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Original Article

Relationships between calf muscle density and muscle strength, mobility and bone status in the stroke survivors with subacute and chronic lower limb hemiparesis

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Abstract

Objective: To determine the relationship between muscle density and neuromusculoskeletal status in stroke survivors with subacute and chronic hemiparesis. **Methods:** Community-dwelling adults were recruited into one of 3 groups (11 per group): subacute stroke group (SSG, <6 months post-stroke), chronic stroke group (CSG, >1 year post-stroke), or age- and gender-matched control group (CG). Muscle density, muscle mass and tibial bone status (cortical density, mass and polar stress-strain index (pSSI)) were measured bilaterally at the tibial 66% site using peripheral quantitative computed tomography. Muscle strength of ankle plantarflexors and knee extensors was assessed using isokinetic dynamometry. Mobility was assessed using the Berg Balance Scale. Univariate regression analyses by group tested whether side-to-side differences in muscle density and measures of neuromusculoskeletal status were related. **Results:** In the SSG and CG, relationships were observed for muscle density and ankle plantarflexor strength (R^2= 0.365 and 0.503). Muscle density related to muscle mass in the CG only (R^2= 0.889). Muscle density related to cortical bone density in the SSG (R^2= 0.602) and pSSI in the CSG (R^2= 0.434). **Conclusions:** Muscle density may provide insight into the side-to-side changes in muscle and bone strength following hemiparetic stroke.

Keywords: Muscle Density, Muscle Strength, Bone Strength, pQCT, Hemiparesis

Introduction

In stroke survivors, muscle function is a determinant of mobility and bone strength[1]. Indeed, paresis and reduced mobility are both linked to loss of bone tissue and alterations in geometric properties, which are critical to bone strength[1-3]. Bone loss is observed in the paretic limb 3 to 4 months following the immediate decrease in muscle strength and mobility[4]. Cross-sectional data reveal that lean muscle mass in the paretic lower limb of chronic stroke survivors is a significant predictor of proximal hip bone mineral density (BMD, g/cm^2)[5] and mechanical strength of the tibia in the paretic limb[6]. However, measures of regional body composition in people who suffered their first stroke revealed that bone loss occurs in the lower limb one year post-stroke regardless of whether baseline levels of leg lean mass are restored[2]. Measures other than muscle mass may be preferable for monitoring the relationship between neuromuscular function and bone strength in individuals following hemiplegic stroke.

With aging, muscle tissue is replaced with fatty deposits which negatively affects muscle strength and, if severe, is associated with decreased physical function in older adults[7]. For individuals aging with stroke-related disability, the accelerated decline in muscle mass and strength is clear whereas results of studies investigating fat accumulation in this population are mixed. Using computed tomography, a cross-sectional assessment of fatty infiltration within the thigh muscles in 60 chronic stroke survivors (averaging 3 years post-stroke) found no side-to-side difference[8]. However, fat mass in the lower limbs of 25 acute stroke survivors (1 week post-stroke), measured using dual energy x-ray absorptiometry (DXA), increased by 9% in the paretic leg and 6% in the non-paretic leg over a one year period[2]. Perhaps the greater fat accumulation in the paretic leg

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reflects the greater neuromuscular deficits in that limb but interpretation of the longitudinal data in terms of fat accumulation and muscle function is limited by the methodology. DXA, a planar technique, is unable to discriminate fat within different tissue compartments and therefore may not reflect fat accumulation within the muscle where it could negatively impact muscle function. Thus, it is unclear if fat accumulation within the muscle compartments is a marker for accelerated declines in muscle strength and physical function in stroke survivors.

Assessment of the distribution of fatty deposits within muscle tissue *in vivo* is possible using computed tomography-based medical imaging methods[8-10]. For example, muscle density can be measured using peripheral quantitative computed tomography (pQCT). This method quantifies the linear attenuation of the x-ray beam per volume of muscle at the 66% site of the tibia where the calf circumference is the largest[10]. Muscle density is thought to be associated with muscle strength[10] although no direct investigation of this relationship could be found. However, pQCT-based measures of calf muscle density in community-dwelling older adults demonstrate a positive association with measures of physical function and mobility[11].

