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Title: Relative impact of neuromuscular and cardiovascular factors on bone strength index of the hemiparetic distal radius epiphysis among individuals with chronic stroke.

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Mini-abstract

The objective of this study was to examine the associations of neuromuscular and cardiovascular impairments with the bone strength index of the hemiparetic distal radius epiphysis in chronic stroke survivors. The results showed that grip strength is the most predominant predictor of the bone strength index.

ABSTRACT

Purpose: To examine the associations of neuromuscular and cardiovascular impairments with the bone strength index of the hemiparetic distal radius epiphysis in chronic stroke survivors.

Methods: Sixty-five chronic stroke survivors and 34 healthy control subjects underwent scanning of the distal radius epiphyseal site on both sides using peripheral quantitative computed tomography to measure trabecular volumetric bone mineral density (vBMD) (mg/cm^3), total vBMD (mg/cm^3), total area (mm^2), and compressive bone strength index (cBSI) (g^2/cm^4). Various indicators of neuromuscular (grip strength, spasticity) and cardiovascular function (vascular elasticity, oxygen consumption during six minute walk test) were evaluated.

Results: Analysis of variance revealed a significant main effect of side ($p<0.001$) and group × side interaction ($p<0.05$) for total BMC, total vBMD, trabecular vBMD, and cBSI ($p<0.05$), with the stroke group showing greater side-to-side difference in these variables. However, no significant side-to-side difference in total area was detected in either group ($p>0.05$). Sex-specific analysis yielded similar results. Multiple regression analyses revealed that the cBSI of the hemiparetic distal radius epiphysis had a stronger association with neuromuscular factors than cardiovascular factors. Overall, grip strength was the strongest determinant of the cBSI of the hemiparetic distal radius epiphysis ($p<0.01$).

Conclusions: Muscle weakness is the most predominant determinant of cBSI in the hemiparetic distal radius epiphysis among chronic stroke patients. Future studies should investigate the efficacy of different muscle strengthening strategies in enhancing bone strength of this skeletal site in the chronic stroke population.

Keywords: hemiplegia; cerebrovascular accident; muscle; rehabilitation; osteoporosis

INTRODUCTION

Fragility fractures are prevalent among stroke patients [1]. Of all skeletal sites, the wrist region is the second most common site of fragility fractures after stroke [1]. Therefore, studying bone health in the distal forearm region is clinically relevant. While dual-energy X-ray absorptiometry (DXA) is commonly used in earlier studies to examine upper extremity bone health in stroke patients [2,3], a few recent studies have used peripheral quantitative computed tomography (pQCT) [4-6]. One of the advantages of pQCT over DXA is that pQCT is capable of evaluating volumetric bone mineral density (vBMD) and bone geometry, both of which are important determinants of bone strength. In a longitudinal study, Lazoura et al. [6] showed that the bone strength index of the radius distal epiphysis was reduced by 19%-29% during a follow-up period between 3 months and 12 months post-stroke. However, physical impairments (e.g., muscle weakness) were not documented in their study, nor were changes in bone geometry reported.

Neuromuscular impairments after stroke may have important influence on bone changes. Ashe et al. [4] demonstrated a significant relationship between the bone strength index of the hemiparetic radius mid-shaft and composite muscle strength score. In another study, Pang et al. [5] found that the percentage side-to-side difference in cortical bone mineral content and cortical thickness in the radius diaphysis was independently associated with the percentage side-to-side difference in upper limb muscle strength and spasticity. These studies seem to suggest the importance of recovery of neuromuscular function in maintaining the integrity of bone tissue in the hemiparetic radius diaphysis. It remains uncertain, however, whether the different neuromuscular impairments are also important determinants of bone strength at the distal radius epiphyseal site (a more common site of fracture in stroke patients). Indeed, previous research in the lower limb suggests that the diaphyseal region of the bone may respond to the same stroke impairments differently from the epiphyseal region. For example, muscle mass tended to be more strongly related to tibial bone strength index at the diaphyseal site than the epiphyseal site [7,8].

Besides neuromuscular impairments, cardiovascular factors may also contribute to alterations of bone health status. It is well known that stroke patients often have poor cardiovascular health [9,10]. The association between cardiovascular disease and osteoporosis has been demonstrated in a good number of studies [11-13]. For example, high aortic calcification scores have been related to lower BMD in the spine among healthy middle-aged women independent of age and other shared risk factors (e.g., physical activity, weight) between osteoporosis and cardiovascular disease [12]. Griffith et al. [14] have also shown a positive relationship between bone marrow

perfusion and hip aBMD in patients with osteoporosis and osteopenia. In stroke patients, cardiorespiratory fitness, as measured by maximal oxygen consumption rate (maximal VO_2), has been strongly associated with the tibial bone strength indices [7,8]. Whether cardiovascular factors are associated with bone strength in upper extremity skeletal sites remains elusive.

