Progressive Exercise for Anabolism in Kidney Disease (PEAK): A Randomized, Controlled Trial of Resistance Training during Hemodialysis

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Skeletal muscle wasting is common and insidious in patients who receive maintenance hemodialysis treatment for the management of ESRD. The objective of this study was to determine whether 12 wk of high-intensity, progressive resistance training (PRT) administered during routine hemodialysis treatment could improve skeletal muscle quantity and quality *versus* usual care. Forty-nine patients (62.6 ± 14.2 yr; 0.3 to 16.7 yr on dialysis) were recruited from the outpatient hemodialysis unit of the St. George Public Hospital (Sydney, Australia). Patients were randomized to PRT + usual care ($n = 24$) or usual care control only ($n = 25$). The PRT group performed two sets of 10 exercises at a high intensity (15 to 17/20 on the Borg Scale) using free weights, three times per week for 12 wk during routine hemodialysis treatment. Primary outcomes included thigh muscle quantity (cross-sectional area [CSA]) and quality (intramuscular lipid content *via* attenuation) evaluated by computed tomography scan. Secondary outcomes included muscle strength, exercise capacity, body circumference measures, proinflammatory cytokine C-reactive protein, and quality of life. There was no statistically significant difference in muscle CSA change between groups. However, there were statistically significant improvements in muscle attenuation, muscle strength, mid-thigh and mid-arm circumference, body weight, and C-reactive protein in the PRT group relative to the nonexercising control group. These findings suggest that patients with ESRD can improve skeletal muscle quality and derive other health-related adaptations solely by engaging in a 12-wk high-intensity PRT regimen during routine hemodialysis treatment sessions. Longer training durations or more sensitive analysis techniques may be required to document alterations in muscle CSA.

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Skeletal muscle wasting is common and insidious in ESRD (1,2). Factors such as acidosis (3), protein-energy malnutrition, comorbid illnesses, corticosteroid use, biologic aging, oxidative stress, dialysis treatment (4), and very low levels of physical activity all can contribute markedly to the loss and atrophy of muscle fibers and the accrual of intramuscular lipid in this cohort (1,5). This loss of muscle quantity and quality is associated with metabolic and functional deficits and reduced quality of life. Furthermore, muscle wasting is recognized as one of the strongest predictors of mortality in ESRD (6).

High-intensity progressive resistance training (PRT) has been prescribed successfully to enhance skeletal muscle and related physiologic and psychologic attributes in frail elders and those with chronic catabolic illnesses, including nursing facility residents and cardiac patients (7). The prevalence of muscle wasting in ESRD suggests that PRT is indicated and may be of significant benefit in this patient population as well (8–10). In fact, recent evidence suggests that moderate to vigorous physical activity confers a survival advantage in this cohort, although limitations exist in pursuing such activities (11).

The rationale for prescribing PRT to patients with ESRD in an attempt to counteract muscle wasting is extremely strong (8,9). However, barriers to regular exercise participation in this cohort are many, including, most notably, the sedentariness that is incurred by attending 12 to 18 h of dialysis treatment per week. Behaviors that dominate dialysis treatment time include sleeping and watching television, and few clinical units worldwide have promoted an active approach toward this patient "down time" despite much evidence for the health and clinical benefits of intradialytic cycling (9,12).

To date, only one trial has investigated the efficacy of prescribing PRT during routine hemodialysis treatment. Johansen *et al.* (13) reported that patients with ESRD can improve quad-

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riceps muscle area secondary to 12 wk of moderate intensity, lower body PRT with either placebo or nandrolone decanoate injections.

The purpose of this study was to determine whether an isolated, full-body, high-intensity PRT regimen administered during routine hemodialysis treatment could safely induce favorable shifts in skeletal muscle quantity and quality in patients who receive maintenance hemodialysis treatment for the medical management of ESRD. We hypothesized that our novel intervention (14) would increase skeletal muscle cross-sectional area (CSA) and reduce intramuscular lipid infiltration while inducing additional health-related adaptations, including improved exercise capacity, psychologic health, inflammatory markers, nutritional status, and quality of life in our exercising patients.

