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Muscle atrophy in patients receiving hemodialysis: Effects on muscle strength, muscle quality, and physical function

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Background. Dialysis patients are less active and have reduced functional capacity compared to individuals with normal renal function. Muscle atrophy and weakness may contribute to these problems. This investigation was undertaken to quantify the extent of atrophy in the lower extremity muscles, to determine whether defects in muscle specific strength (force per unit mass) or central nervous system (CNS) activation are present, and to assess the relationship between muscle size and physical performance in a group of patients on hemodialysis.

Methods. Thirty-eight dialysis subjects (aged 55 ± 15 years) and nineteen healthy sedentary controls (aged 55 ± 13 years) were enrolled. Magnetic resonance imaging of the lower leg was used to determine the total cross-sectional area (CSA) and the area of contractile and non-contractile tissue of the ankle dorsiflexor muscles. Isometric dorsiflexor strength was measured during a maximal voluntary contraction with and without superimposed tetanic stimulation ($N = 22$ for dialysis subjects, $N = 12$ for controls). Physical activity was measured by accelerometry, and gait speed was recorded as a measure of physical performance.

Results. Dialysis subjects were weaker, less active, and walked more slowly than controls. Total muscle compartment CSA was not significantly different between dialysis subjects and controls, but the contractile CSA was smaller in the dialysis patients even after adjustment for age, gender, and physical activity. Central activation and specific strength were normal. Gait speed was correlated with contractile CSA.

Conclusions. Significant atrophy and increased non-contractile tissue are present in the muscle of patients on hemodialysis. The relationship between contractile area and strength is intact in this population. Muscle atrophy is associated with poor physical performance. Thus, interventions to increase physical activity or otherwise address atrophy may improve performance and quality of life.

Key words: end-stage renal disease, hemodialysis, magnetic resonance imaging, muscle, strength, physical performance.

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Dialysis patients are less active [1] and have reduced exercise capacity [2–5] and poor physical functioning [6, 7] when compared to the general population. Impaired physical functioning has been related to low quality of life and high mortality in this population [6, 8]. The causes of poor physical functioning have not been fully elucidated, but it is likely that muscle abnormalities contribute to this problem.

Several studies have shown that dialysis patients are weaker than healthy subjects [9–13] and that the weakness includes proximal and distal muscle groups [12]. The causes of this weakness have not been fully elucidated. In general, causes of muscle weakness can include loss of muscle mass (atrophy), a decrease in the ability to generate force per unit mass or specific strength (myopathy), a reduction in the capacity of the central nervous system to activate otherwise normal motor units (central activation failure), or a combination of these mechanisms [14, 15]. Several muscle biopsy studies have been performed in patients with renal failure [16–19]. These studies have demonstrated abnormal muscle architecture that is more prominent in patients on dialysis than in patients with chronic renal failure not yet on dialysis and have provided support for all three potential causes of weakness. Atrophy, particularly of type II fibers has been demonstrated [16–19]. In addition, some have reported fiber type grouping as potential evidence of a neuropathic process [16–18]. Finally, mitochondrial and other ultrastructural abnormalities have been noted [16, 19], consistent with a myopathy. Potential causes of such a myopathy include acidosis, abnormalities in vitamin D metabolism or in serum calcium concentration, prolonged inactivity, malnutrition, inadequate dialysis or hyperparathyroidism [10, 16, 20–24]. Presence of a myopathy might be accompanied by a change in the usual relationship between muscle size and strength, but this possibility has not been systematically addressed.

The purpose of the current study was to evaluate the

potential contributions of muscle atrophy, decreased central activation, and abnormal contractile function to the weakness observed in the dialysis population. In order to achieve this, muscle contractile cross-sectional area, strength, and activation were measured in the anterior tibialis muscle compartment in dialysis subjects and controls. In addition, we tested the hypothesis that the identified muscle abnormalities are related to physical functioning measured by gait speed.

METHODS

Study subjects

Thirty-eight dialysis subjects were recruited from University of California, San Francisco-affiliated dialysis units, including the San Francisco VA Medical Center, UC-Mt. Zion Dialysis Center, and the UC Renal Center at San Francisco General Hospital. Entry criteria included receipt of chronic hemodialysis for three months or more with adequate dialysis delivery (Kt/V $\geq$1.2). Subjects were excluded if they had reasons for being in a catabolic state such as HIV infection, known malignancy, or infection requiring intravenous antibiotics within two months prior to enrollment, or if they had musculoskeletal limitations to mobility. Charts were reviewed to determine whether subjects had the following comorbid conditions: coronary artery disease, hypertension, diabetes mellitus, cerebrovascular disease, and peripheral vascular disease.