Examining the relationship between neuromuscular or cardiovascular factors and bone health in stroke patients has high clinical relevance in that it would inform clinical treatment of osteoporosis in this high-risk group. It provides important information on whether neuromuscular or/and cardiovascular impairments should be the main targets in bone-enhancing intervention programs. Hence, the objectives of the present study were to compare the densitometric and geometric variables of the radius distal epiphysis between stroke and control subjects, and to determine the associations of bone strength index of the hemiparetic radius distal epiphysis with neuromuscular and cardiovascular function among chronic stroke patients.

It was hypothesized that (1) the side-to-side difference in pQCT variables measured at the radius distal epiphysis would be significantly different between the stroke and control groups, and that (2) both the neuromuscular and cardiovascular factors would be significantly associated with the bone strength index of the hemiparetic radius distal epiphysis.

METHODS

Subjects

Individuals with stroke were recruited from the stroke self-help groups in the community and the existing database of stroke patients who had participated in previous studies of the research team. The inclusion criteria were: 1. a diagnosis of stroke with onset of 6 months or more, which should allow enough time to ensure a plateau in recovery because as it has been shown that the best possible paretic upper extremity function is achieved by over 95% of patients within 11 weeks after stroke onset [15]; 2. aged 18 years or more; 3. medically stable; and 4. an Abbreviated Mental Test score of 7 or higher. Additionally, only people of Chinese origin were selected, because Chinese constitutes over 95% of the population in Hong Kong [16]. As bone outcomes are affected by ethnicity, including people of other ethnic groups may introduce an additional extraneous variable in the study. A larger sample size is necessary if the effect of ethnicity is to be accounted for in the multiple regression analysis. The exclusion criteria were: 1. recurrent stroke; 2.other neurological conditions (e.g., multiple sclerosis); 3.significant

musculoskeletal conditions (e.g., amputations); 4. metal implants in the upper extremity; 5. previous fracture of the upper extremity; 6.were taking medications for treatment of osteoporosis before or after stroke (e.g., bisphosphonates); and 7. other serious illnesses that precluded participation in the study. Ethical approval was obtained from the ethics committee of the University. Each subject gave informed written consent before participating in the study. All experimental procedures were conducted in accordance with the Declaration of Helsinki.

Age-matched healthy control subjects were recruited from community elderly centers, and an existing database of healthy subjects who had participated in previous studies of the research team. The eligibility criteria were the same as those for the stroke group, except that the subjects should not have a history of stroke.

Outcome measurements

Demographics

Relevant information (e.g., medical history) was obtained by medical records and subject interview. The Physical Activity Scale for the Elderly (PASE) questionnaire was administered by the researcher to assess the physical activity level [17].

Bone imaging

Peripheral QCT (XCT 3000, Stratec Medizintechnik GmbH; Pforzheim, Germany) was used to generate three-dimensional cross-section scans of the radius on each side. After proper positioning, a scout view was obtained and the anatomical reference line was placed at the cortical end plate of the distal radius. A voxel size of 0.4 mm and scan speed of 25 mm/sec was used. One-millimeter-thick scans were obtained at the radius epiphysis (at 4% of the total bone length proximal to the distal endplate of the radius). All the analyses were performed using customized software (Stratec software, Version 6.0). Different density thresholds were used to identify different tissues within each scan. For image analysis, CALCB Contour (outer edge-detection) Mode 2 (iterative contour detection) and Peel Mode 2 were used with outer threshold/inner threshold of 169/400 mg/cm^3. The outer edge of the bone was detected using a threshold of 169 mg/cm^3. A threshold of 400 mg/cm^3 was used to separate the trabecular from the subcortical bone.

The variables of interest were total bone mineral content (total BMC, mg/mm), total volumetric bone

mineral density (total vBMD, mg/cm^3), and trabecular vBMD (mg/cm^3) and total area (mm^2). A compressive bone strength index (cBSI, g^2/cm^4) was computed using the formula (total area × total vBMD^2). This cBSI has been used in previous studies to indicate the strength of the bone segment against compressive forces in distal end of long bones [18,19]. This is appropriate, considering that long bone epiphysis is primarily subjected to axial compression [20]. The precision of the pQCT scanner was established by testing 30 healthy subjects twice, with repositioning after the first scan. The coefficient of variation (CV%) value for total BMC, total vBMD, trabecular vBMD, total area, and cBSI was 3.79%, 2.90%, 1.76%, 3.02%, 5.30%, respectively.

Neuromuscular factors

Maximal handgrip strength was selected as a neuromuscular outcome, because bone modeling is highly influenced by muscle loading. A strong relationship between muscle strength and bone outcomes has also been found in other populations [21-23]. Grip strength is easy to measure and is also highly related to muscle strength of other muscle groups in the upper limb [24], and multiple indicators of upper-limb impairment, activity, and participation in stroke patients [25,26]. Handgrip strength (kg) was measured with a Jamar dynamometer (Sammons Preston, Mississauga, Ontario, Canada). Subjects were asked to sit on a chair; the test position was standardized with shoulder placed at neutral, 0°flexion, elbow in 90° flexion, and wrist in neutral position. Subjects were instructed to squeeze the dynamometer as hard as possible for 5 seconds, with a 1-minute rest period in between to avoid fatigue. Three trials were performed to obtain the mean handgrip strength on both sides. Based on the data obtained from these three trials, the test-retest reliability was found to be high ($ICC_{3.1}$ = 0.943-0.984).