To date, muscle density in stroke survivors has not been reported and the relationship between muscle density and neuromuscular status is not known. We hypothesized that the side-to-side difference in calf muscle density would be related to side-to-side differences in calf muscle mass and calf muscle strength in individuals with recent hemiparesis due to stroke given the immediate and dramatic decreases in muscle strength experienced at that time. Further we hypothesized that in individuals with hemiparesis due to stroke more than 1 year ago, the side-to-side difference in calf muscle density would be related to measures of global muscle strength (side-to-side differences in knee extensor muscle strength), mobility, and side-to-side differences in bone strength given the longer time for adaptation to altered habitual loading patterns. Therefore, the primary objective of our study was to determine the relationship between side-to-side differences in muscle density and neuromusculoskeletal status in stroke survivors with subacute and chronic hemiparesis. As measures of calf muscle density in stroke survivors have not been published previously, our secondary objective was to provide parameter estimates of the side-to-side differences in calf muscle density in stroke survivors shortly after hemispheric stroke and over the longer term and in age- and gender-matched controls.

Methods

Study Design

Subjects reported to the laboratory on a single occasion lasting approximately 2 hours. All subjects provided informed written consent. The institutional research ethics board approved the study procedures.

Subjects

Hemiparetic stroke survivors and healthy control subjects living in the community responded to newspaper advertisements seeking volunteers. All subjects were screened to ensure they were not taking medications or vitamin supplements known to alter bone metabolism (e.g. corticosteriods, thyroxine, anti-convulsants, bone building medications) or had a known medical condition other than stroke (e.g. mobility limiting arthritis, cancer, metabolic bone disease). Inclusion criteria for respondents with stroke were: 1) a single hemispheric stroke within the last 6 months (subacute) or more than one year ago (chronic), and 2) self-reported residual unilateral leg weakness, which was later confirmed by strength testing. The chronic stroke group (CSG) were recruited first and 13 respondents were eligible for enrolment. However, data for two participants could not be included due to inability to acquire pQCT images (lower leg did not fit in the gantry and scanner malfunction). Eleven of the 17 respondents eligible for inclusion in the subacute stroke group (SSG) and 11 of the14 respondents eligible for inclusion in the control group (CG) were selected based on best matches for age (within 2 years) and gender.

Measures

Peripheral quantitative computed tomography (pQCT): Bilateral images of the lower leg were acquired at the tibial 66% site using pQCT (XCT-2000L, Stratec Medizintecnik, Germany; software version 6.0B). The length of each tibia was measured (in millimeters) and subjects were seated comfortably with their lower leg positioned in the pQCT gantry such that the tibia was parallel to the floor with the limb supported at the distal thigh and foot. A scout view was obtained and the anatomical reference line was positioned at the distal medial edge of the tibia. The scanner then automatically positioned the gantry at 66% of the tibial length and acquired the cross-sectional image (in-plane resolution: 0.5 mm, a slice thickness: 2.5 mm, scan speed: 30 mm/s).

Calf muscle density and mass were calculated based on measures of muscle and bone cross-sectional area and mass using the manufacturer's suggested analysis parameters. A median filter was applied to the pQCT images prior to segmentation. For segmenting muscle and bone from the subcutaneous fat, we used an iterative edge detection algorithm (contour mode 3, peel mode 1) using a threshold of 40, which exceeds the photon linear attenuation coefficient for subcutaneous fat. For segmenting bone from the surrounding muscle, we used an iterative edge detection algorithm (contour mode 1, peel mode 2) using a threshold of 280, which exceeds the photon linear attenuation coefficient for muscle. The total mass of the tibia and fibula was subtracted from the total mass of the muscle and bone to determine muscle mass (mg/mm). The tibia and fibula cross-sectional area was subtracted from that of the muscle and bone cross-sectional area to determine muscle cross-sectional area (mm^2). Then muscle mass was divided by the muscle area and multiplied by 0.001 to derive muscle density (mg/cm^3).