Nineteen controls who reported no kidney disease were recruited from the community. Control subjects were required to be sedentary, defined as participation in no routine exercise or fitness-related activities within two months of study enrollment.

All subjects gave informed consent for study participation. The study was approved by the Committees on Human Research at the University of California San Francisco and the San Francisco VA Medical Center.

Clinical measurements

Patients were studied in the General Clinical Research Center at San Francisco General Hospital and in the Magnetic Resonance Unit at the San Francisco VA Medical Center. Height and weight were recorded with subjects wearing only a hospital gown, and body mass index was calculated as weight in kg divided by the square of height in meters. Dialysis subjects were weighed following a dialysis session. Routine monthly laboratory results were recorded for dialysis subjects including serum albumin concentration, hemoglobin, and single-pool Kt/V calculated from pre- and post-dialysis blood urea nitrogen (BUN) measurements. Physical activity was measured by accelerometry as previously described [1]. Briefly, three-dimensional accelerometers (Tritrac R3D; Professional Products, Madison, WI, USA) were worn for one week during waking hours, and the vector magnitude was summed over the period and reported in arbitrary units. Subjects were timed twice while walking 20 feet at their usual pace, and gait speed was calculated from the faster of the two trials.

Muscle contractile and non-contractile measurements

Magnetic resonance images (MRI) were obtained on a day following a dialysis session. Proton T1-weighted magnetic resonance axial images of the anterior compartment of the leg were acquired at 1.5T (Siemens, Vision) using a 31-cm-diameter extremity coil, as performed previously [25, 26]. The right leg was studied except in cases where there was hardware or previous injury that appeared to distort the anatomy of the right leg (one dialysis subject and three control subjects). Data were acquired with the subject in a supine position. The belly of the tibialis anterior muscle (primary dorsiflexor in the anterior compartment) was located using a sagittal scout image, and the grid for the transverse (axial) slices was centered at the belly of this muscle. This procedure ensured inclusion of the maximal anterior compartment cross-sectional area (CSA) in our image acquisitions.

The image parameters were as follows: echo time of 14 ms, field of view equal to 210 mm^2, matrix equal to 256×256, slice thickness of 4 mm, 33 slices, total acquisition time of 13 minutes. These parameters were selected to optimize differences in signal intensity between contractile (muscle) and noncontractile (such as, fat) tissue. Slices were acquired in two passes, with a 4-mm gap between slices for each pass and the second pass offset by 4 mm relative to the first. This procedure allowed acquisition along the entire length of the muscle belly while cross talk between adjacent slices was prevented. Before analysis, the 33 slices were arranged anatomically (total length 132 mm), and the single slice with largest anterior compartment was selected for full analysis. The anterior compartment was identified and manually outlined (Fig. 1). The same investigator (TS) analyzed all images.

A customized software program written in IDL (Research Systems, Inc., Boulder, CO, USA) allowed for the separate quantitation of contractile and noncontractile components of the anterior compartment of the leg, which contains the ankle dorsiflexor muscles [14]. The software produced the following output: total compartment CSA (cm^2), contractile tissue CSA (cm^2), noncontractile CSA (cm^2), percent contractile tissue (contractile CSA/total CSA), percent noncontractile tissue (noncontractile CSA/total CSA), signal intensity threshold value, and total number of pixels. Each subject's image was analyzed three times, and the average values for each variable were recorded. The within-subject variabilities (SD/mean) were established using the data from the three analyses: total compartment area = 0.6%, contractile CSA = 2.7%, noncontractile CSA = 12.2%. The