Spasticity was also selected as one of the neuromuscular measures, as it is a distinct phenomenon from muscle weakness and is quite common among stroke patients [27]. Previous studies have also suggested a relationship between spasticity and bone outcomes in the radius diaphysis [5] and tibial epiphysis [8]. Spasticity of the elbow as measured by the MAS has also been identified as a significant determinant of activity participation [25]. The Modified Ashworth Scale (MAS) was used to assess resistance to passive movements in the elbow on the hemiparetic side [29]. The MAS has demonstrated acceptable reliability (Kendall's tau correlation =0.847) [28].

Cardiovascular factors

Arterial compliance was chosen as one of the cardiovascular measures. It is known that high arterial

stiffness is related to lower fitness level and other risk factors associated with the occurrence of stroke [29,30]. Compromised arterial compliance has also been related to bone loss and fractures in other populations [11-13]. We used the HDI/PulseWave CR-2000 Research CardioVascular Profiling System (Hypertension Diagnostics Inc., Eagan, MN, USA) to measure the large (C_1) and small (C_2) artery elasticity index [31-33]. The system is a reliable, valid, and non-invasive tool commonly used in research to measure vascular elasticity. Generally, the higher the value, the more elastic and healthy the arteries are. C_1 is a measure of the elasticity of the aorta and large arteries. With aging or in the presence of atherosclerotic disease, the walls of these large arteries will show increasing stiffness [33]. Reduced C_1 is indicative of more advanced cardiovascular dysfunction. On the other hand, C_2 has been correlated with flow-mediated vasodilatation, a well-established indicator of endothelial function [34]. A reduction in C_2 is often the first sign of a developing atherosclerosis [35].

To measure C_1 and C_2, the subject was asked to rest in a supine position, and a blood pressure cuff was placed on the left upper-arm and a rigid plastic wrist stabilizer was placed on the right wrist to minimize movement of the radial artery during the measurement. With the right forearm resting in a supine position, a piezoelectric-based, acoustical sensor was placed over the radial artery adjacent to the styloid process of the radius by the wrist. The sensor was adjusted to the highest relative signal strength. Blood pressure was measured by a linear dynamic deflation method. When the waveform was stable and satisfactory, the radial arterial blood pressure waveform data over a 30-second period was acquired for compliance analysis [31]. Four trials were performed, and the two trials that showed the closest readings were averaged to yield the mean value of C_1 and C_2. A 1-minute rest period was provided between trials. The subjects were categorized to have abnormal or borderline or normal C_1 and C_2 values according to the reference values provided by the manufacturer [31]. To establish the test-retest reliability of the system, the measurement procedures described above were repeated after a brief rest period. The test-retest reliability was found to be excellent, regardless of whether the acoustic sensor was placed on the paretic side (or non-dominant side for controls) or non-paretic side (or dominant side for controls) ($ICC_{3,2}$ = 0.946-0.976 for C_1, and 0.957-0.976 for C_2). Thus, for subsequent analysis, only the values obtained when the sensor was placed on the paretic side (stroke group) or the non-dominant side (control group) were used.

Reduced cardiovascular fitness, often indicated by maximal VO_2, is a major problem for people with stroke and has been related to tibial bone strength indices in stroke [7,8]. While maximal VO_2 is often used to indicate cardiovascular fitness, it is often difficult to obtain a true maximalVO_2 values in chronic stroke patients because

many stroke patients are unable to achieve the standard criteria for maximal VO_2 (e.g., respiratory exchange ratio greater than 1.0, etc.)[36]. Additionally, close monitoring of the electrocardiograph by a physician is needed because of the higher cardiovascular risks among stroke patients. Therefore, the VO_2 (in ml/kg/min) during the six-minute-walking-test (6MWT) (a submaximal exercise) was measured instead to evaluate the cardiovascular fitness level among our subjects. Subjects were instructed to walk along a 15 m corridor and cover as much distance as they could in six minutes while the VO_2 was measured by the FitMate™ metabolic system (Cosmed, Rome, Italy). The reliability and validity of the system has been previously demonstrated [37]. Data on VO_2 during the last 30 seconds of the 6MWT were averaged for each subject [38]. The VO_2 obtained during the 6MWT has a good correlation with maximal VO_2 in different patient populations, including people with stroke (r=0.66) [38].

Statistical analysis

Based on a previous study on radius diaphysis in chronic stroke, a significant side-to-side difference in cortical BMC was detected, with a medium to large effect size of 0.7 [5]. A similar effect size was thus estimated for the within-subject and between-group comparisons of pQCT variables. With an effect size of 0.7, alpha at 5%, and power at 80% (t-test), the estimated sample size required to detect a significant difference in bone outcomes was 34 subjects for each of the stroke and control groups.

