Hylonome

**Original Article**

# Bone geometric response to chronic disuse following stroke: A pQCT study

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**Abstract**

**Objectives:** The objectives of this study were to 1) assess volumetric bone geometry and density at the distal radius of individuals with chronic stroke and 2) assess whether bone strength is associated with measures of muscle strength and impairment. **Material and methods:** Cross-sectional study of bone and muscle parameters in 15 community-dwelling people living with the residual effects of a stroke (between 1 and 9 years post-incident stroke). **Results:** The 4% site of the distal radius had significantly lower bone mineral content and density on the paretic side (p<0.006). There was a significant difference in pQCT measures of bone cortical density (p<0.03), area (p<0.05) and bone strength [Stress-Strain Index; SSI] (p<0.01) (lower on the paretic side) at the 30%. We found significant correlations between composite muscle strength score of the upper extremities and pQCT-generated bone strength. **Conclusions:** This cross-sectional study highlights lower bone strength on the paretic limb and an adaptive response to disuse.

**Keywords:** Stroke, Peripheral Quantitative Computed Tomography (pQCT), Disuse, Muscle Strength, Radius

## Introduction

In the first year following a cerebrovascular accident (CVA) or stroke, 40% of individuals are likely to sustain a fall[1]. Within two years post-stroke, one third of survivors sustain a hip fracture and 24% sustain a wrist fracture[2]. Although a number of factors contribute to this increased fracture risk (e.g., poor balance and number of falls), bone properties are an important contribution to fragility fractures.

Following a stroke, predictable musculoskeletal changes occur that mimic a model of physiological osteopenia that exists in bone when there is muscle weakness[3]. The precise relationship between muscle and bone is an emerging field of research. In the late 1980s, Frost and co-workers proposed

the Utah Paradigm and the concept that mechanical loads determine bone strength and muscle generates the greatest load on bone[4]. However, a key limitation in understanding how muscle strength impacts on bone parameters has been the imaging technologies. Until recently, most researchers have relied on dual energy X-ray absorptiometry (DXA) to describe bone characteristics. Areal BMD (aBMD) is useful for describing the planar projection of bone mass but it only provides a two-dimensional view of a three-dimensional structure. Although aBMD provides a "surrogate measure for bone strength"[5], it overlooks the structural features of cortical and trabecular bone[6]. DXA is unable to assess geometric adaptations because of its planar nature[7]. That is, a larger bone will be seen as having more density, and thus can hide any differences that may exist between limbs. Peripheral quantitative computed tomography (pQCT) provides a measure of the amount of volumetric bone mineral density (vBMD) and defines bone's geometric properties. Peripheral QCT results can also be used to generate a bone strength index that reflects the combined strength of bone trabecular and cortical bone to resist bending or torsion.

Previous investigations of bone health in a stroke population have relied on DXA. They report an initial rapid decrease in areal bone mineral density (aBMD) in the paret-

ic limb compared with the non-paretic limb in the early phase (within 6-12 months), and the magnitude of the loss in bone density ranged from 5-12%, and 3-5% in the paretic, and non-paretic limb, respectively[8-12]. After the acute phase, cross-sectional observations suggest that bone mass, following disuse or with aging, responds to the overall decrease in physical activity, or more plausible, there are adaptations that occurred to maintain bone strength[13-15]. That is, when bone mass decreases in response to disuse, aging or space-flight, an increase in bone area may occur to maintain the overall strength of the bone by increasing the cross-sectional moment of inertia[16,17].

Cortical bone is present in the shafts of long bones and provides structure and stability to the skeleton. Previous *ex vivo* investigations have highlighted the important contribution of cortical bone to the overall strength of the radius[18,19] and this enforces the need to be able to distinguish bone compartments for analysis. Understanding the relative contribution of observed changes in response to disuse can assist in preventative strategies.

Runge and co-workers investigated changes in tibial bone parameters (over the first 2 months and >6 months following a stroke) using pQCT and muscular response to functional activities such as walking[20]. In this preliminary investigation, the authors noted a significant relation between muscle force and bone response but with large variability between participants. To our knowledge, no previous study has used pQCT to measure bone geometric response or the muscle-bone strength relationship in the upper extremity in a chronic stroke population (defined as effects lasting longer than 1 year).