Materials and Methods

Patient Population and Recruitment

The Progressive Exercise for Anabolism in Kidney Disease (PEAK) trial was conducted at the outpatient hemodialysis unit of St. George Public Hospital (Sydney, Australia). All patients who regularly attended the dialysis unit were evaluated for eligibility between October 2002 and July 2005, *via* medical chart review, physical examination by a study physician, and clearance from the patient's nephrologist before solicitation of interest and written informed consent. Eligibility criteria included (*1*) ≥18 yr of age, (*2*) on hemodialysis for >3 mo, (*3*) without acute or chronic medical conditions that would preclude PRT or collection of outcome measures, (*4*) independent ambulation with or without an assistive device for ≥50 m, (*5*) adequately dialyzed (Kt/V ≥1.2) and stable during dialysis, (*6*) cognition and English language sufficient to understand research procedures and provide written informed consent, and (*7*) willingness to be randomly assigned and to undergo study protocols.

Study Design

The South Eastern Sydney Area Health Service and the University of Sydney Human Research Ethics Committees approved all procedures, and written informed consent was obtained from all participants (Australian Clinical Trials Registry 12605000101684). Patients were randomly assigned *via* computer-generated randomly permuted blocks stratified by gender in blocks of four to PRT + usual care (PRT), or usual care control. Patients were not stratified by diabetic status. Randomization assignments were generated by an investigator who was not involved in testing or training and delivered to patients in opaque sealed envelopes on the completion of all baseline testing.

PRT Intervention

Patients who were randomly assigned to PRT exercised under the direct supervision of an exercise physiologist during routine hemodialysis treatment three times per week for 12 wk as described previously (14). All PRT exercises were performed in a seated or supine position in a standard hemodialysis chair (LA-Z-BOY Pty Ltd, Moorebank, Australia). The limb that contained the forearm arteriovenous or Gortex fistula was exercised immediately before each dialysis session. A temporary vas catheter access precluded upper body training only.

During each PRT session, two sets of eight repetitions of 10 exercises that targeted major muscle groups of the upper and lower extremities were performed at a rating of perceived exertion of 15 to 17 of 20 ("hard" to "very hard"). Upper body exercises that were performed using free-weight dumbbells (Australian Barbell Co., Mordialloc, Australia) included the shoulder press, side shoulder raise, triceps extension, biceps curl, and external shoulder rotation. Lower body exercises, performed unilaterally using weighted ankle cuffs (Australian Barbell Co.), included seated knee extension, supine hip flexion, supine hip abduction, and supine straight-legged raise. Seated hamstring curls were also performed, using Thera-Band tubing (Akron, OH) attached to a fixed position on the weight trolley. Abdominal musculature was targeted with bilateral leg raises in a supine position or bilateral leg lifts in a seated position, depending on patient preference and level of ability.

Usual Care Control Group

Patients who were randomly assigned to the control group were provided usual care but no instructions to exercise or access to equipment.

Outcome Measures

All outcomes measures were collected at baseline and 12 wk after randomization.

Primary Outcomes

Computerized tomography (CT) of the nondominant mid-thigh was performed on a nondialysis day using a General Electric High Speed CTi Scanner (model CEE0459; Milwaukee, WI) to determine thigh muscle CSA and attenuation (*i.e.*, intramuscular lipid infiltration [15]). Muscle CSA provided an index of muscle quantity, whereas muscle attenuation provided an index of muscle quality. Lower measures of muscle attenuation indicate less intramuscular lipid and thus better muscle quality. CT scans also provided areas of subcutaneous and total fat of the mid-thigh. All CT scans were collected and analyzed blindly as previously reported (16). Coefficient of variability of triplicate analysis of area and attenuation measures in this cohort is 0.005%.

Secondary Outcomes and Clinical Covariates

Peak force (kg) of the knee extensors, hip abductors, and triceps was measured bilaterally in triplicate with the best score recorded, using an isometric digital dynamometer (Chatillon CSD 200 Dynamometer; AMETEK, Paoli, PA; coefficient of variability 9.4%). These individual strength measures were summed to create a total strength measure.

The 6-min walk (17) was used as an index of exercise capacity. The coefficient of variability of this test is reported to be 5 to 10% in older or clinical cohorts (18).