Another objective of the study was to identify the associations of bone strength index with the neuromuscular and cardiovascular impairments. Based on a previous pQCT study on the radius diaphysis [5], spasticity and muscle strength were shown to be independently associated with side-to-side difference in cortical BMC (R^2=0.294-0.321). Thus, a similar effect size was estimated for this study. Based on hierarchical regression analysis, a minimum sample size of 57 stroke subjects was required to detect a significant association of four stroke-impairment variables with cBSI, after accounting for age, sex, body mass index (BMI), and post-stroke duration (alpha=5%, power=80%, effect size=0.25, total of 8 predictors).

The following analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and a significance level of 0.05 (two-tailed). In the primary analysis, analysis of variance (ANOVA) with mixed design [within-subject factor: side (paretic or non-dominant Vs non-paretic or dominant), between-subject factor: group (stroke Vs control)] were performed for each pQCT variable. Post-hoc paired t-tests were then used to compare the bone outcomes between the two sides as appropriate. The level of significance was adjusted according to the number of

comparisons made (i.e., Bonferroni's correction). In the secondary analysis, the data collected from men and women were analyzed separately using the above statistical methods.

Pearson product-moment correlation (r) was used to determine the degree of association of the cBSI with grip strength, vascular elasticity indices, and VO_2 within the stroke group. Spearman's rho was used to determine the relationship between cBSI and spasticity score (ordinal data). Hierarchical multiple regression analyses were then performed to identify the significant determinants of the cBSI among stroke patients. Among the various pQCT variables, cBSI was chosen as the dependent variable in the regression analysis because it is a bone strength measure that incorporates both the bone material and its distribution (geometry)[20]. The cBSI measured at the distal end of long bones has also been validated in a human cadaver study. Kontulainen et al. [20] showed that at the distal tibial epiphysis, the failure load is more strongly associated with the cBSI (R^2 = 85%) than total BMC (R^2=75%), total vBMD (R^2=68%), trabecular BMC (R^2=54) or trabecular vBMD (R^2=56%).

The selection of the predictor variables was based on biological relevance and the results from the bivariate correlations. First, age, sex, BMI, and post-stroke duration were forced into the regression model (Enter method). Next, those stroke impairments that were found to have significant association with the dependent variable in the bivariate correlation analysis ($p<0.05$) were then entered into the model (Enter method). In regression analysis, the spasticity score was dichotomized to create a dummy variable (no or mild spasticity: MAS score = 0-1.5), moderate to severe spasticity: MAS score = 2-4). To check for multicollinearity, bivariate correlation analyses were performed to assess the degree of association among the stroke impairment variables. Any predictor variables that had a correlation of > 0.5 should not be included in the same regression model.

RESULTS

Subject characteristics

Sixty-five stroke patients and 34 control subjects participated in this study. The demographic data of the subjects are presented in Table 1. The stroke group also had significantly higher proportion of people with various cardiovascular co-morbidities than controls ($p<0.001$).

The neuromuscular and cardiovascular variables are displayed in Table 2. The handgrip strength on the paretic side was significantly lower by 44.5% when compared with the non-paretic side, indicating substantial paresis on the affected side (Table 2). The majority of the subjects did not have severe spasticity in the affected

upper extremity, with ten stroke subjects (18.5%) having a MAS score of ≥2. The mean VO_2 during the 6MWT was significantly lower in the stroke group than controls ($p<0.001$). There was no significant between-group difference in C_1 and C_2 when all subjects were analyzed. In sex-specific analysis, a significantly lower C_2 value in the female stroke group was found, compared with their control peers ($p=0.020$).

Comparison of pQCT variables

The pQCT images obtained from a representative stroke subject are shown in Fig. 1a & 1b. When compared with the non-paretic side (Fig. 1b), it was obvious that the paretic side (Fig. 1a) had less trabecular bone surrounded by a thinner cortical shell. Such a pronounced side-to-side difference in bone properties was not observed in the control subject (Fig. 1c & 1d).

In the primary analysis of group data, there was a significant main effect of side and side × group interaction effect for total BMC, total vBMD, trabecular vBMD, and cBSI ($p<0.05$), but not total area ($p>0.4$) (Table 3). Post-hoc analysis revealed that in the stroke group, the paretic side had significantly lower total BMC ($p<0.001$), total vBMD ($p<0.001$), trabecular vBMD ($p<0.001$) and cBSI ($p<0.001$) than the non-paretic side. In contrast, the side-to-side difference in these variables was not statistically significant in the control group ($p>0.2$). Moreover, no significant difference in total area was identified between the two sides in both groups of subjects. Sex-specific analysis yielded similar results (Table 3).

Associations with cBSI: bivariate correlation analysis

In bivariate correlation analyses, cBSI of the paretic distal radius epiphysis was significantly correlated with grip strength ($r=0.689$, $p<0.001$) and MAS score ($\rho=-0.465$, $p<0.001$). Among the various cardiovascular factors, C_1 ($r=0.332$, $p=0.007$) and C_2 ($r=0.517$, $p<0.001$), but not VO_2 during 6MWT ($r=0.112$, $p=0.375$) showed a significant correlation with cBSI.

