001**
	Antispasmodic agents, n	6	0	**0.011**
	PPI/ Gastric agents, n	25	2	**<0.001**
	SSRI/ Antidepressants, n	8	1	**0.016**
Other	Alcohol history (yes/no), n	14/50	24/40	0.053
	Alcohol consumption (drinks/day)	0.2 ± 0.3	0.1 ± 0.3	0.276
	Smoking history (yes/no), n	15/49	14/50	0.833
	Tobacco use (packs/day)	0.7 ± 0.4	0.6 ± 0.3	0.428
	Vitamin D supplementation (yes/no), n	4/60	4/60	1.000
	Calcium supplementation (yes/no), n	3/61	7/57	0.188

p ≤ 0.05 Statistically significant between-groups difference
AMT = Abbreviated Mental Test, PASE = Physical Activity Scale for the Elderly, CSS-Total = Composite Spasticity Scale-Total, FMA-UE = Fugl-Meyer Assessment-Upper Extremity, MAL-AOU = Motor Activity Log-Amount of Use, PPI = Proton Pump Inhibitor, SSRI = Selective Serotonin Reuptake Inhibitor

Table 2. Comparison of HR-pQCT variables

	Stroke Group (n=64)			Control Group (n=64)			Main Effect: Side (Within)		Main Effect: Group (Between)		Side × Group Interaction Effect		AIC
	Paretic	Non-Paretic	%SSD	Non-Dominant	Dominant	%SSD	t	p	t	p	t	p	
Density	Total vBMD (mg HA/cm^3)												
	292.0 ± 83.5	**352.8 ± 62.8**	**18.1 ± 13.7**	339.4 ± 60.0	337.9 ± 62.3	-0.84 ± 6.83	-5.077	**<0.001**	-1.351	0.179	3.678	**<0.001**	2858.099
	Trabecular vBMD (mg HA/cm^3)												
	116.3 ± 49.3	**147.0 ± 36.1**	**23.1 ± 21.7**	137.3 ± 38.5	139.5 ± 39.6	0.74 ± 10.24	-4.225	**<0.001**	-1.126	0.262	2.778	**0.006**	2606.427
	Cortical vBMD (mg HA/cm^3)												
	871.1 ± 75.2	**912.0 ± 53.0**	**4.6 ± 4.7**	914.9 ± 55.4	913.0 ± 51.5	-0.21 ± 2.36	-3.884	**<0.001**	0.109	0.913	2.874	**0.004**	2788.872
Area	Trabecular Area (mm^2)												
	194.1 ± 51.8	187.9 ± 53.3	**-4.25 ± 10.5**	194.8 ± 56.6	**199.9 ± 50.6**	3.1 ± 7.7	0.667	0.506	1.309	0.193	-0.855	0.393	2737.855
	Cortical Area (mm^2)												
	56.7 ± 15.6	**66.3 ± 13.7**	**15.1 ± 12.4**	65.6 ± 12.6	**67.3 ± 14.2**	1.89 ± 6.85	-3.897	**<0.001**	0.427	0.670	2.272	**0.024**	2063.140
Trabecular Microstructure	Trabecular Number (1/mm)												
	1.08 ± 0.28	**1.23 ± 0.20**	**12.3 ± 16.5**	1.20 ± 0.19	**1.24 ± 0.19**	2.75 ± 9.19	-3.813	**<0.001**	0.292	0.770	2.003	**0.046**	-38.853
	Trabecular Thickness (mm)												
	0.22 ± 0.02	0.23 ± 0.02	0.89 ± 6.02	**0.23 ±0.02**	0.22 ± 0.02	-1.14 ± 3.18	-0.766	0.445	-1.069	0.287	1.094	0.275	-1295.352
	Trabecular Separation (mm)												
	0.98 ± 0.47	0.78 ± 0.20	**-24.3 ± 36.0**	0.80 ± 0.17	**0.77 ± 0.20**	-4.34 ± 15.4	4.106	**<0.001**	-0.257	0.797	-2.463	**0.015**	34.002
	Trabecular Bone Volume Fraction (%)												
	0.17 ± 0.06	**0.21 ± 0.05**	**21.1 ± 18.1**	0.20 ± 0.05	0.20 ± 0.06	0.95 ± 9.4	-4.239	**<0.001**	-1.142	0.256	2.781	**0.006**	-719.383
Cortical Microstructure	Cortical Thickness (mm)												
	1.04 ± 0.26	**1.21 ± 0.20**	**14.4 ± 13.3**	1.18 ± 0.18	1.19 ± 0.20	-0.04 ± 8.3	-4.445	**<0.001**	-0.470	0.639	3.005	**0.003**	-41.254
	Cortical Perimeter (mm)												
	66.2 ± 8.4	66.2 ± 8.3	0.04 ± 3.84	66.9 ± 8.5	**68.1 ± 7.7**	**1.85 ± 3.26**	-0.039	0.969	1.289	0.200	-0.551	0.582	1797.729
	Intra-cortical Porosity (%)												
	0.010 ± 0.006	0.011 ± 0.007	-8.63 ± 63.9	0.0095 ± 0.006	0.0093 ± 0.006	-7.46 ± 43.4	-0.786	0.433	-1.447	0.150	0.702	0.483	-1809.399
µFE	Estimated Failure Load (N)												
	2980 ± 1066	**3865 ± 949**	**23.8 ± 15.1**	3738 ± 983	**3868 ± 1033**	2.9 ± 8.5	-4.965	**<0.001**	0.013	0.990	2.996	**0.003**	4221.801