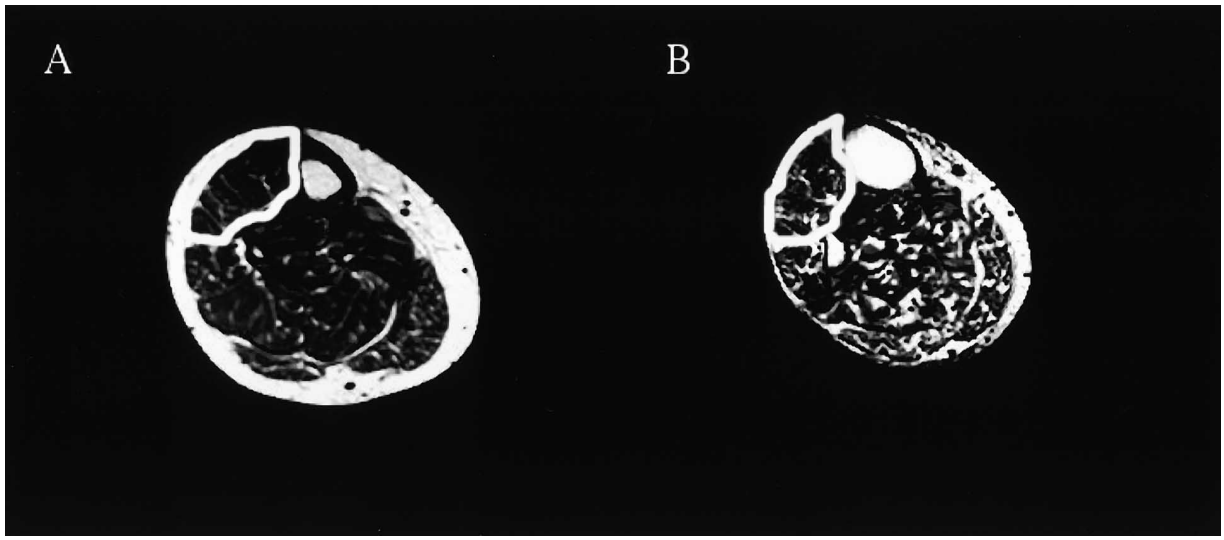

Fig. 1. Representative magnetic resonance images of the lower right leg. (*A*) A 72-year-old female control subject. (*B*) A 70-year-old female hemodialysis subject. Contractile tissue appears dark, while fat and bone appear white. The region of interest (anterior compartment) is outlined in white. There is more noncontractile tissue in the anterior compartment of the dialysis subject.

higher variability of the noncontractile measure was consistent with its relatively small area.

Muscle strength and central activation ratio

Isometric maximum voluntary contraction (MVC) and superimposed electrically-stimulated (50 Hz, 500 ms) force of the dorsiflexor muscles were recorded with subjects in a seated position [27, 28]. The same leg studied using MRI was fixed with the knee extended, and the foot was held firmly against a foot platform at 120 degrees of plantar flexion with an adjustable Velcro strap across the metatarsal heads. Two non-magnetic stimulating electrodes 10 mm in diameter (Grass-Telefactor, West Warwich, RI, USA) were applied longitudinally over the peroneal nerve 1 cm distal to the fibular head. Force output was measured with a non-magnetic force transducer (West Coast Research, Los Angeles, CA, USA) that was attached beneath the foot platform. The transducer was mounted on a bridge such that dorsiflexion leads to compression of the transducer [28]. The signal from the force transducer was amplified, converted to a digital signal and displayed using Labview Software (National Instruments, Austin, TX, USA). Three MVCs (3 to 5 seconds each) were performed with two minutes of rest between contractions. A tetanic stimulation (50 Hz, 500 ms) was superimposed on the last MVC when the MVC force plateaued. The central activation ratio (CAR) was calculated as the highest force generated by a MVC divided by the force generated during the superimposed tetanic stimuli [28]. A ratio of <1.0 indicates incomplete voluntary activation of the muscle.

Statistical analysis

Group data are presented as mean $\pm$ standard deviation unless otherwise noted. Dialysis and control subjects were compared using unpaired t tests for normally-distributed continuous variables, Chi square analysis for dichotomous variables, and Mann-Whitney rank sum test for continuous variables that are not normally distributed (PTH and physical activity levels). T tests or univariate regression analyses were performed to assess whether dialysis status, age, gender, or physical activity were associated with muscle size or strength. Multivariate regression analyses were performed to determine whether dialysis status was associated with muscle size and strength after adjustment for gender, age, and level of physical activity. Physical activity level was log-transformed because the distribution was not normal. Linear regression analysis was performed to assess the relationship between muscle size and strength. An interaction term (group $\times$ CSA) was included in the model to test whether the slope of the relationship between muscle size and strength was the same for dialysis and control subjects. Linear regression analysis was also performed to determine whether anterior compartment CSA and muscle CSA were associated with gait speed. Statistical significance for all analyses was established when a two-tailed P value was less than 0.05. All analyses were performed using STATISTICA software (StatSoft Inc., Tulsa, OK, USA).

