Randomized Controlled Trial of Intradialytic Resistance Training to Target Muscle Wasting in ESRD: The Progressive Exercise for Anabolism in Kidney Disease (PEAK) Study

Bobby Cheema, PhD,[1,2] Haifa Abas, BApplSc,[1] Benjamin Smith, BApplSc,[1] Anthony O'Sullivan, MBBS,[3] Maria Chan, MNutrDiet,[4] Aditi Patwardhan, MNutrDiet,[5] John Kelly, MBBS,[6] Adrian Gillin, MBBS,[7] Glen Pang, MNutrDiet,[4] Brad Lloyd, BApplSc,[1] and Maria Fiatarone Singh, MD[1,8,9]

Background: To determine whether prolonged (24 weeks) intradialytic progressive resistance training (PRT) could counteract muscle wasting more effectively than short-duration training (12 weeks) in patients with end-stage renal disease.

Study Design: Randomized controlled trial.

Setting & Participants: 49 patients (age, 62.6 ± 14.2 years; 0.3 to 16.7 years on hemodialysis therapy) were randomly assigned to PRT plus usual care for 24 weeks (24WK group) or a crossover control group that received usual care for the first 12 weeks, then PRT plus usual care for the latter 12 weeks (12WK group).

Intervention: Two sets of 10 free-weight PRT exercises were performed at a high intensity during routine thrice-weekly hemodialysis treatment under direct supervision.

Outcomes & Measurements: Primary outcomes include thigh muscle cross-sectional area by means of computed tomography and intramuscular lipid content estimated through attenuation. Secondary outcomes include muscular strength, exercise capacity, and C-reactive protein level.

Results: The 24WK group increased muscle cross-sectional area (+1.82 ± 3.25 cm^2) compared with losses in the 12WK group (−1.37 ± 6.87 cm^2; relative effect size, 0.59; 95% confidence interval [CI], −0.27 to 6.65; $P = 0.04$). However, this outcome did not achieve the level of statistical significance required ($P = 0.025$) after Bonferroni correction for multiple primary outcomes. There was no significant change in intramuscular lipid content between groups (+0.19 ± 1.32 versus +0.16 ± 1.69 Hounsfield units in the 24WK and 12WK groups, respectively; $P = 0.31$). Log C-reactive protein level tended to decrease in the 24WK group compared with the 12WK group (relative effect size, −0.63; 95% CI, −0.27 [−0.54 to 0.00]; $P = 0.05$). The 24WK group improved muscular strength measures and exercise capacity throughout the trial.

Limitations: Single geographic site used; no control group without exercise exposure; unblinded assessment of some secondary outcome measures.

Conclusions: Prolonged intradialytic PRT did not significantly improve muscle cross-sectional area or intramuscular lipid content compared with a shorter duration of exercise. Future trials are required to more thoroughly investigate the clinical importance and magnitude of myogenic adaptations to PRT in this cohort.
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INDEX WORDS: Exercise; quality of life; dialysis; survival; mortality; standard of care.

According to the US Renal Data System, more than 335,000 patients in the United States currently receive maintenance hemodialysis treatment for the management of end-stage renal disease (ESRD).[1] This patient population has more than doubled since 1988.[1] With additional growth expected in the years ahead, influenced largely by the type 2 diabetes epidemic,[2] greater efforts must

From the [1]School of Exercise and Sport Science, University of Sydney, Sydney, Australia; [2]Institute of Food, Nutrition, and Human Health, Massey University, Wellington, New Zealand; [3]Department of Medicine, University of New South Wales; [4]Department of Nutrition and Dietetics, St George Hospital; [5]Department of Nutrition and Dietetics, Royal Prince Alfred Hospital; [6]Department of Renal Medicine, St George Hospital; [7]Department of Renal Medicine, Royal Prince Alfred Hospital; [8]Faculty of Medicine, University of Sydney, Sydney, Australia; and [9]Hebrew SeniorLife and Jean Mayer USDA Human Nutrition Center on Aging, Tufts University, Boston, MA.

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Address correspondence to Bobby Cheema, PhD, Institute of Food, Nutrition and Human Health, Te Kura Hangarua o Kai-oranga-a-tangata, Massey University, Wellington Campus, Private Bag 756, Wellington, New Zealand. E-mail: b.cheema@massey.ac.nz

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be directed toward improving the excess morbidity and mortality of this vulnerable patient population.