Associations with cBSI: multivariate analysis

In multiple regression analyses, the absolute value of the cBSI of the paretic radius distal epiphysis was used as the dependent variable. As there was a significant moderate correlation between grip strength and MAS)($r>0.5$), separate regression models were used to avoid multicollineraity (Table 4).

After accounting for age, sex, BMI, and years after stroke onset (Table 4), grip strength (model 1) and MAS score (model 2) remained independently associated with cBSI ($p<0.05$). The associations of cBSI with C_1 and C_2 were no longer significant after adjusting for the effects of other relevant factors ($p>0.05$). Overall, these models explained 64.3-67.3% of the variance in cBSI ($p<0.05$). When comparing the two regression models, grip strength was a stronger determinant of cBSI than spasticity, as reflected by the greater magnitude of both the R^2 change value (6.8%) and beta weight (0.364).

DISCUSSION

This study showed that the cBSI of the hemiparetic radius distal epiphysis is significantly lower than that on the non-paretic side, which is mostly explained by the lower total vBMD in the former. Among the various potential clinical correlates, grip strength is the most predominant predictor of cBSI.

Side-to-side difference in pQCT variables

The paretic side had significantly lower total vBMD and trabecular vBMD than the non-paretic side, but there was no significant side-to-side difference in total area. Only two studies have used pQCT to examine the radius distal epiphysis [4,6] and in general, their results are consistent with what was reported here. In a small sample of 15 chronic stroke patients, Ashe et al. [4] reported a significantly lower total vBMD (15%) at the 4% radius site on the paretic side, with no side-to-side difference in total area. Lazoura et al. [6] also showed that at one-year post-stroke, the tabecular vBMD at the 4% radius site on the paretic side was 14% lower than that on the non-paretic side but no information on bone geometry was reported. Nevertheless, our results indicate that the overall bone size is relatively preserved on the paretic side, despite the lower vBMD. This observation is distinct from the bone changes associated with aging, which are characterized by reduction of vBMD with concomitant increase in total area [39].

Despite the preservation of the total area on the paretic side, the cBSI remained significantly lower than on the non-paretic side by 17.8%, owing to the effects of compromised total vBMD. The lower cBSI denotes reduced ability of the bone segment to resist compressive loads, which may, in turn, increase the risk of fracture. Only one study has examined the bone strength index at the radius distal epiphysis in stroke patients, although geometric properties were not specifically reported. Based on a sample of 67 stroke patients, Lazoura et al. [6] showed that differential changes in vBMD on paretic and non-paretic sides with time resulted in a side-to-side difference in the

p-SSI of 27% at 12 months post-stroke. The extent of side-to-side difference in the bone strength index at the radius epiphysis reported in their study seemed to be greater than that observed in this study. The difference in severity of stroke impairments may be a potential explanation. However, details on upper extremity function in their subjects were not documented, whereas a thorough examination of neuromuscular and cardiovascular function was included in our study protocol. Moreover, different bone strength indices were used. The cBSI was used in this study, whereas the p-SSI (a torsional bone strength index) was used in Lazoura et al. [10]. The variables involved in computation of cBSI are different from those of p-SSI. The former is derived from the total area and total vBMD [8] whereas the latter is based on the density and distribution of cortical bone [5,7]. At the epiphyseal region, it is more appropriate to use the cBSI rather than the p-SSI, as compressive loads are more predominant at this site than torsional loads are [20].

Relative contributions of neuromuscular and cardiovascular factors

Among the neuromuscular factors, reduced grip strength turned out to be the most predominant determinant of the cBSI. It is well known that muscle contractions provide a good source of mechanical strain, and play an important role in osteogenesis. Reduced muscle loading after a stroke event may thus have a negative impact on bone health. Our results thus extend the findings of previous studies in highlighting the intimate relationship between bone health and muscle strength in other populations such as older adults, post-menopausal women and spinal cord injury [21-23]. Taken together, the results support the muscle-bone unit theory, which proposes that muscle force and bone mass may form a functional biological unit [40]. The muscle-bone relationship has also been reported in previous stroke studies. A recent study by MacIntyre et al. [41] showed that side-to-side difference in p-SSI of the tibial diaphysis (66% site) was significantly related to side-to-side difference in muscle density at the same site. Ashe et al. [4] demonstrated a positive relationship between the composite paretic arm muscle score and p-SSI measured at the 30% site of the radius in a small sample of 15 chronic stroke patients (R^2=0.72). However, Pang et al. [5] found that the percent side-to-side difference in paretic arm muscle strength was not correlated with percent side-to-side difference in p-SSI in a group of 47 chronic stroke patients ($r=0.224$, $p>0.05$), which is in contrast with the results of the present study. Firstly, the difference in measurement site (epiphysis vs diaphysis) may account for the difference in results. It is likely that different regions of the long bone may react to muscle weakness to a different degree. Interestingly, patients with spinal cord injury showed a similar phenomenon. The lower limb

muscle function was also more strongly associated with bone strength indices at the distal tibia region than at the tibia shaft [24]. Secondly, the paretic arm composite muscle strength score was used in their study, whereas the grip-strength score was used here. It is known that muscle weakness is typically more severe in the distal part of the extremity than in the proximal part [42]. It is thus likely that the grip-strength score is a stronger predictor of bone health of the distal skeletal sites of the upper limb, such as the radius. Finally, this study had a larger sample size. The associated increase in statistical power would increase the ability to detect a significant association.