RESULTS

Subject characteristics are shown in Table 1. There were no significant differences between dialysis subjects

Table 1. Characteristics of study participants

Variable	Dialysis subjects ($N = 38$; mean ± SD)	Control subjects ($N = 19$; mean ± SD)	P
Age	55 ± 15	55 ± 13	0.92
Gender	20M/18F	12M/7F	0.45
Race/ethnicity			<0.001
Caucasian	0	9 (47%)	
African American	21 (55%)	5 (26%)	
Hispanic	3 (8%)	1 (5%)	
Asian	14 (37%)	4 (21%)	
Body mass index kg/m^2	25.0 ± 4.9	24.1 ± 3.6	0.47
Physical activity[a] *arbitrary units*	53.1 [37.0, 115.3]	186.6 [132.4, 237.0]	<0.0001
Gait speed *cm/s*	100.2 ± 33.2	149.2 ± 35.3	<0.0001
Comorbid conditions			
Hypertension	27 (71%)	5 (26%)	0.002
Diabetes mellitus	15 (39%)	1 (5%)	0.006
Coronary artery disease	14 (37%)	0	0.001
Peripheral vascular disease	4 (11%)	0	0.2
Cerebrovascular disease	5 (13%)	0	0.1
Hemoglobin	11.7 ± 1.6		
Kt/V	1.5 ± 0.4		
Vintage *years*	2.9 ± 2.7		
Albumin *mg/dL*	3.9 ± 0.4		
Calcium *mg/dL*	9.2 ± 0.8		
Phosphorus *mg/dL*	6.3 ± 1.9		
Intact Parathyroid hormone[b]	209 [120, 489]		

[a] $N = 44$ (16 control, 28 dialysis), statistics are median (25%, 75%)
[b] $N = 27$, statistics are median (25%, 75%)

and controls in age or gender distribution, but the ethnic and racial composition was different with fewer Caucasians and more African Americans in the dialysis group. The dialysis subjects were well nourished and well dialyzed [29]. All subjects dialyzed three times per week (3.2 ± 0.5 hours per session) using polysulfone membranes (F-80; Fresenius, Inc., Bad Homburg, Germany). Subjects had been receiving dialysis for an average of 2.9 years. As expected, dialysis subjects were less active and had a slower gait speed compared to the sedentary control group.

Representative MR images of the anterior compartment of the lower extremity are shown in Figure 1, and results of the analysis of total, contractile and non-contractile CSA are presented in Table 2 and Figure 2. There was no significant difference between dialysis subjects and controls in total CSA of the anterior compartment. However, the composition of the muscles differed significantly. Dialysis subjects had less contractile tissue and more non-contractile tissue than controls. Age, gender, and physical activity level were associated with percent contractile area in univariate analyses. Men had a significantly greater percentage of contractile area ($P = 0.004$). There was a negative association between age and percentage of contractile area ($r = -0.43$, $P = 0.0008$) and a positive association between the natural log of activity level and percentage of contractile area ($r = 0.32$, $P = 0.03$). When these variables were included in multiple regression analysis, dialysis subjects still had lower percent contractile area (that is, a higher percent of noncontractile area; $P = 0.005$). No significant effect of race was appreciated in multivariable analysis.

Table 2. Muscle strength, activation, and cross-sectional area data

Variable	Dialysis subjects ($N = 22$)	Controls ($N = 17$)	P value
Total CSA cm^2	10.8 ± 2.6	10.9 ± 2.2	0.93
Contractile CSA cm^2	7.2 ± 3.1	9.1 ± 2.0	0.02
Noncontractile CSA cm^2	3.7 ± 2.3	1.8 ± 0.5	0.001
MVC N	169.6 ± 65.5	217.7 ± 69.1	0.03
CAR	0.94 ± 0.12	0.96 ± 0.09	0.66
MVC/total CSA	15.0 ± 4.8	19.7 ± 4.6	0.003
MVC/contractile CSA	21.9 ± 7.2	23.4 ± 5.3	0.48

Data are mean ± SD. Abbreviations are: CSA, cross-sectional area; MVC, maximal voluntary contraction; CAR, central activation ratio.