Therefore, the aims of this study were: 1) to compare side-side differences in vBMD, bone geometric properties (ultimately affecting bone strength) at the radius; and 2) to compare physical measures of muscle strength to pQCT generated bone strength (Stress-Strain Index; SSI) in a sample that was between 1 and 10 years post-stroke. Specifically, we hypothesized that the paretic limb would have increased side-side differences in total and cortical area, density and mineral content; and cortical thickness compared with the non-paretic side. Secondly, we hypothesized that these bone parameters would relate to physical measures of muscle strength and motor impairment. Understanding the mechanisms of bone loss can provide the foundations upon which to develop rehabilitation strategies to improve bone health and reduce the risk of fragility fractures.

## Materials and methods

### Experimental participants

We recruited men and women who were part of a large prospective study investigating post-stroke balance[21] to participate in this study. The study was approved by the University of British Columbia Institutional Review Board.

### Inclusion-exclusion criteria

Eligible participants were: i) community dwelling; ii) aged 50 years or older; iii) able to walk, with or without an assistive device, for a minimum of 10 meters; iv) had sustained a single stroke that had occurred at least one year previously; and v) had a greater than 10% side-side difference in upper extremity muscle strength. Participants were excluded if they: i) were not medically stable; ii) had neurological conditions not related to stroke (e.g., Parkinson's disease) or severe musculoskeletal conditions (e.g., recent joint replacement surgery, amputation); and iii) scored less than 22 on Folstein's Mini-Mental State Exam[22]. Each participant's physician confirmed the presence of stroke and the inclusion/exclusion criteria. For pQCT measurements, participants were excluded if there was any metal fixation in the radius or any obvious tremor or spasticity that would prevent or affect positioning within the gantry.

### Measurements

We undertook standard measurement of height to the nearest millimeter with a customized wall-mounted stadiometer (Seca Model # 242, Hanover, MD). The mean of two measures was used for analysis. We assessed body weight with an electronic scale to the nearest 0.1 kg and used the mean of two measures for analysis. Arm length was measured using the manufacturer recommended ulnar styloid tip to olecrannon process.

### Functional ability and impairment

We assessed the functional ability of participants with the American Heart Association (AHA) Stroke Functional Classification[23]. This five-level scale provides a classification score of residual impairment and disability from stroke in the areas of basic (BADL) and instrumental activities of daily living (IADL). Level one indicates independence in both BADL and IADL and level five indicates complete dependence.

We also assessed each participant with the upper extremity score of the Fugl-Meyer Scale to evaluate physical recovery from a stroke. This scale is based on the work of Brunnstrom[24] and rates movement, co-ordination, and reflex action about the shoulder, elbow, forearm, wrist and hand. The maximum motor performance for the upper extremity is 66 points.

### Composite muscle strength score

We assessed upper extremity strength using a Jamar Hand Dynamometer (JLW Instruments, Chicago, IL). We assessed shoulder flexion, extension and abduction, elbow and wrist flexion and extension measured in kilograms and combined the mean of three trials into a composite muscle strength score. We calculated a percentage side-to-side difference and considered a difference between arms >10% more than normal side to side age-matched upper extremity strength differences[25].
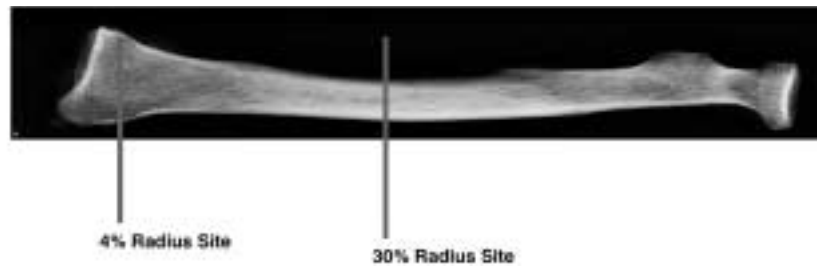
**Figure 1.** X-ray of distal radius to highlight pQCT data acquisition sites. The 4% site is predominately trabecular bone with a thin cortical shell. The 30% site consists mostly of cortical bone[43].
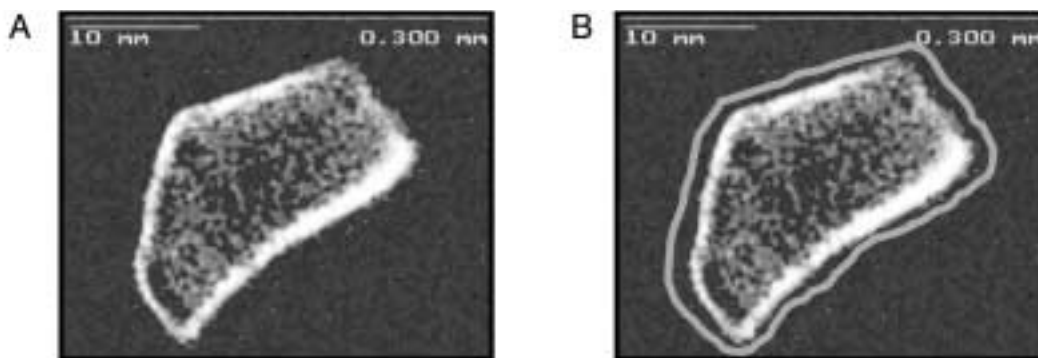