None of the cardiovascular factors are independently associated with cBSI. This is in contrast with the results reported in the tibia [7,8]. Maximal VO_2 has been found to be significantly associated with the cBSI at the tibial epiphysis [8] and the p-SSI at the tibial diaphysis [7] among chronic stroke patients. The difference in results may be explained by several factors. Firstly, the method of VO_2 measurement differed. We measured the VO_2 during the 6MWT (a submaximal exercise test), whereas maximal VO_2 was evaluated during a maximal exercise test using cycle ergometry in previous studies. Secondly, the site of bone measurement was different. The association between VO_2 and bone health may be stronger in the lower extremity sites than in the upper extremity sites. Poor cardiovascular fitness is common among chronic stroke patients [10] and lack of ambulatory activity may be a major contributing factor. It is known that the ambulatory activity, which is a weightbearing activity in itself, is extremely low (mean=2,837 steps per day) among chronic stroke patients compared with that of sedentary older adults (5,000-6,000 steps per day) [43]. This lack of ambulatory activity may thus adversely influence both lower extremity bone health and cardiovascular health, which may partially explain the stronger association of cardiovascular health indicators with bone health outcomes measured in weightbearing skeletal sites.

Although C_1 and C_2 showed a significant, positive association with cBSI in bivariate correlation analysis, their effects were diminished in multivariate regression analysis. One possible explanation is that there is no real relationship between the two entities. The significant relationship found in bivariate analysis may be due to the effect of some other factors that are related to both cBSI and vascular elasticity (e.g., age, gender). The lack of significant findings may also be related to the fact that the stroke patients in this study were all community-dwelling and actively participating in self-help groups. Therefore, the subjects in this study tended to be more physically able than their counterparts who did not participate in these self-help groups, which may partially explain the lack of significant between-group difference in C_1 and C_2. Another explanation may be that C_1 and C_2 are indicators of systemic vascular health only. Perhaps measures of localized blood flow in the paretic wrist region may be more

strongly associated with the cBSI on the same side.

Clinical and research implications

Among the various stroke impairments, grip strength is the strongest determinant of cBSI of the radius distal epiphysis. Grip-strength assessment may be an easy-to-administer, inexpensive and reliable clinical tool to screen those stroke patients who have compromised upper extremity bone health. Our results suggest that muscle strength should merit more attention in the treatment of osteoporosis in the distal forearm. Previous studies have shown that muscle-strengthening work can induce corticalization of trabecular bone at the endosteal surface and periosteal apposition in the ultradistal radius region among post-menopausal women [44]. Whether muscle strengthening (i.e., resistance training, electrical muscle stimulation, etc.) can enhance bone strength index of the distal radius in stroke patients remains to be investigated.

Limitations

This study has several limitations. Firstly, a cross-sectional design was used and the influence of stroke on bone was assessed mainly by examining the side-to-side difference in bone outcomes and inclusion of a control group. It could not be ruled out that changes in both the paretic and non-paretic sides may contribute to the observed side-to-side difference in bone outcomes. Prospective studies are required to examine the changes in both aBMD and geometry in the forearm region.

The resolution of the pQCT images (0.4mm voxel size) was not high enough to accurately measure cortical thickness in the distal radius epiphysis. Partial volume effect occurs when there is heterogeneous material within a single voxel [45]. This is particularly an issue for the distal radius epiphysis on the paretic side, where the cortical bone shell is thin (<2mm) [45]. Therefore, cortical thickness was not used as an outcome measure in this study.

Finally, our various regression models explained only 64-67% of the variance in cBSI, indicating that some potentially important factors underlying bone health post-stroke were not captured (e.g., nutrition). Further studies should employ a larger sample size and address the relationship between these factors and bone health in chronic stroke patients.

Conclusion

The results showed more compromised vBMD values in the paretic radius epiphysis when compared with controls, leading to lower cBSI, despite no significant side-to-side difference in total area. Overall, among the various stroke-related neuromuscular and cardiovascular impairments, grip strength is the most important determinant of the cBSI. Promoting muscle strength may be an important treatment strategy to enhance or maintain bone strength in the radius distal epiphysis, and warrants further investigation.

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CONFLICT OF INTEREST

No disclosures.

FIGURE LEGENDS

Fig.1 Difference in macrostructure of the distal radius epiphysis between a stroke subject and a control subject

The figure shows the pQCT images of the paretic side (a) and non-paretic side (b) of a woman in the stroke group and those of the non-dominant side (c) and dominant side (d) of a woman in the control group. It is clear that the paretic side has substantially less trabecular bone content and a thinner cortical shell than the non-paretic side. The side-to-side difference is not apparent in the control subject.