Value expressed as mean ± SD unless otherwise indicated
p ≤ 0.017 Statistically significant between-sides difference (post hoc paired t-test)
p ≤ 0.017 Statistically significant side-to-side difference between two groups (post hoc independent t-test)
p ≤ 0.05 Statistically significant results (linear mixed model)
%SSD = percent side-to-side difference, vBMD = volumetric bone mineral density, HA = Hydroxyapatite, N = Newtons, µFE = finite element analysis

Table 3. Comparison of ultrasound and functional impairment variables

		Stroke Group (n=64)			Control Group (n=64)			Main Effect: Side (Within)		Main Effect: Group (Between)		Side × Group Interaction Effect		AIC
		Paretic	Non-Paretic	%SSD	Non-Dominant	Dominant	%SSD	t	p	t	p	t	p	
Ultrasound	Cross-Sectional Area (cm^2)													
		7.60 ± 2.18	**8.93 ± 2.38**	**13.7 ± 16.1**	8.32 ± 2.72	8.55 ± 2.73	2.28 ± 10.1	-2.978	**0.003**	-0.841	0.402	1.750	0.081	1200.120
	Shear Wave Velocity (m/s)													
		3.34 ± 0.97	3.06 ± 0.92	-15.1 ± 38.6	2.83 ± 0.77	2.76 ± 0.83	-8.7 ± 36.5	1.821	0.070	-1.971	0.051	-0.934	0.351	667.621
	Echo Intensity													
		113.4 ± 12.7	104.8 ± 12.4	**-9.18 ± 13.9**	96.5 ± 14.0	98.6 ± 15.2	0.86 ± 15.8	3.576	**<0.001**	-2.541	**0.012**	-3.159	**0.002**	2051.158
	Peak Systolic Velocity (cm/s)													
		77.4 ± 15.4	76.8 ± 15.1	-2.65 ± 19.9	73.7 ± 17.4	**78.3 ± 15.2**	5.35 ± 16.3	0.218	0.828	0.565	0.573	-1.326	0.186	2126.646
IPT	Isometric Peak Torque (N/m)													
		18.4 ± 9.3	**29.6 ± 11.2**	**31.6 ± 49.7**	26.5 ± 10.3	27.0 ± 11.1	-0.14 ± 11.6	-6.077	**<0.001**	-1.340	0.183	4.097	**<0.001**	1918.171

Value expressed as mean ± SD unless otherwise indicated
p ≤ 0.017 Statistically significant between-sides difference (post hoc paired t-test)
p ≤ 0.017 Statistically significant side-to-side difference between two groups (post hoc independent t-test)
p ≤ 0.05 Statistically significant results (linear mixed model)
%SSD = percent side-to-side difference, kPa = Kilopascals, N/m = Newton/meters

Table 4. Regression analysis: Relative contributions of different bone parameters to %SSD in estimated failure load for the stroke group

Parameter	Model Summary				Regression Coefficients			
	R^2	ΔR^2	ΔF	Sig. ΔF	Beta	95% CI		Sig.
Trabecular vBMD (%SSD)	.334	.334	31.071	**.000**	1.106	.413	1.125	**.000**
Cortical vBMD (%SSD)	.437	.103	11.156	**.001**	.048	-.507	.817	.641
Trabecular Area (%SSD)	.453	.016	1.746	.191	-.096	-.398	.124	.296
Cortical Area (%SSD)	.581	.129	18.134	**.000**	.658	.489	1.118	**.000**
Factor 1 (Trabecular Microstructure)	.621	.040	6.083	**.017**	-.674	-17.843	-2.526	**.010**
Factor 2 (Cortical Microstructure)	.656	.035	5.853	**.019**	-.318	-8.781	-.828	**.019**