**Figure 2. A)** is a sample of a pQCT image from the 4% site (300 μm resolution) of a 75-year-old woman. **B)** is the same image showing an operator drawn region of interest (ROI) around the bone site of interest. Density is based on a colour or grey scale; thick white areas represent higher density cortical bone and the lighter-grey is trabecular bone, and the dark colour represents marrow or soft tissue.
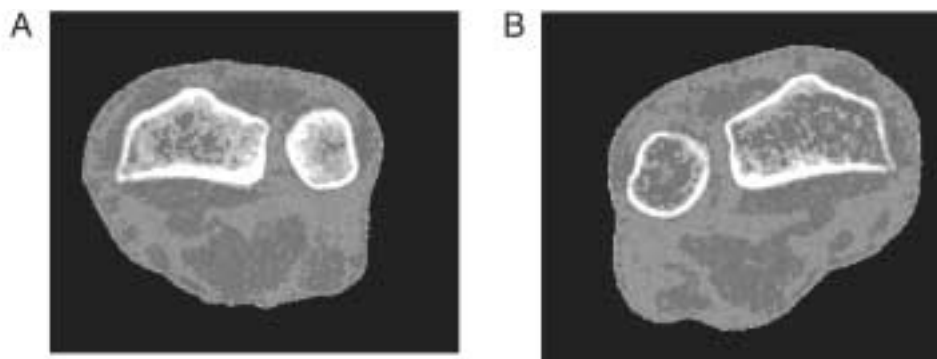


**Figure 3.** Examples of paretic and non-paretic radius and ulna at the 4% site highlighting differences between bone parameters. **A)** represents the 4% site of the non-paretic distal radius in a 68-year-old woman who sustained a stroke 4 years previously. **B)** represents the radius from the same participant on the paretic side. Note the differences for bone inside the cortical shell between the paretic and non-paretic limbs, particularly evident on the ulna in Figure 3B.

## pQCT scan acquisition

We measured participants' bilateral forearms using peripheral quantitative computed tomography (pQCT, Stratec Medizintecnik XCT 2000, software version 550, Pforzheim, Germany). All participants were seated comfortably in a chair adjacent to the pQCT gantry. We obtained a scout view and positioned the anatomical reference line at the distal medial edge of the radius. We used this to obtain a single 2.5 mm slice at the 4% and 30% site of the distal radius (Figure 1). The

| | N=15 |
|---|---|
| Gender (Women: Men) | 4:11 |
| Age (years) | 66.6 ± 5.8 |
| Height (cm) | 168.6 ± 9.9 |
| Mass (kg) | 81.5 ± 14.5 |
| Time since stroke (months) | 46.8 ± 22.6 |
| Fugl-Meyer Score (Upper Extremity) | 64.5 ± 16.1 |
| AHA Stroke Classification* | 2 |
| *Median reported | |

**Table 1.** Participant descriptive characteristics.

voxel size was 500 μm and scan speed was 25 mm/sec to minimize the potential for fatigue or movement/tremor.