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Table 1. Subject characteristics

	Stroke group (n=65)			Control group (n=34)			p
Basic demographics	**Men (n =33)**	**Women (n=32)**	**all (n=65)**	**Men (n =17)**	**Women (n=17)**	**all (n=34)**	
Age, year	60.9±10.3	59.4±11.3	60.1±10.7	60.7±7.3	59.6±9.8	60.2±8.5	0.997
Gender (men/women), n			33/32			17/17	0.920
Body Mass Index, kg/m^2	24.5±3.5	23.3±3.4	23.9±3.5	23.8±2.4	24.7±3.7	24.2±3.1	0.439
Number of postmenopausal women, n		23			13		0.862
Postmenopausal years (women only)		10.3±11.5			10.1±11.3		0.951
Physical activity score	103.1±63.4	85.0±53.9	94.0±59.15	160.0±81.6	138.3±38.9	152.3±61.7	**<0.001***
Receiving physiotherapy or occupational therapy, n	2	6	8	NA	NA	NA	---
Side of hand dominance (left/right), n	2/31	1/31	3/62	0/17	0/17	0/34	---
Stroke characteristics							
Type of stroke (ischemic/hemorrhagic/ unknown), n	22/9/2	14/15/3	36/24/5	NA	NA	NA	---
Paretic side (left/right), n	21/12	7/25	28/37	NA	NA	NA	---
Duration after stroke, month	45.3±43.7	48.3±41.8	47.8±46.0	NA	NA	NA	---
Medical history							
Hypertension, n	27	21	48	8	6	14	**0.001***
Diabetes, n	7	11	18	1	0	1	**0.003***
High cholesterol, n	12	11	23	0	2	2	**0.001***
Total number of co-morbid conditions, n	1.6±1.0	1.9±1.3	1.7±1.2	0.7±0.8	0.8±0.9	0.7±0.8	**0.026***
Medications/supplements							
Antihypertensive agents, n	20	20	40	3	4	7	**<0.001***
Anticoagulants, n	22	19	41	0	0	0	**<0.001***
Anticonvulsive agents, n	2	2	4	0	0	0	0.140
Hypolipidemic agents, n	12	14	26	1	0	1	**<0.001***
Hypoglycemic agents, n	2	5	7	0	0	0	**0.047***
Analgesics, n	0	2	2	0	0	0	0.301
Vitamin D supplementation, n	1	1	2	2	2	4	0.089
Calcium supplementation, n	3	3	6	1	3	4	0.710

[a]Data are mean ± SD unless indicated otherwise

[b]NA = not applicable

*statistically significant difference between the stroke and control groups ($p<0.05$)

Table 2. Comparison of pQCT variables

	Stroke group (n=65)		Control group (n=34)		Main effect: Side		Main effect: Group		Side × group interaction effect	
	Paretic	Non-paretic	Non-dominant	Dominant	F	p	F	p	F	p
Total bone mineral content (mg/mm)										
Men	116.2±25.4	125.6±19.8‡	116.1±24.3	118.3±21.6	8.203	**0.006***	0.321	0.573	3.139	0.083
Women	71.0±20.2	81.5±18.2‡	81.3±11.4	84.9±12.7	11.543	**0.001***	2.123	0.152	2.689	0.108
All	94.0±32.2	103.9±29.1†	98.7±25.7	101.6±24.3	20.001	**<0.001***	0.043	0.837	5.910	**0.017***
Total area (mm^2)										
Men	313.9±43.3	317.6±41.1	320.5±54.3	322.8±65.1	0.462	0.500	0.183	0.671	0.023	0.879
Women	269.8±42.5	264.5±47.8	248.4±37.4	253.9±40.9	<0.001	0.990	1.766	0.190	1.192	0.280
All	292.2±48.0	291.4±51.6	284.5±58.7	288.4±64.0	0.228	0.634	0.242	0.624	0.489	0.486
Total volumetric bone mineral density (mg/cm^3)										
Men	372.9±79.2	398.1±59.4‡	365.4±65.9	372.0±58.9	5.143	**0.028***	0.788	0.379	1.743	0.193
Women	268.8±85.8	313.3±71.4‡	332.3±58.0	340.5±60.9	10.492	**0.002***	4.985	**0.030***	4.977	**0.030***
All	321.7±97.2	356.3±77.9†	348.9±63.4	356.3±61.1	15.344	**<0.001***	0.708	0.402	6.431	**0.013***
Trabecular volumetric bone mineral density (mg/cm^3)										
Men	199.8±42.0	215.7±31.0‡	208.8±27.7	211.6±27.9	10.321	**0.002***	0.063	0.802	4.993	**0.030***
Women	149.1±38.9	173.7±28.9‡	183.4±28.0	180.9±33.9	10.860	**0.002***	4.876	**0.032***	16.237	**<0.001***
All	174.9±47.6	195.0±36.5†	196.1±30.3	196.3±34.3	20.725	**<0.001***	1.966	0.164	19.953	**<0.001***
Compressive bone strength index (g^2/cm^4)										
Men	0.45±0.17	0.50±0.13‡	0.43±0.14	0.44±0.12	5.870	**0.019***	2.771	0.103	2.771	0.103
Women	0.21±0.12	0.26±0.10‡	0.27±0.07	0.29±0.08	12.928	**0.001***	3.072	0.086	3.170	0.081
All	0.33±0.19	0.39±0.17†	0.35±0.14	0.37±0.13	17.142	**<0.001***	0.007	0.935	5.868	**0.017***