Force and specific strength data are presented in Table 2. As expected, dialysis patients were weaker than control subjects. The central activation ratio was not significantly different between groups, suggesting that the reduced strength was not the result of reduced volitional effort or of decreased central nervous system activation. It is well established in healthy individuals that there is a linear relationship between muscle CSA and muscle strength [30]. Whereas myopathy is often associated with a change in the ratio of muscle strength to muscle size, muscle atrophy is not expected to affect specific strength. To evaluate whether the relationship between muscle size and strength was intact in this group of dialysis patients, the ratio of MVC/total CSA and MVC/contractile CSA in dialysis subjects and controls were compared (Table 2).

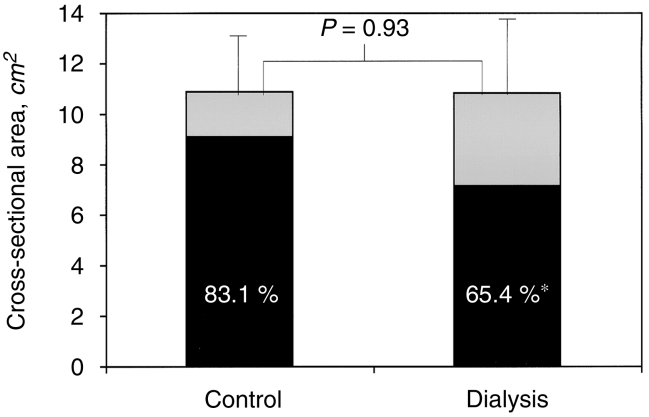

Fig. 2. Total, contractile (■), and noncontractile (▨) muscle area. Error bars represent the standard deviations for total cross-sectional area. There is no significant difference in total cross-sectional area ($P = 0.93$), but dialysis subjects have significantly less contractile tissue and more non-contractile tissue ($P = 0.001$ for both comparisons).

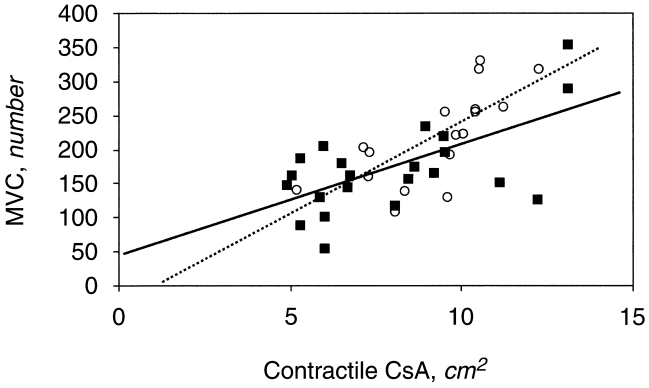

Fig. 3. Relationship between contractile cross-sectional area (CSA) and maximum voluntary contraction (MVC). The relationship between contractile CSA and MVC is not significantly different ($P = 0.13$) in dialysis subjects (■) and healthy sedentary control subjects (○). For dialysis subjects, $r = 0.60$, $P = 0.003$, and for control subjects, $r = 0.73$, $P = 0.001$.

The ratio of MVC/total CSA was lower in HD ($P = 0.003$), but the ratio of MVC/contractile CSA was not significantly different between the groups ($P = 0.48$). Figure 3 shows that the linear relationship between muscle size and strength is not different in dialysis subjects and controls ($r = 0.66$, $P < 0.001$).

Since the major abnormality identified in the muscle of dialysis subjects was atrophy, we tested the hypothesis that muscle atrophy was related to the reduced physical performance noted in this population. Gait speed was significantly correlated with contractile CSA in dialysis subjects and controls ($r = 0.61$, $P < 0.0001$), but dialysis subjects had a slower gait speed even after adjustment for contractile area ($P < 0.0001$). Similar results were obtained when the relationship between muscle strength and gait speed was explored ($r = 0.47$, $P = 0.003$ and $P = 0.01$ for the effect of group), consistent with the normal relationship between muscle contractile area and strength in this population.

DISCUSSION

This study demonstrates that the ankle dorsiflexor muscles of dialysis patients are weaker than those of healthy sedentary control subjects. In addition, our results indicate that atrophy and not central activation failure is the primary mechanism for this weakness. Although the total cross-sectional area of the anterior tibialis compartment is not smaller in dialysis patients than controls, it is clear that the amount of contractile tissue is reduced and atrophy is present. Specific strength (MVC/contractile area) is preserved in this patient group. The correlations of muscle contractile area and strength with gait speed lend support to the idea that muscle atrophy and resulting weakness is an important cause of reduced physical functioning in the dialysis population.