A blinded dietitian collected all nutritional and anthropometric measures after dialysis, including body weight, height, waist, and mid-arm and mid-calf circumferences, using standard protocols. Limb circumference measures were collected on the right side of the body, as per standard protocol. The Mini-Nutritional Assessment was used because it is an objective, well-validated instrument to evaluate nutritional status in clinical and older cohorts and comprises medical history, reported dietary intake, and anthropometric measures (19). Dietary intake during the previous month was evaluated at baseline and week 12 using an Australian Food Frequency Questionnaire (20), analyzed using FoodWorks software (Version 3; Xyris Software, Highgate Hill, Queensland, Australia).

All blood samples were drawn before dialysis, before the midweek dialysis session, at least 48 h after the previous exercise bout. Urea kinetics evaluation included the collection of blood urea after midweek and before end-of-week dialysis sessions. Samples that potentially were affected by acute illness or trauma were discarded and repeated. C-reactive protein (CRP) was evaluated as an index of catabolism and systemic inflammation using a high-sensitivity assay, as were albumin,

creatinine, and complete blood count (coefficient of variability 1.5 to 4.8%).

The Medical Outcomes Trust Short Form-36 (SF-36) (21) survey was used to measure health-related quality of life. The Geriatric Depression Scale (22) was used to evaluate depressive symptoms. The Physical Activity Scale for the Elderly (23) was used as a valid instrument to evaluate occupational, leisure, and daily habitual activity level apart from the study exercise prescription.

Compliance and Adverse Events

Compliance to training was defined as the number of training sessions attempted divided by the number offered multiplied by 100%. Change of health status, including acute illnesses, falls, changes in medication usage, dialysis-related complaints (*e.g.*, headaches, hypotension, cramping), and visits to health care professionals were documented *via* weekly interview using a structured questionnaire developed *a priori*, open-ended questions, and weekly review of clinical notes. PRT-related adverse events were defined as any injury or exacerbation of underlying disease that potentially was attributable to the PRT regimen.

Statistical Analyses

Sample size estimates were calculated by hypothesized differences between the PRT and control groups in thigh muscle CSA on CT scan. On the basis of previous studies (16), the control group was estimated to have no change, whereas the PRT group was hypothesized to have a +3.5% change in CSA with an SD of ±4.5% after 12 wk. Using a two-tailed test of significance and setting the α at 0.05 and β at 0.20, a total of 44 patients were estimated to be required; this was inflated to 50 in anticipation of dropout/less-than-complete adherence to the protocol.

All available data were included regardless of patient compliance to the intervention in an intention-to-treat analysis performed using StatView statistical software package (Version 5.0; SAS Institute, Cary, NC). Data from patients who were unavailable for follow-up assessments at week 12 were carried forward from baseline values. All data were inspected visually and statistically for normality. Normally distributed data were described using mean ± SD and non-normally distributed data using median and ranges. Non-normally distributed continuous variables were log-transformed before entry into linear models or analyzed by Mann-Whitney *U* test. Variables with non-normal distributions were reported as median and range values with 95% confidence intervals (CI) expressed as a difference between medians. Between-group differences over time were expressed as PRT minus control group adjusted mean differences and 95% CI, as well as relative effect size (ES), calculated as change in treatment group minus change in control group divided by pooled SD, corrected for sample size (Hedge's bias corrected ES) (24). Group effect was analyzed by analysis of covariance (ANCOVA) using change scores (final minus baseline) as the dependent variables and baseline value of the dependent variable in the model as a covariate. Additional covariates for the ANCOVA models were identified by comparison of group means and CI at baseline for clinically meaningful differences in characteristics that were identified *a priori* as potential confounders (age and hemodialysis vintage), because these factors might confound the change in the dependent variable as a result of their potential to influence anabolic adaptations to PRT. $P < 0.05$ and/or 95% CI not inclusive of 0 was considered indicative of statistical significance. Clinical significance was evaluated *via* consideration of the magnitude of differences that were observed between groups relative to known clinically meaningful differences as well as the relative ES calculated.