### pQCT data analysis

Two investigators reviewed and accepted scans by consensus. All scans were analyzed with XCT 550 software. The algorithms of this software are divided into two modes that correspond to the analyses of: 1) total and 2) cortical bone. That is, total bone was assessed using CALCBD (Contour Mode 3, Peel Mode 2) and cortical bone was assessed using CORTBD Mode 4. We used density thresholds 130-400 mg/cm$^3$ for ToA at the 4% radius and 169-710 mg/cm$^3$ for ToA and 710-710 mg/cm$^3$ for CoA at the 30% site. This means we detected the outer edge of the bone at the distal sites using 130 mg/cm$^3$ and separated trabecular from subcortical bone using 400 mg/cm$^3$. Cortical bone at the 30% site was defined as densities greater than 710 mg/cm$^3$. We drew the regions of interest (ROI) using the XCT 550 custom feature whereby the operator sets the cursor in centre of the bone image and initiates the threshold-based outlining process (Figure 2)[26]. The software automatically detects the outer bone edge and defines the ROI for analysis.

The primary outcomes from the radial pQCT measurements were side-side difference in: total area (mm$^2$) at 4% and 30% sites; cortical area (mm$^2$) at the 30% site; total density (4 and 30% site); and cortical density (30% radius) vBMD (mg/cm$^3$); total and cortical mineral content (mg); and cortical thickness (mm). We used polar stress strain index (SSI; mm$^3$) at the 30% site to estimate bone strength. The polar Stress-Strain Index is calculated using the cortical volumetric density and the cross-sectional moment of inertia. We do not report cortical parameters at the distal sites because of the thin cortical shell and the known computed tomography limitations that cortical bone should be 2.0-2.5 mm minimum thickness to avoid the partial volume effect that can cause an underestimation of bone parameters[27].

### Statistical analysis

We report characteristics of the participants as means ± standard deviation, except the AHA Stroke Classification,

which is presented as the median. We used paired t-tests to compare side-side differences in bone outcomes. We assessed the relationships between SSI, composite muscle strength scores and impairment measure (Fugl-Meyer) muscle using simple linear regression. Significance was set at p<0.05 for all statistical tests. We used SPSS version 12 (SPSS, Chicago, IL).

## Results

Fifteen participants were examined for bone and muscle strength parameters and Fugl-Meyer score of impairment. Table 1 provides descriptive characteristics of the participants. The participants were predominantly men, mean age 67 years and the mean time since stroke was 4 years. All participants had greater than 10% difference in composite muscle strength; the non-paretic limb had 10% more strength compared with the paretic limb.

### pQCT analysis

In Table 2, we report the pQCT results. We found the paretic limbs had 9% less total density and content at the 30% site compared to the non-paretic limbs. At the 4% site, we found 15% less total density and 11% less total mineral content on the paretic side. Figures 3A-B is a visual representation of the 4% sites of the radius comparing the paretic to the non-paretic limbs of 68-year-old women who had sustained a stroke 4 years previously. Figures 3 and 4 highlight the individual responses for each participant. Figure 3 represents 4% total density for all participants comparing the non-paretic arm with the paretic limb. Figure 4 represents 30% cortical density for all participants.

### Muscle-bone relations

We found significant relations between SSI, composite muscle strength score and motor impairment. Table 3.

## Discussion

We describe volumetric bone mineral and geometric differences in cortical and total bone content, area and density using peripheral quantitative computed tomography. We report a significant reduction in bone strength on the paretic side compared with the non-paretic side at the 30% site of the radius and report significant correlations between bone strength indices and physical measurements of muscle strength and motor impairment. Our work extends previous work using DXA areal assessment that show a lower bone mineral density on the paretic side[28,29] by reporting specific bone compartment adaptation to disuse.