Cortical bone density (mg/cm^3) and mass (mg/mm), and mechanical strength - polar stress-strain index, pSSI (mm^3), were measured in the same 66% site image using CORT mode 4, inner/outer thresholds of 600/650 mg/cm^3.

Isokinetic dynamometry: Muscle strength during concentric isokinetic contractions was determined bilaterally for the ankle

Variable*	Control	Subacute Stroke	Chronic Stroke
Sex (male/female)	6/5	6/5	6/5
Age (years)	71 (13) 54/84	69 (9) 52/87	72 (12) 55/86
Height (cm)	170 (7) 159/181	164 (11) 152/183	164 (9) 152/179
Weight (kg)	70 (9) 57/88	71 (15) 52/96	71 (17) 46/101
Body mass index (kg/m^2)	24.4 (2.8) 20.9/30.1	26.3 (5.3) 18.3/38.9	26.2 (5.1) 18.1/35.8
Paretic side (left/right)	NA	5/6	6/5
Time post-stroke (mo.)	NA	3.2 (1.7) 1/6	60.0 (35.8) 17/121
Walking aid (yes/no)	0/11	5/6	8/3
Berg Balance Scale (Max score = 56)	55.3 (1.0) 53/56	45.2 (16.0) 7/56	29.0 (14.0) 4/50

**Values are n or mean (SD) minimum/maximum values, NA = not applicable*

Table 1. Subject characteristics.

plantarflexors (APF, contributing the greatest muscle bulk in the calf at the 66% site) and knee extensors (KE, as a measure of global lower limb strength) using an isokinetic dynamometer (System 3, Biodex Medical Systems, Inc., Shirley, NY). Subjects were seated with the joint axis (ankle or knee) aligned with the mechanical axis of the dynamometer. Straps stabilized the subject and the test limb to limit torque production to the muscle group of interest. After a few practice trials, subjects were instructed to push as hard and as fast as possible against the attachment. Five maximum concentric contractions were performed at 30°/s (ankle) and 60°/s (knee). Torque values generated about the knee were gravity corrected to compensate for the mass of the limb. The peak torque generated over five repetitions was recorded and normalized to body weight (Nm/kg).

Berg Balance Scale (BBS): To characterize general mobility and neuromuscular function, each subject completed the 14 item BBS, which assesses static and dynamic balance ability[12]. Each item is scored on an ordinal scale then summed to provide a total test score out of 56 points; a higher score indicates better balance ability[13].

Statistical Analysis

Descriptive statistics (means and standard deviations or frequencies) were used to summarize subject demographics and all measures by group (control, subacute and chronic) and by limb (non-paretic (*right in controls*) and paretic (*left in controls*)). Univariate regression analyses were used to determine the relationship between side-to-side differences (non-paretic leg minus paretic leg) in calf muscle density and side-to-side differences (non-paretic leg minus paretic leg) in ankle calf muscle mass, APF strength, KE strength, cortical bone density, mass and pSSI, and BBS for each subject group. The sample size was based on the recommendation of 10 subjects per dependent variable and the *a priori* plan for univariate analyses given the anticipated correlations among the variables in this preliminary investigation. Side-to-side difference in each measure except BBS was investigated to characterize the anticipated preferential deficits in the paretic leg of individuals with hemiplegia affecting the lower limb following stroke. Relationships that described at least 35% of the contribution to the variance were considered to be of significant statistical and clinical importance. For parameter estimation, side-to-side difference in each outcome is summarized as the mean and 95% confidence intervals for each group.