Skeletal muscle wasting is common and insidious in patients with ESRD. Catabolic factors that accelerate muscle wasting in this cohort compared with healthy adults are myriad and may include systemic inflammation, acidosis, protein-energy malnutrition, comorbid illnesses, corticosteroid use, hemodialysis treatment,[3] and long-term inactivity exacerbated by thrice-weekly dialysis treatment. Metabolic consequences include insulin resistance,[4] immune system dysfunction,[5] and decreased peripheral oxygen extraction.[6] Recent investigations documented a powerful association between muscle wasting and mortality in patients with ESRD.[7]

High-intensity progressive resistance training (PRT) has become well established as a safe and effective exercise modality for ameliorating sarcopenia and related health deficits in frail elders and individuals with diagnoses of various chronic illnesses.[8] The prevalence of muscle wasting in patients with ESRD suggests that PRT is indicated and may be of significant benefit in this patient population as well.[9]

The Progressive Exercise for Anabolism in Kidney Disease (PEAK) trial was conducted to evaluate the efficacy of isolated high-intensity PRT in patients with ESRD by prescribing a novel PRT intervention[10] during routine hemodialysis treatment sessions. We recently reported results of the first phase of this randomized controlled trial in which 12 weeks of intradialytic PRT improved intramuscular lipid content, strength, C-reactive protein (CRP) level, and indices of body composition and quality of life versus 12 weeks of usual care.[11] We anticipated, and the results of this first phase of the trial showed,[11] that the duration of PRT (12 weeks), during which time strength adaptations in previously untrained individuals are driven primarily by restructuring of the neuromuscular system,[12] may have been too short to observe measurable effects on muscle cross-sectional area (CSA) in this cohort, evaluated by using computed tomography.[11]

Our trial therefore intentionally was designed in 2 distinct phases to allow comparison of 12 versus 24 weeks of PRT for the investigation of our primary outcomes, muscular hypertrophy and intramuscular lipid content. We hypothesized that patients randomly assigned to 24 weeks of intradialytic PRT would experience significantly greater muscle hypertrophy and decreased intramuscular lipid content compared with patients randomly assigned to 12 weeks of intradialytic PRT.

METHODS

Patients

The PEAK trial was conducted at the outpatient hemodialysis unit of St George Public Hospital, Sydney, Australia. The South Eastern Sydney Area Health Service and the University of Sydney Human Research Ethics Committees approved all procedures. Written informed consent was obtained from all patients (Australian Clinical Trials Registry no. 12605000101684). All patients attending the dialysis unit were evaluated for eligibility between October 2002 and July 2005 by using medical record 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 years or older, (2) on hemodialysis therapy for longer than 3 months, (3) without medical contraindications to PRT or collection of outcome measures, (4) independent ambulation with or without an assistive device for 50 m or greater, (5) adequately dialyzed (most recent Kt/V $\geq$ 1.2) and stable during dialysis, (6) cognition and English language sufficient to understand research procedures and provide informed consent, and (7) willingness to be randomly assigned and undergo study protocols.

Study Design and Randomization

The PEAK study was conducted in 2 phases. Phase 1 was a 12-week randomized controlled trial of PRT versus usual-care controls. Phase 2 began at week 12, at which time the controls crossed over and began the active intervention (PRT) and the experimental group continued PRT for an additional 12 weeks. This study design provided preplanned comparisons of both 12 weeks of PRT versus usual care as previously reported[11] and comparisons of 12 versus 24 weeks of PRT as reported here. The crossover allowed for a dose-response evaluation of PRT in this cohort. After baseline testing, all patients were assigned by means of a computer-generated randomization list stratified by sex to an experimental group that received PRT plus usual care for 24 weeks (24WK group) or a crossover control group (12WK group) that received usual care for only the first 12 weeks of the trial and then crossed over to PRT plus usual care for the second 12 weeks of the trial. An investigator not otherwise involved with patients prepared the randomization list. Assignments were handed to patients in sealed envelopes.