Results

Flow of Participants

Forty-nine eligible patients consented to participate, composing 35% of the entire dialysis cohort ($n = 142$) available during the period of recruitment (October 2002 to July 2005; Figure 1). Among the 49 patients who were randomly assigned, five (10%) were unavailable for follow-up testing (Figure 1). Only 26 (18%) of the 142 patients were medically excluded from participating in the trial, and 20 (14%) patients died before being recruited.

Baseline Characteristics

Baseline characteristics are shown in Table 1. No statistically significant differences were observed between groups at baseline according to the descriptive characteristics evaluated, including tobacco use history and prevalence of comorbid illnesses (*e.g.*, diabetes, myocardial infarction, stroke; Table 1). However, because of potentially clinically important differences in age and hemodialysis vintage between groups, these variables were included in all ANCOVA models of absolute change scores as covariates.

Outcome Measures

Primary Outcomes. Thigh muscle CSA did not change significantly between groups by 12 wk ($P = 0.40$); however, the

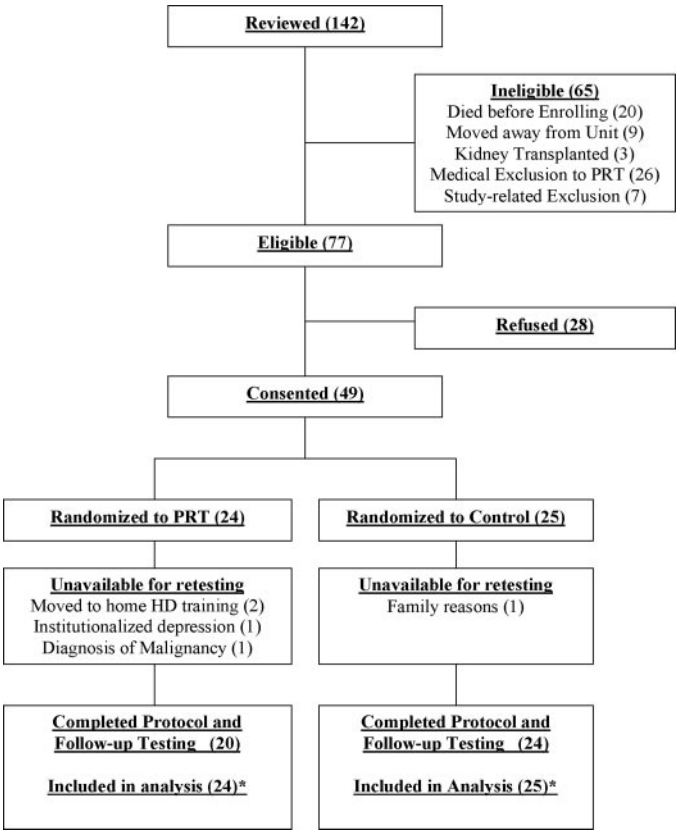

Figure 1. Flow of participants through the Progressive Exercise for Anabolism in Kidney Disease (PEAK) trial. *Baseline data carried forward for four progressive resistance training (PRT) participants and one control participant lost to follow-up.

Table 1. Baseline characteristics of the total cohort and groups[a]

Characteristic	Total Cohort ($n = 49$)	PRT Group ($n = 24$)	Control Group ($n = 25$)
Age (yr)	62.6 ± 14.2	60.0 ± 15.3	65.0 ± 12.9
Men:women	34:15	17:7	17:8
Hemodialysis vintage (yr; median [range])[b]	2.2 (0.3 to 16.7)	3.3 (0.3 to 16.7)	1.6 (0.6 to 10.3)
Body weight (kg)	75.7 ± 18.3	74.9 ± 19.5	76.5 ± 17.4
Height (cm)	165.6 ± 10.2	166.2 ± 9.1	165.1 ± 11.3
BMI (kg/m^2)	27.5 ± 5.8	27.0 ± 6.0	28.0 ± 5.7
Medications/d (*n*)	8.6 ± 2.8	8.8 ± 3.2	8.4 ± 5.7
Tobacco use history (*n*)	28	11	17
Chronic diseases (*n*)[c]	5.1 ± 1.8	4.9 ± 1.6	5.2 ± 2.0
hypertension	49	24	25
depression[d]	17	8	9
diabetes	16	5	11
MI	11	3	8
stroke	6	1	5
Etiology of ESRD (*n*)			
glomerulonephritis	12	6	6
diabetes	9	3	6
hypertension	6	2	4
ischemia	4	3	1
PCKD	4	3	1
IgA nephropathy	4	3	1
analgesic use	3	1	2
SLE	1	1	0
other	6	2	4