Results

The demographic, anthropometric and balance and mobility characteristics of the three groups of participants are summarized in Table 1. Of those with stroke, all were ambulatory (with or without a gait aid) with the exception of one person with chronic stroke who used a wheelchair. Table 2 summarizes the muscle and bone measurements for the study participants and the side-to-side differences included in the regression analyses. The expected preferential decrease in muscle strength in the paretic limb is observed for the SSG and CSG where the mean difference and 95% confidence intervals fall above 0.

Figure 1 illustrates the relationship between side-to-side differences in calf muscle density and other measures of neuromuscular status. Side-to-side differences in calf muscle density and APF muscle strength were related in both the SSG and CG (Figure 1A). Side-to-side differences in calf muscle density

Variable	Control Group (n=11)			Subacute Stroke (n=11)			Chronic Stroke (n=11)		
	Right	Left	Difference*	Non-paretic	Paretic	Difference*	Non-paretic	Paretic	Difference*
Muscle Density (mg/cm³)	74.36 (1.95)	74.08 (2.25)	0.28 (-8.41, 0.98)	73.77 (1.95)	73.05 (2.31)	0.72 (-0.49, 1.92)	70.89 (5.11)	70.23 (5.68)	0.66 (-0.53, 1.84)
Muscle Mass (mg/mm)	492.9 (58.1)	484.0 (55.2)	8.88 (-2.92, 20.68)	456.5 (110.7)	435.9 (111.1)	20.63 (-1.80, 43.07)	460.5 (83.4)	456.8 (92.4)	3.74 (-22.44, 29.92)
APF† Strength (Nm/kg)	0.71 (0.29)	0.70 (0.26)	0.003 (-0.12, 0.37)	0.47 (0.18)	0.21 (0.21)	0.27 (0.13, 0.40)	0.55 (0.19)	0.30 (0.16)	0.24 (0.07, 0.41)
KE‡ Strength (Nm/kg)	1.15 (0.26)	1.12 (0.33)	0.02 (-0.12, 0.17)	1.04 (0.40)	0.69 (0.34)	0.35 (0.21, 0.50)	0.72 (0.21)	0.55 (0.21)	0.17 (0.03, 0.31)
Tibia Cortical Bone Density (mg/cm³)	1019.7 (64.7)	1020.6 (61.3)	0.93 (-11.41, 9.56)	1088.7 (49.4)	1094.1 (54.1)	-5.34 (-15.14, 4.47)	1014.8 (67.3)	1014.5 (68.8)	0.27 (-8.96, 9.50)
Tibia Cortical Bone Mass (mg/mm)	339.4 (83.0)	345.9 (87.6)	-6.48 (-15.85, 2.90)	318.2 (104.0)	319.3 (98.7)	-1.04 (-9.57, 7.49)	324.3 (96.8)	313.6 (94.8)	10.67 (-2.50, 23.84)
Tibia pSSI§ (mm³)	2205 (679)	2131 (655)	73.86 (-142, 290)	2193 (803)	2159 (748)	34.44 (-108, 226)	2154 (761)	2061 (699)	92.68 (-86.7, 272)

** Difference, Non-paretic/Right minus Paretic/Left, is expressed as the mean (95% confidence interval). † APF: Ankle plantarflexors isokinetic concentric peak torque at 30°/sec normalized to body weight. ‡ KE: Knee extensors isokinetic concentric peak torque at 60°/sec normalized to body weight. § pSSI: Polar stress-strain index.*

Table 2. Mean (SD) measurements of muscle and bone status in each limb and for the three groups.