Previous studies of the acute phase following a stroke show a rapid decline in bone on the paretic side[30] that is followed by another phase where the bone mass of the paretic
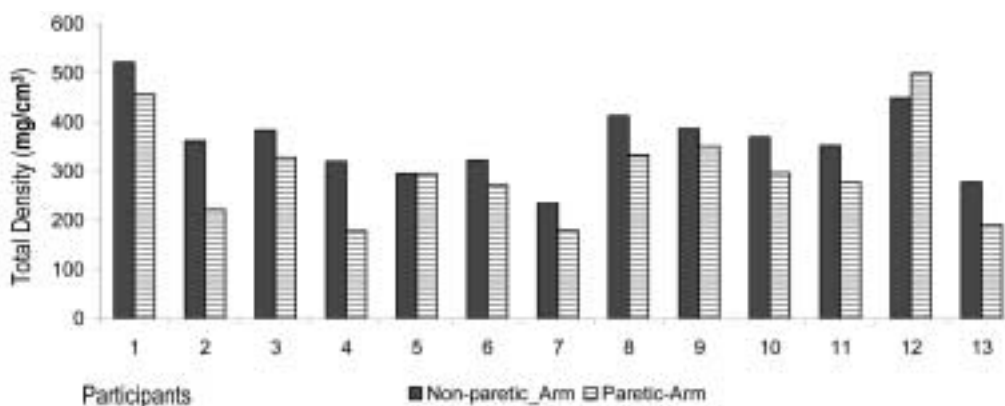
**Figure 4.** This figure compares the non-paretic arm with the paretic arm for total density at the 4% site of the distal radius for all participants.
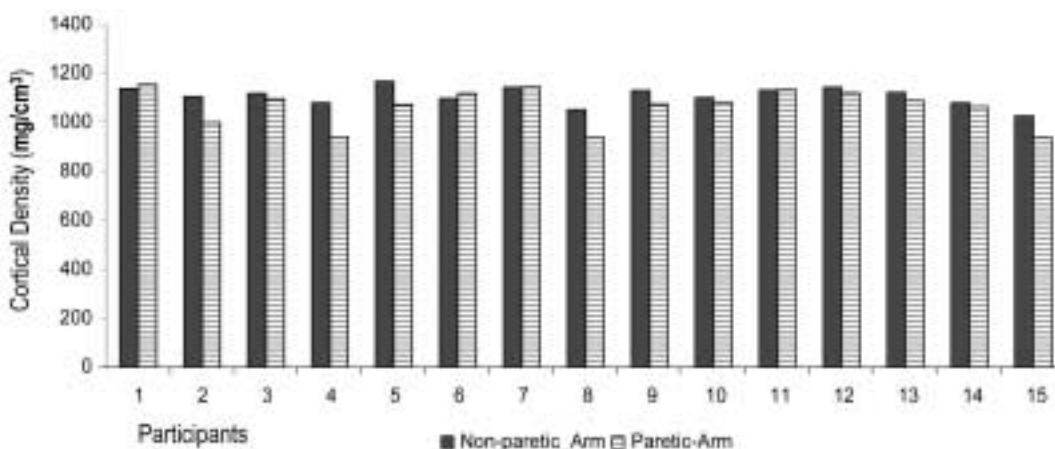


**Figure 5.** This figure compares the non-paretic arm with the paretic arm for cortical density at the 30% site of the distal radius for all participants.

limb responds to the decrease in physical activity. That is, when bone mass decreases in response to disuse, aging or spaceflight, there is an increase in bone area and a change in the distribution of the bone mass. This translates into an increase in the cross-sectional moment of inertia and a maintenance of bone strength[16,17]. In the present study, we observed significantly lower values for total and cortical content on the paretic side. However, we did not observe a concurrent increase in area. This may partially explain why there was significantly lower bone strength on the paretic side.

Another novel feature of this study is the significant correlations between SSI and physical measures of muscle strength and impairment. We found a strong relationship between Fugl-Meyer motor impairment scores and muscle-bone strength measures. These data support the concept that there is a muscle-bone interaction-mechanical loads determine bone strength and muscle generates the greatest load on bone[4]. Further, it highlights a potential role for

rehabilitation to maintain muscle and bone strength after a stroke. We note that there was only a small variation with individual pQCT results (4%>30% site) (Figures 3 and 4) and this differed somewhat from the study by Runge and co-workers[20]. The difference between the two studies may be that we investigated the radius and all our participants had at least 10% or greater muscle composite score on the non-paretic side, and therefore the group was more homogenous.

Previous *in vivo* exercise studies that used animal models and humans (but not those with a stroke) have suggested that exercise can alter bone parameters[31-38]. Specifically related to the upper extremity, Adami and coworkers tested a 6-month exercise intervention and showed geometric changes at the distal radius (4% site). The intervention used an intensive 70 minutes strengthening regime that maximized the brachioradialis muscle (inserts on the radial styloid process)[39]; the authors observed a significant increase in