[a]Data are means ± SD for normally distributed variables. BMI, body mass index; MI, myocardial infarction; PCKD, polycystic kidney disease; PRT, progressive resistance training; SLE, systemic lupus erythematosus.
[b]Non-normal distribution.
[c]Includes diagnosis of ESRD.
[d]Mild to severe depression diagnosed according to the Geriatric Depression Scale (22).

ES was 0.30, and the range of plausible results varied from a 1.9-cm^2 reduction compared with control to a 6.1-cm^2 increase for PRT. The upper bound, favoring PRT, represents a clinically important difference (Table 2). The other primary outcome, muscle quality (thigh muscle attenuation indicative of intramuscular lipid infiltration), improved to a statistically significant degree in the PRT group *versus* the control group, with a moderate ES of −0.52 (Table 2).

Secondary Outcomes and Clinical Covariates. There were statistically significant and clinically meaningful increases in total strength, body weight, body mass index (BMI), and mid-arm and mid-thigh circumference in the PRT group as compared with the control group (Table 2). Similarly, a large ES of −0.85 was demonstrated for the reduction in the inflammatory marker log CRP, which was statistically significantly different between groups, decreasing in the PRT group while increasing in controls (Table 2). The PRT group also statistically significantly improved two of eight domains of quality of life, Physical Function and Vitality, *versus* the control group, in whom both of these measures worsened (Table 2). All of these adaptations occurred despite no statistically significant or clinically important changes between groups in habitual physical activity or dietary energy or protein intake (Table 3). No other secondary outcomes or clinical covariates significantly changed between groups, including depression, dialysis adequacy, and other measures related to nutritional and clinical health status (Tables 2 and 3). Notably, no significant changes were observed between groups over time in measures of total or subcutaneous fat of the mid-thigh, as evaluated by CT scan (Table 2), or waist circumference as an estimate of central adiposity.

Compliance

Compliance to the training program was 85.1% in the 20 PRT patients who completed both assessments and 79.8% including the four PRT patients who were unavailable for follow-up testing.

Adverse Events

No statistically significant differences were observed between the PRT group and controls for the number of dialysis-related complaints, including headaches (PRT 0 [0 to 2]; control 0 [0 to 3]; 95% CI 0 to 0), hypotension (PRT 1 [0 to 7]; control 0

Table 2. Summary of primary and secondary outcome measures[a]