[a]Data are mean ± SD

*Statistically significant results (two-way ANOVA, $p<0.05$)

† Primary analysis: statistically significant difference between the two sides (post-hoc paired t-test, $p<0.025$)

‡ Sex-specific analysis: statistically significant difference between the two sides (post-hoc paired t-test, $p<0.012$)

Table 3. Neuromuscular and cardiovascular variables

	Stroke group (n=65)			Control group (n=34)			p
	Men	**Women**	**all**	**Men**	**Women**	**all**	
Neuromuscular variables							
Grip strength, kg							
Paretic side (stroke) or non dominant side (control)	20.3±11.1	6.4±7.3	13.5±11.7	29.3±6.2	21.6±5.1	25.1±6.7	<0.001
Non-paretic side (stroke) or dominant side (control)	30.8±6.7	17.5±5.1	24.3±9.0	32.2±7.0	20.8±4.0	26.9±8.1	0.147
Modified Ashworth Scale score							
0/1/1+/2/3/4, n	17/8/4/3/1/0	8/8/8/7/1/0	25/16/12/10/2/0	NA	NA	NA	---
Median±interquartile range	0.0±1.25	1.25±1.63	1.0±1.5	NA	NA	NA	---
Cardiovascular variables							
C_1 (mL/mmHg × 10)	14.7±4.9	12.6±5.5	13.6±5.3	15.9±45.8	13.5±4.5	14.7±5.2	0.339
C_1(Abnormal/borderline/normal),n	0/6/27	1/10/21	1/16/48	0/1/16	0/3/14	0/4/30	0.164
C_2 (mL/mmHg × 100)	6.0±4.1	3.3±2.1	4.6±3.5	5.0±1.9	4.9±2.4	4.9±2.1	0.676
C_2 (Abnormal/borderline/normal),n	15/5/13	21/6/5	36/11/18	9/5/3	3/5/9	12/10/12	0.918
Six Minute Walk distance (m)	318.4±108.1	214.1±116.8	267.0±123.3	445.1±50.3	446.6±53.1	445.8±50.9	**<0.001***
Oxygen consumption rate (VO_2) during 6MWT (mL/kg/min)	12.8±3.1	10.7±3.1	11.8±3.3	14.8±4.5	15.2±3.4	15.0±3.9	**<0.001***

[a]Data are mean ± SD unless indicated otherwise
[b]NA = not applicable
[c]6MWT = Six Minute Walk Test
[d]C_1=large artery elasticity index
[e]C_2=small artery elasticity index
*Statistically significant difference between stroke group and control group (all subjects) (independent t-tests, p<0.025)

Table 4. Regression analyses for predicting absolute value of compressive bone strength index at the hemiparetic radius distal epiphysis

Predictor	F	R^2 change	B	95%CI	Beta	P
Model 1						
Age	16.735	0.605	-0.005	-0.009, -0.002	-0.310	0.001*
Sex (men=1, women=2)			-0.161	-0.238, -0.083	-0.429	<0.001*
Body mass index			0.003	-0.006, 0.011	-0.049	0.545
Post-stroke duration			0.000	-0.001, 0.001	0.038	0.663
Large artery elasticity index (C_1)		0.068	0.000	-0.006, 0.006	0.006	0.945
Small artery elasticity index (C_2)			0.003	-0.008, 0.013	0.046	0.645
Grip strength			**0.006**	**0.002, 0.010**	**0.364**	**0.002***
Model 2						
Age	14.675	0.605	-0.006	-0.009, -0.003	-0.342	<0.001*
Sex (men=1, women=2)			-0.223	-0.291, -0.155	-0.596	<0.001*
Body mass index			0.004	-0.005, 0.013	0.078	0.354
Post-stroke duration			2.725E-5	-0.001, 0.001	0.006	0.946
Large artery elasticity index (C_1)		0.038	0.001	-0.006, 0.007	0.021	0.820
Small artery elasticity index (C_2)			0.004	-0.007, 0.015	0.072	0.494
MAS (no/mild spasticty=1, moderate/severe spasticty=2)			**-0.097**	**-0.183, -0.011**	**-0.200**	**0.028***

[a]B = Unstandardized regression coefficient
[b]Beta = Standardized regression coefficient
[c]95%CI = 95% confidence interval
[d]MAS = Modified Ashworth Scale
*Statistically significant (p<0.05)