| Bone Site | Paretic Limb | Non-paretic Limb | p Value | % Difference |
|---|---|---|---|---|
| **30% Total Bone (N=15)** | | | | |
| ToA (mm²) | 110.9±30.5 | 112.9±31.9 | 0.20 | 2 |
| ToD (mg/cm³) | 806.06±194.6 | 886.7±126.4 | 0.07 | 9 |
| ToCNT (mg) | 92.0±37.5 | 101.5±32.7 | 0.03* | 9 |
| SSI (mm³) | 301.5±121.5 | 325.9±123.7 | 0.01** | 7 |
| **30% Cortical Bone** | | | | |
| CoA (mm²) | 100.03±32.6 | 106.3±29.5 | 0.05* | 6 |
| CoD (mg/cm³) | 1063.3±75.0 | 1097.8±40.9 | 0.03* | 3 |
| CoCNT (mg) | 108.1±39.5 | 117.5±34.7 | 0.03* | 8 |
| CThk (mm) | 4.3±1.3 | 4.8±1.2 | 0.06 | 10 |
| **4% Total Bone (N=13)** | | | | |
| ToA (mm²) | 404.4±79.4 | 387.4±89.4 | 0.42 | -4 |
| ToD (mg/cm³) | 312.8±93.2 | 367.6±66.7 | 0.006** | 15 |
| ToCNT (mg) | 126.2±39.0 | 141.2±35.6 | 0.000** | 11 |

ToCNT=total content; ToA=total area; ToD=total density; CoCNT=cortical content; CoA=cortical area; CoD=cortical density; CoThk=cortical thickness; SSI=stress strain index.* significant at p<.05; ** significant at p<.01.

**Table 2.** Bone area, strength and vBMD by pQCT at the radius 4% and 30% sites from participants who exhibited a greater than 10% difference in muscle composite score. Results are reported as mean±sd and p-values.

| Comparison | R² | Significance |
|---|---|---|
| Paretic SSI – Paretic Muscle Score | 0.72 | 0.00 |
| Paretic SSI- Fugel Meyer Score | 0.38 | 0.04 |
| Paretic Muscle Score - Fugel-Meyer Score | 0.42 | 0.03 |
| Non-Paretic SSI - Non-Paretic Muscle Score | 0.61 | 0.00 |
| Paretic Muscle Score= composite muscle strength score and motor impairment; SSI= Stress-Strain Index | | |

**Table 3.** Relation between SSI, composite muscle strength score and impairment for the group (N=15).

cross-sectional area and density of the cortical compartment. In a spinal cord injured population, functional electrical stimulation (FES) augmented lower limb muscle strength and bone aBMD as measured by DXA[40]. In a 24 week-one hour-five times a week intervention used with 14 spinal cord injured patients, there was a significant increase in aBMD at the distal femur and proximal tibia. Muscle stimulation, either passive FES or electromyogram (EMG)-triggered neuromuscular stimulation has been evaluated on arm and hand functions following a stroke[41], but there have not been any reports of bone adaptations in response to the electrical stimulation. In light of the potential for exercise or FES to maintain or even improve bone health, clinical trials are necessary to investigate the potential benefits of site-specific muscle strengthening as part of rehabilitation on bone health following a stroke.

We note several study limitations. First, we used a relatively low resolution (500 μm voxel) for image acquisition of the pQCT with a fast scan speed acquisition (25 mm/sec).

This was done intentionally to limit the time that each participant was in the scanner and to reduce movement artifacts. Accuracy for cortical bone maybe decreased at a lower resolution[42] and predisposes to the presence of a partial volume effect which occurs when there is heterogeneous material contained within the same imaging voxel (or volumetric element). A second limitation that affects the generalizibility of our findings is that our participants were reasonably healthy and exhibited only moderate levels of function. The American Heart Association Stroke Functional Classification median score of two indicates only minimal level of dysfunction, i.e. the participants were functioning at a relatively high level but were still dependent for some activities of daily living. Even though our participants were diverse, we intentionally designed the study to make a within-participant comparison (paretic side to non-paretic side). Finally, the cross-sectional nature of the study limits conclusions about the temporal nature of any 'bone loss' that may have occurred and the relatively low participant numbers limited the use of multiple regression modeling to examine predictors of bone strength over time.

In summary, in this novel study, we report a significant side-side difference (paretic<non-paretic) in volumetric bone density, content, cortical thickness and strength at the radius as measure by pQCT. Muscle strength was significantly correlated with pQCT bone strength parameters. The distal radius is an excellent model to investigate stroke-disuse muscle-bone interventions with the ultimate goal of preventing fragility fractures. This cross-sectional study suggests the need for prospective research to investigate the muscle-bone interaction, and describe longitudinal bone geometric changes in response to unloading following a stroke.

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