Outcome Measure	PRT Group		Control Group		Adjusted Mean Difference (95% CI)[b]	Effect Size	P^b
	Baseline	12-Wk Change	Baseline	12-Wk Change			
Primary outcomes							
muscle CSA (cm^2)	104.2 ± 25.6	+1.2 ± 5.8	98.9 ± 21.5	−0.9 ± 7.9	2.1 (−1.9 to 6.1)	0.30	0.40
muscle attenuation (Hounsfield unit)	85.7 ± 2.5	−0.1 ± 0.9	87.0 ± 2.2	+0.3 ± 0.6	−0.4 (−0.8 to 0.0)	−0.52	0.04
Secondary outcomes							
regional fat estimates							
total mid-thigh fat (cm^2)	73.8 ± 35.1	+0.9 ± 7.7	78.4 ± 25.0	+1.0 ± 3.7	−0.1 (−3.6 to 3.4)	−0.02	0.95
subcutaneous mid-thigh fat (cm^2)	61.7 ± 27.5	+0.5 ± 7.2	66.1 ± 24.0	+0.9 ± 3.3	−0.4 (−3.6 to 2.8)	−0.07	0.93
functional measures							
total strength (kg)	98.1 ± 36.6	+15.2 ± 15.4	86.0 ± 33.8	−2.4 ± 13.8	17.6 (9.2 to 26.0)	1.19	0.002
6-min walk (m)	496.6 ± 133.3	+16.7 ± 40.5	406.4 ± 122.9	−2.9 ± 25.8	19.6 (0.2 to 39.0)	0.57	0.16
Physical Function (21) (0 to 100)	73.5 ± 26.3	+7.6 ± 11.8	64.4 ± 21.6	−1.8 ± 17.6	9.4 (0.8 to 18.1)	0.46	0.02
anthropometric measures							
mid-thigh circumference (cm)	47.5 ± 6.0	+0.7 ± 1.1	47.8 ± 5.9	−0.3 ± 1.7	1.0 (0.2 to 1.8)	0.68	0.04
mid-arm circumference (cm)	30.1 ± 4.0	+0.4 ± 1.4	30.1 ± 4.0	−0.6 ± 0.9	1.0 (0.3 to 1.7)	0.84	0.004
body weight (kg)	74.9 ± 19.5	+0.8 ± 1.5	76.5 ± 17.4	−0.1 ± 1.4	0.9 (0.1 to 1.7)	0.61	0.02
BMI (kg/m^2)	27.0 ± 6.0	+0.3 ± 0.5	28.0 ± 5.7	−0.1 ± 0.5	0.4 (0.1 to 0.7)	0.79	0.02
mid-calf circumference (cm)	35.3 ± 3.8	+0.2 ± 1.2	35.3 ± 3.4	+0.1 ± 0.8	0.1 (−0.5 to 0.7)	0.11	0.41
inflammatory and nutritional measures							
log CRP	0.78 ± 0.60	−0.08 ± 0.37	0.72 ± 0.55	+0.24 ± 0.37	−0.32 (−0.53 to −0.11)	−0.85	0.02
Mini-Nutritional Assessment (19) (0 to 30)	26.5 ± 1.8	+0.3 ± 1.2	25.7 ± 2.7	+0.5 ± 2.7	−0.2 (−1.4 to 1.0)	−0.09	0.48
protein catabolic rate (g/kg per d)	1.06 ± 0.03	+0.02 ± 0.31	1.10 ± 0.02	−0.04 ± 0.17	0.06 (−0.08 to 0.20)	0.24	0.63
psychological measures							
Vitality (21) (0 to 100)	57.7 ± 22.2	+2.8 ± 16.3	55.8 ± 23.7	−7.0 ± 14.1	9.8 (1.1. to 18.6)	0.63	0.02
Geriatric Depression Scale (22) (0 to 30)	7.2 ± 7.1	−0.3 ± 3.6	8.1 ± 6.4	+1.0 ± 2.9	−1.3 (−3.2 to 0.6)	−0.39	0.11

[a]Data are means ± SD. CI, confidence interval; CRP, C-reactive protein; CSA, cross-sectional area.
[b]Estimates based on the final model that included baseline assessment value, age, and log hemodialysis vintage as covariates.

Table 3. Clinical covariates[a]

Outcome Measure	PRT Group		Control Group		Adjusted Mean Difference (95% CI)[b]	Effect Size	P^b
	Baseline	12-Wk Change	Baseline	12-Wk Change			
Dialysis adequacy (Kt/V)	1.5 ± 0.4	+0.1 ± 0.5	1.7 ± 0.7	+0.1 ± 0.4	0.0 (−0.3 to 0.3)	0.00	0.73
Energy intake (20) (kcal/kg per d)	32.3 ± 7.3	+0.8 ± 3.2	29.7 ± 7.4	+0.3 ± 2.7	0.5 (−1.2 to 2.2)	0.17	0.16
Protein intake (20) (g/kg per d)	1.5 ± 0.3	+0.0 ± 0.1	1.3 ± 0.3	+0.1 ± 0.2	−0.1 (−0.2 to 0.0)	−0.62	0.94
Albumin (g/L)	34.5 ± 3.1	+0.3 ± 2.4	33.6 ± 7.9	−0.16 ± 2.4	0.5 (−0.9 to 1.8)	0.19	0.45
Creatinine (μ mol/L)	940.9 ± 185.9	−5.0 ± 89.6	825.3 ± 200.6	−28.0 ± 199.7	23.0 (−66.6 to 112.6)	0.15	0.47
White blood cell count ($\times 10^9$)	6.9 ± 1.9	−0.3 ± 1.4	7.2 ± 2.1	0.0 ± 1.3	−0.3 (−1.1 to 0.5)	−0.22	0.70
Lymphocytes ($\times 10^9$/L)	1.49 ± 0.54	+0.05 ± 0.30	1.51 ± 0.54	+0.15 ± 0.48	−0.10 (−0.33 to 0.13)	−0.24	0.35
Waist circumference (cm)	96.7 ± 18.5	+0.3 ± 2.7	100.0 ± 16.4	+0.3 ± 1.9	0.0 (−1.3 to 1.3)	0.00	0.84
Physical Activity Scale (23) (0+)	89.5 ± 54.1	+11.2 ± 45.2	60.9 ± 44.5	+0.3 ± 22.2	10.9 (−9.4 to 31.2)	0.30	0.21