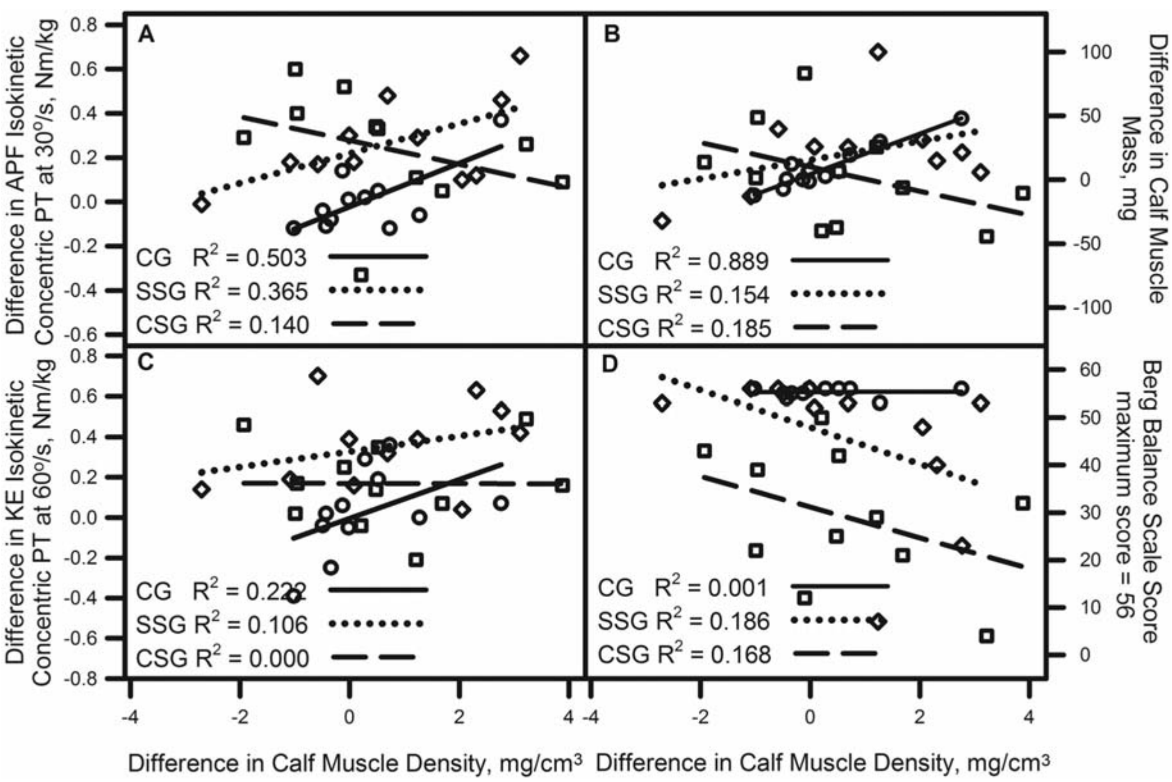

Figure 1. Relationship between side-to-side difference (Non-paretic/Right leg minus Paretic/Left leg) in calf muscle density and A) difference in ankle plantarflexor (APF) peak torque (PT) normalized to body weight, B) difference in calf muscle mass, C) difference in knee extensor (KE) peak torque (PT) normalized to body weight, D) total score on the Berg Balance Scale for the control group (CG, ○), the subacute stroke group (SSG, ◇) and the chronic stroke group (CSG, □). Regression coefficients and linear fits are shown.

and calf muscle mass were related in the CG only (Figure 1B). Side-to-side differences in calf muscle density and our measures of global muscle strength and mobility are unrelated in all groups (Figures 1C and D).

Figure 2 depicts the relationships between side-to-side differences in calf muscle density and measures of tibial cortical bone. For the SSG, side-to-side differences in muscle density and cortical bone density were positively related (Figure 2A). Side-to-side differences in muscle density and cortical bone mass were unrelated in all groups (Figure 2B). For the CSG, side-to-side differences in muscle density and tibial bone mechanical strength were positively related (Figure 2C).