The observation of a similar muscle compartment size but a smaller contractile CSA in dialysis patients clarifies the discrepancy between studies that report a reduction in overall muscle mass in patients on dialysis [31–35] and studies that report that muscle mass determined by anthropometric methods is not reduced [34–36]. Our results agree with those of others who have used techniques such as total body nitrogen [33] and dual-energy X-ray absorptiometry [34, 35] to measure lean body mass. Use of muscle imaging adds information beyond what has been obtained by these other techniques because a more precise region of interest (such as specific muscle groups as in the current investigation) can be studied, allowing more precise correlation between form and function. In the anterior compartment of the lower leg, total muscle compartment CSA does not accurately represent contractile content in hemodialysis subjects. Therefore, methods of measuring muscle mass that rely directly or indirectly on total CSA (for example, anthropometry) will underestimate the degree of muscle wasting.

When the area of contractile tissue was used to measure specific strength, rather than the CSA of the whole muscle compartment, the muscle of the dialysis subjects was capable of generating tension equivalent to that of muscle of sedentary control subjects. This suggests that the observed weakness was related directly to atrophy rather than to reduced muscle quality that could result from changes in fiber length, angle of insertion, or metabolic or ultrastructural abnormalities.

Exercise training studies in patients on hemodialysis have generally shown an increase in VO_{2peak} [19, 37–42]. While the interventions and results have been variable, the average increase in one review was 16.4%, comparable to the expected effects of aerobic training in healthy individuals, but not enough to raise VO_{2peak} to normal

levels [43]. The improvement in VO_{2peak} that can be achieved by exercise training in this population is mainly driven by peripheral, or intramuscular, adaptations [4, 19, 44]. One study that included seven patients showed a remarkable 48% increase in VO_{2peak} after six months of exercise training [19]. Interestingly, this is the only study of which we are aware to have incorporated strength training as part of the regimen. Thus, aerobic training alone can increase VO_{2peak}, but a regimen that increases muscle mass can produce a more dramatic response. These findings support a role of atrophy in the reduced exercise capacity of patients on hemodialysis.

Some potential causes of muscle atrophy were explored in the current investigation, including aging and inactivity. Our results suggest that while inactivity may be the cause of some of the observed atrophy, dialysis subjects had smaller amounts of contractile tissue even after adjustment for physical activity level. Thus, factors related to renal failure or hemodialysis may contribute also to muscle atrophy in this population. These might include a uremic neuropathy [12], hyperparathyroidism [23, 24, 45], 1,25-$(OH)_2$-vitamin D deficiency [22], acidosis [46], or malnutrition [21].

Strengths of this study include the highly quantitative method of measuring muscle contractile content and force as well as the use of tetanic stimuli during a MVC. The methods of recording force data used in this study afford a great deal of precision and preclude any influence of the investigator on the measurements. The use of tetanic stimuli during an MVC allowed us to be certain that the observed differences in muscle strength were not related to differential subject motivation. A weakness of the study was the large difference in physical activity between dialysis subjects and sedentary healthy controls. It would be preferable to compare muscle size in two groups with similar activity level. However, the present physical activity results agree with previous results obtained using a different group of dialysis subjects and controls that showed that dialysis patients are considerably less active than even sedentary controls [1]. Collection of quantitative physical activity data from subjects and controls allowed for adjustment of the analysis for the difference in activity level. We believe that since dialysis patients will be less active than almost any control group investigators can assemble, measurement of physical activity level is critical to analyses of muscle size and function.

In summary, dialysis patients had a smaller contractile area (atrophy) of the tibialis anterior compartment compared to a group of sedentary control subjects with a similar distribution of age and gender. The atrophy was associated with weakness that was in proportion to the degree of atrophy. There was no evidence of reduced muscle quality as measured by the ratio of muscle strength to contractile CSA (specific strength). Central nervous system activation of motor units was also normal in dialysis subjects. Atrophy was associated with reduced physical activity in the dialysis subjects, but a large difference persisted between dialysis subjects and controls even after adjustment for level of physical activity. Finally, muscle atrophy was associated with reduced physical performance. Greater emphasis should be placed on the development and evaluation of strategies to increase muscle mass and strength in this population.

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