[a]Data are means ± SD.
[b]Estimates based on the final model that included baseline assessment value, age, and log hemodialysis vintage as covariates.

[0 to 6]; 95% CI −2 to 1), cramping (PRT 0 [0 to 8]; control 0 [0 to 6]; 95% CI 0 to 0), and fistula cannulation difficulties (PRT 0 [0 to 2]; control 0 [0 to 3]; 95% CI 0 to 0). No fistula infections or angina was reported in either group during the trial. The incidence of falls was low and did not differ significantly between groups (PRT 0 [0 to 1]; control 0 [0 to 2]; CI not computed because of rarity of events). No differences were observed between groups in acute illness (PRT 2.45 ± 1.64; control 1.83 ± 1.93; 95% CI −1.65 to 0.41) or number of visits to health care professionals (PRT 3.80 ± 1.40; control 4.83 ± 2.63; 95% CI −0.19 to 2.25) during the trial. No case of cannula dislodgement was observed during exercise in any patient during the course of the trial. One adverse event was documented: An elderly woman in the PRT group (73.3 yr, 3.8 yr on HD) sustained partial tearing of a right rotator cuff muscle (supraspinatus) in week 6 of training (25). The injury was managed conservatively, and the patient continued with lower body training for the remainder of the trial and underwent final assessment (25).

Sensitivity Analyses

Secondary sensitivity analyses were performed using all available data regardless of compliance without imputation of

missing data from the five patients who did not undergo final assessment. The outcomes of these analyses did not differ with the intention-to-treat primary analysis with respect to statistically significant findings (data not shown).

Discussion

Patients who engaged in our 12-wk intradialytic PRT training regimen experienced statistically significant improvements of muscle quality and a potentially clinically important difference in muscle quantity (*i.e.*, CSA; Table 2). Investigation of secondary outcomes revealed statistically significant increases in total strength, body weight, BMI, and mid-thigh and mid-arm circumference; no increase in fat depots; reduced CRP; and improved Physical Function and Vitality domains of quality of life. Unexpected, the PRT regimen did not increase muscle CSA to a statistically significant degree as hypothesized according to the method used.

Accrual of intramuscular lipid (*i.e.*, muscle attenuation) has been associated with aging, frailty, mobility impairment, muscle weakness, insulin resistance, visceral obesity, and type 2 diabetes (15,26). Exercise-induced improvements in muscle attenuation in older and clinical cohorts result in enhanced insulin sensitivity (27,28). Therefore, our finding that intradialytic PRT can enhance muscle attenuation may be of clinical importance given that diabetes has become the leading cause of ESRD (29).

The reduction of intramuscular lipid is potentially initiated *via* PRT-induced muscle damage, which, through the activation of the immune system, satellite cells (30), and growth factors, degrades necrotic muscle fibers and promotes the synthesis of muscle fibers of higher integrity (31). In this process, the intramuscular lipid is potentially used as a substrate and oxidized, perhaps in place of muscle glycogen (27,32,33). Several studies have noted an improvement of muscle attenuation with exercise relative to sedentary controls in other cohorts (27,28,34), and our findings demonstrate for the first time that this beneficial adaptation occurs in ESRD as well.