$p \leq 0.05$ Statistically significant F-value change (Sig. ΔF)
$p \leq 0.05$ Statistically significant predictor (Sig.)
Factor 1 (Trabecular Microstructure) = %SSD Trabecular Number, %SSD Trabecular Thickness, %SSD Trabecular Separation, %SSD Trabecular Bone Volume Fraction
Factor 2 (Cortical Microstructure) = %SSD Cortical Thickness, %SSD Cortical Perimeter, %SSD Intracortical Porosity
R^2 = total variance, ΔR^2 = additional predictor variance, ΔF = F-value change, Beta = standardized regression coefficient, CI = confidence interval, %SSD = percent side-to-side difference, vBMD = volumetric bone mineral density

Table 5. Regression analysis: Associations between stroke-related functional impairments and %SSD in estimated failure load

Parameter	Model Summary				Regression Coefficients			
	R^2	ΔR^2	ΔF	Sig. ΔF	Beta	95% CI		Sig.
Cortical Perimeter (%SSD)	0.010	0.010	0.639	0.427	0.121	-.544	1.494	0.354
Factor 1	0.243	0.233	18.741	**<0.001**	-0.480	-10.657	-3.846	**<0.001**
Factor 2	0.246	0.003	0.276	0.601	0.064	-2.458	4.394	0.573
Factor 3	0.280	0.034	2.756	0.102	-0.186	-6.230	0.599	0.104
Factor 4	0.292	0.012	1.017	0.317	-0.113	-5.103	1.703	0.321
Factor 5	0.294	0.001	0.095	0.759	0.035	-2.871	3.926	0.757
Factor 6	0.311	0.018	1.429	0.237	0.130	-1.726	5.659	0.290
Factor 7	0.312	0.001	0.109	0.742	-0.040	-4.022	2.812	0.724
Factor 8	0.320	0.008	0.620	0.434	0.093	-2.162	4.959	0.434

$p \leq 0.05$ Statistically significant F-value change (Sig. ΔF)
$p \leq 0.05$ Statistically significant predictor (Sig.)
Factor 1 = Fugl-Meyer Assessment-Upper Extremity, Motor Activity Log-Amount of Use, Composite Spasticity Scale-Total
Factor 2 = Calcium Supplementation, Vitamin D Supplementation
Factor 3 = Tobacco Use, Alcohol Consumption, Sex
Factor 4 = Stroke Duration
Factor 5 = Total Number of Medications, Total Number of Comorbidities, %SSD Echo Intensity
Factor 6 = %SSD Isometric Peak Torque, %SSD Peak Systolic Velocity; Physical Activity Scale for the Elderly, Age
Factor 7 = Abbreviated Mental Test, %SSD Shear Wave Velocity
Factor 8 = %SSD Cross Sectional Area
R^2 = total variance, ΔR^2 = additional predictor variance, ΔF = F-value change, Beta = standardized regression coefficient, CI = confidence interval, %SSD = percent side-to-side difference

Figure Legends

Figure 1. Bilateral comparison of bone parameters

Figure 1. HR-pQCT generated 3D rendering of the distal radius bone for a representative female participant with flaccid left arm hemiparesis (upper panel) and a female control participant (lower panel). There are comparatively fewer trabeculae with reduced density and network connectivity on the paretic side. The upper panel shows a bilateral view of the trabecular segment (green) and cortical shell (grey) for the (A) non-paretic and (B) paretic radius which is compared to the trabecular and cortical bone of the (C) dominant and (D) non-dominant radius in the lower panel. The degree of bone loss between-sides is more pronounced for the stroke participant compared to the control participant.

Figure 2. Bilateral comparison of muscle parameters

Figure 2. Ultrasound generated images of the BB muscles for a representative male participant with left arm hemiparesis. There are comparatively greater compositional tissue changes and stiffness for the paretic BB muscle. The upper panel shows the ROI (1.89cm^2) used to calculate SWV (0-11.2 m/s). Highest and lowest stiffness values are represented by red and blue pixels, respectively. Non-paretic muscle (A) was less stiff than paretic (B). The lower panel shows the same ROI was used to calculate EI values (0-255). Highest and lowest grayscale pixel intensities are represented by white and black pixels, respectively. Similar to stiffness, non-paretic muscle (C) showed comparatively lower EI than paretic (D).