Discussion

The primary objective of our study was to determine the relationship between side-to-side differences in calf muscle density and neuromusculoskeletal status in stroke survivors with subacute and chronic hemiparesis of the lower limb. Our hypothesis that the side-to-side difference in calf muscle density would be related to side-to-side differences in calf muscle strength (ankle plantarflexor strength) in people with recent hemiparesis due to stroke was supported. However, side-to-side differences in calf muscle density did not demonstrate the expected positive relationship with muscle mass asymmetry in those with hemiparesis due to neurological injury regardless of duration since the stroke event. No relationships between muscle density asymmetry and measures reflecting global lower limb strength (side-to-side difference in knee extensor strength) and mobility were observed. With respect to bone strength, side-to-side difference in muscle density was positively related to side-to-side differences in cortical bone density) in subjects with recent hemiparesis due to stroke and mechanical strength (pSSI) in those with longer term hemiparesis due to stroke. The latter finding aligned with our hypothesis that side-to-side differences in bone strength would reflect the characteristics of the habitual loading patterns experienced by those with longer term hemiparesis. This observation may be contrasted with that of a previous study reporting a significant increase in cortical thickness but not pSSI at the tibial 50% site in 26 chronic stroke survivors (11 women) who completed a 5 month exercise intervention[6,17]. Methodological issues could account for the differences in observed relationships between muscle function and tibial bone mechanical strength in the lower leg in chronic stroke survivors. The previous study[6] evaluated between-group differences for the paretic and non-paretic limbs separately rather than in terms of between-limb differences, performed gender-specific sub-analyses which limited the power to detect adaptations in pSSI, and assessed adaptations in mechanical strength over less than half a year. Moreover our study suggests that muscle density explains attributes of muscle strength that are not captured by measures of muscle mass or global measures of muscle function in stroke survivors. Taken together, these findings suggest that measures of muscle density may provide insight into the relative asymmetric changes in muscle strength and bone status following hemiparetic stroke.

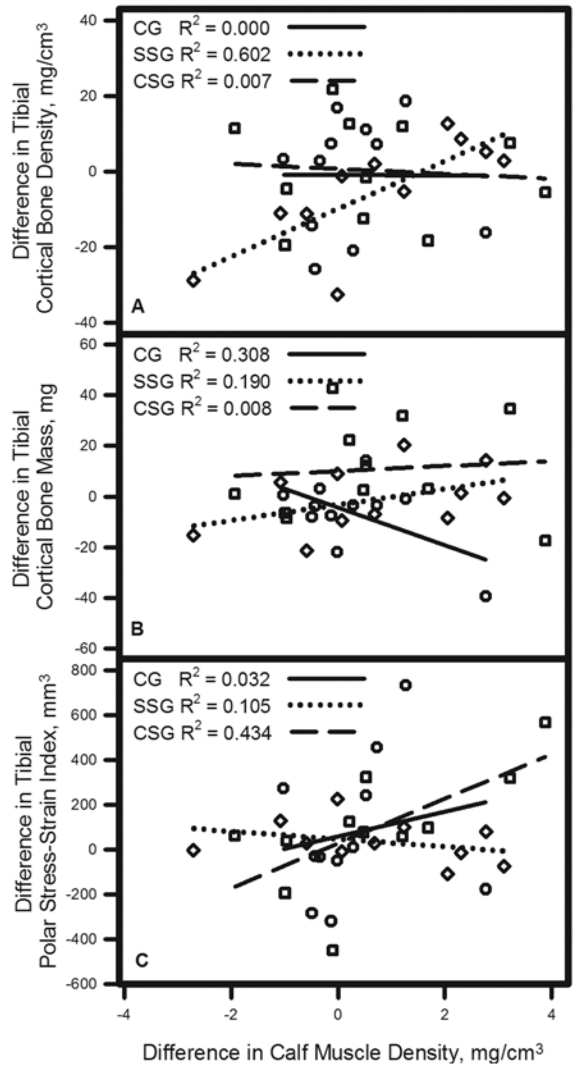

Figure 2. Relationship between side-to-side differences (Non-paretic/Right leg minus Paretic/Left leg) in calf muscle density and tibial A) cortical bone density, C) cortical bone mass, C) polar stress strain index for the control group (CG, ○), the subacute stroke group (SSG, ◇) and the chronic stroke group (CSG, ◻). Regression coefficients and linear fits are shown.