Our training regimen did not significantly increase muscle CSA. However, the 95% CI varied from a 1.9-cm^2 reduction relative to control to a 6.1-cm^2 increase for PRT. The upper bound, favoring PRT, represents a clinically important difference with an ES of 0.30 (Table 2). As such, this finding should be viewed as indeterminate, rather than negative, because our study was powered for a larger ES (0.77) estimated from previous literature. It is also possible that a significant change in muscle CSA may have been detected by investigating muscle biopsies, which are highly sensitive to change. For example, in our previous randomized, controlled trial that compared 12 wk of PRT with sham exercise in 26 patients with chronic renal insufficiency (35), significant type I ($P = 0.03$) and type II ($P = 0.04$) muscle fiber hypertrophy (24 and 22%, respectively), detected *via* muscle biopsies, was demonstrated despite a nonsignificant change in mid-thigh muscle CSA as evaluated *via* CT ($P = 0.11$).

Johansen *et al.* (13) reported that 12 wk of moderate-intensity, lower body intradialytic PRT combined with either placebo or anabolic steroid injections was sufficient to induce statistically significant muscle hypertrophy of the quadriceps muscle group, as evaluated *via* magnetic resonance imaging. However, the investigators evaluated changes within the quadriceps muscle group only, which would have been specifically targeted by the knee extension exercises used (13). By contrast, we measured combined muscle groups of the mid-thigh, despite that the hip extensors, hamstrings, and adductors were not adequately targeted by the exercises that could be performed in a dialysis chair. Therefore, we may have underreported adaptations specific to the quadriceps muscle.

Additional health-related benefits that were experienced by our PRT group occurred despite no significant change between groups in dietary protein and total energy intake or recreational and daily physical activity (Table 3), suggesting that these adaptations occurred secondary to PRT, rather than other lifestyle changes. The changes in body composition that were experienced by our PRT group all were favorable, including increased weight, BMI, and mid-arm and mid-thigh circumference, without an increase in central adiposity or mid-thigh, subcutaneous, or intramuscular lipid (Table 2). Such changes have been associated with survival benefit in this cohort. For example, higher BMI is associated with lower all-cause mortality in patients with ESRD (36,37), particularly when these patients have normal to high muscle mass (36). Johansen *et al.* (13) reported an increase in whole-body fat mass as a result of intradialytic PRT; however, they did not report on dietary intake in this trial, and this outcome requires confirmation, because it is an unexpected outcome of anabolic interventions such as PRT.

Our finding that PRT lowered CRP levels relative to those in control subjects by a clinically significant amount with a large ES of −0.85 is important given the proinflammatory state that is characteristic of patients with ESRD and the morbidity and the excess mortality that are associated with elevation of CRP in this (38) and other cohorts. The mechanism for the reduction in CRP with resistance training is not established. However, PRT, without diet or weight loss, has been shown to reduce visceral fat in other studies, and a subsequent reduction in inflammatory adipokines (including IL-6 and TNF-α) or increase in adiponectin related to visceral fat changes may, in turn, reduce hepatic CRP production (39). Future studies with direct measurements of visceral fat and assessments of other inflammatory cytokines are needed to understand this clinically relevant adaptation more fully.

The improvements of quality-of-life domains, including Physical Function and Vitality, suggest the potential importance of intradialytic PRT as a therapeutic intervention for enhancing physical and psychologic health status in this cohort. Similarly, Painter *et al.* (40) showed that 16 wk of home-based exercise combined with intradialytic cycling improved these same domains of quality of life. Johansen *et al.* (13) also observed an improvement of Physical Function in their trial of intradialytic PRT.

Limitations of our study include the lack of a sham exercise control activity because of the single geographic site used, and the unblinded assessment of secondary outcomes of physical performance measures (6-min walk and strength) measures

and non-nutritional questionnaire data (quality of life and Physical Activity Scale for the Elderly).

Conclusion

Our 12-wk PRT regimen, delivered during routine hemodialysis treatment sessions, resulted in statistically and clinically significant health-related adaptations, including improved muscle quality, strength, body composition, proinflammatory state, and quality of life in patients with ESRD. Compliance was high when delivered in this fully supervised setting; therefore, intradialytic PRT may provide a simple, practical method by which the health status of this cohort can be improved. We believe that further studies to investigate muscle metabolism, long-term clinical outcomes, and survival benefits related to the anabolic adaptations are now warranted.

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Disclosures

None.

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