For comparison, our study included a control group matched for gender and age. Side-to-side differences were not anticipated in this group and the parameter estimates for this comparison group were presented to enable sample size calculations when designing an adequately powered study to determine if the side-to-side difference in calf muscle density differs in stroke survivors. Interestingly, despite having similar calf muscle density and mass and ankle plantarflexor strength in both legs, the anticipated relationships are observed for side-to-side differences in our healthy controls suggesting that pQCT imaging of calf muscle density and mass reflect calf muscle strength associated with healthy aging.

Reduced muscle density is a reflection of increased fatty infiltration into skeletal muscle[9] and is linked to decreased physical function[7,11]. The absolute values in our study suggest that muscle density of the calf is reduced in chronic stroke survivors compared to controls with values for stroke survivors within 6 months of the stroke event falling in between. The seemingly lower muscle density in both limbs from subacute to chronic stages of hemiparetic stroke is consistent with the notion that fatty infiltration is the negative consequence of prolonged limitations in mobility following stroke. On the other hand, Table 2 shows that the mean side-to-side differences in muscle status were closer to the values observed in the control group than to those observed in the subacute stroke group. Indeed attenuated lateral asymmetries could reflect either increased or decreased physical function. In our study, eight of the 11 subjects with chronic stroke had greater knee extensor strength in the non-paretic limb as compare with paretic (Figure 1) and relied on gait aids or a wheelchair for mobility (Table 1). Moreover this group had the poorest scores on the Berg Balance Scale. Thus the attenuated side-to-side difference in muscle density was not significantly related to performance on the Berg Balance Scale. Longitudinal studies are required to determine the magnitude of between-limb changes in muscle density over time and the corresponding changes in physical function using measures other than the Berg Balance Scale. The results of our study provide preliminary support for such investigations.

It should be noted that our study was not designed to determine group differences. Our study does provide parameter estimates for the side-to-side differences observed in our sample which may be used to calculate sample size for future investigations designed to examine these outcomes in the stroke population. For example, in order to determine if the side-to-side difference in the chronic stroke group differs significantly from that observed in the control group using the Kruskal-Wallis Test for independent samples, 70 participants per group are required.

As expected, people with stroke were weaker on the paretic side (see the 95% confidence intervals in Table 2). The weakness is attributed to deficits in descending motor control (reduced voluntary drive and coactivation of the antagonist muscle groups) and reduced force generating capacity of the fibers due to atrophic changes in the muscle[14]. In the case of coactivation, the magnitude of agonist peak torque generated is reduced by the counteracting antagonist torque compromising the validity of the strength measure. Although we do not know the extent to which this was a factor in our subjects with stroke, it may well have attenuated the relationship between muscle density and muscle strength.

The cross-sectional design of this study does not permit conclusions to be drawn about the changes in any measure over time; however, the inclusion of subjects with recent and long-term hemiparesis due to stroke provide new benchmark data for muscle density that have potential importance in evaluating neuromusculoskeletal status in stroke survivors. For example, muscle density in the paretic limb of chronic stroke survivors in this study was comparable to older adults with frailty syndrome[11]. Although our subjects were not frail in terms of body mass, the chronic stroke group had poor mobility as indicated by the dependence on mobility aids and low scores on the Berg Balance Scale (mean: 29 points) which compare to frail elderly living in residential care facilities (mean: 30 points)[15]. The implication of this observation is not immediately clear but could suggest that muscle density may predict general deterioration in overall health for stroke survivors as was found for older adults from the Health, Aging and Body Composition Study[16]. Longitudinal studies are warranted to confirm our observation of the tendency toward abnormally low muscle density in acute stroke and markedly lower muscle density in chronic stroke is progressive and to evaluate how therapeutic interventions aimed at improving muscle function and mobility influence muscle density and the bony adaptations observed following stroke.

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