Intervention

All PRT sessions were directly supervised by an exercise physiologist during routine hemodialysis treatment 3 times weekly with the patient in a seated or supine position in a standard dialysis chair (LA-Z-BOY Pty Ltd, Moorebank, NSW, Australia).[10] Two sets of 8 repetitions of 10 PRT exercises were performed at a rating of perceived exertion of 15 to 17 ("hard"

to "very hard") on the Borg Scale.[13] The limb containing the arteriovenous fistula or Gortex graft (W.L. Gore & Associates, Flagstaff, AZ) was exercised immediately before the dialysis session. Upper-body exercises performed using free-weight dumbbells (Australian Barbell Company, Mordialloc, Australia) included the shoulder press, side shoulder raise, triceps extension, biceps curl, and external shoulder rotation. Lower-body exercises were performed using weighted ankle cuffs (Australian Barbell Company) and included seated knee extension, supine hip flexion, supine hip abduction, and supine straight-legged raise. Seated hamstring curls also were performed using Thera-Band tubing (Akron, OH) attached to a fixed position on the weight trolley. Abdominal musculature was targeted without weights by prescribing bilateral leg raises in a supine position or bilateral leg lifts in a seated position, depending on subject preference and level of ability. Rest periods of 1 to 2 minutes were taken between sets and exercises.

Outcome Measures

All outcome measures were collected at baseline and 12 and 24 weeks for all available patients regardless of compliance with PRT.

Primary Outcomes

Computed tomography of the nondominant midthigh to determine muscle CSA and attenuation (ie, intramuscular lipid infiltration[14]) were collected at baseline and 12 and 24 weeks at the Royal Prince Alfred Hospital, Camperdown, Australia, by using a General Electric High Speed CTI Scanner (model CEE0459, Milwaukee, WI). For the baseline scan, thigh length was measured by using an anthropometric tape from the inguinal crease to the proximal pole of the patella, and the midpoint was marked with a black marker and a metal ball bearing. A scout film was obtained of the thigh region to include the entire knee joint with the ball bearing visualized. The ball bearing then was removed, and a 1-mm slice was obtained at the marker by using the following settings: 100 kV, 170 mA, and 1-second scan time. Field of view was adjusted to accommodate the size of the thigh. The resulting image was saved to a computer in raw Digital Imaging and Communications in Medicine (DICOM) format. Scans were analyzed for muscle CSA and attenuation using a modification of NIH Image, version 1.62, developed by G. Solares and M.F.S., as previously reported.[15] Repeated scans involved localization of the cross-sectional slice site after an initial scout using the distances, angles, and field of view determined in the initial scan. Coefficient of variability (CV) of triplicate analysis of CSA and attenuation measures in this cohort was 0.005%.

Secondary Outcomes

Functional Measures. Muscular strength (kilograms) of the knee extensors, hip abductors, and triceps was measured bilaterally in triplicate, with the best score recorded, by using an isometric digital dynamometer fixed to a stand (Chatillon CSD 200 Dynamometer; Ametek Inc, Paoli, PA; CV, 9.4%). Total strength summary measures also were created by adding all strength measures obtained for the knee extensors, hip abductors, and triceps. Specific tension (kilograms per square centimeter) was calculated by dividing isometric strength (kilograms) of the nondominant thigh by midthigh CSA (square centimeters), which was evaluated by means of computed tomography. The 6-minute walk[16] was used as an index of overall exercise capacity. The CV of this test was reported to be 5% to 10% in older or clinical cohorts.[17]

Nutritional Measures. A blinded dietitian evaluated dry body weight and waist, midarm, and midcalf circumferences by using standard protocol postdialysis treatment. Nutritional status was assessed by using the Mini-Nutritional Assessment.[18]

Systemic Inflammation. Samples for CRP were drawn predialysis before a midweek dialysis session at least 48 hours after the previous exercise bout to minimize any acute training-induced effects. Samples possibly affected by acute trauma or illness were discarded and drawn again at the next appropriate dialysis session. CRP assays were performed using the Dade Behring Dimension RXL (Deerfield, IL). This method is based on a particle-enhanced turbidimetric immunoassay technique[19] using the Dade Behring Dimension RCRP calibrator for standardization. CV for this test was 2.3%.

Clinical Covariates

Full blood count with differential, Kt/V, and protein catabolic rate were evaluated by using standard techniques (CV, 1.5% to 4.8%). Samples possibly affected by acute trauma or illness were discarded and drawn again.

Compliance and Adverse Events

Compliance with training was defined as number of training sessions attempted divided by number offered × 100%. Change in health status, including acute illnesses, falls, changes in medication use, dialysis-related symptoms (ie, headaches, hypotension, and cramping), and visits to health care professionals were documented by means of weekly interview and clinical note review. PRT-related adverse events were defined as any injury or exacerbation of underlying disease potentially attributable to the PRT regimen.

Statistical Analyses

Primary analyses compared differences in primary and secondary outcomes between the 12WK and 24WK groups by using per-protocol analysis to provide information about the efficacy of the study, with participants lost to follow-up excluded from analysis. The rationale for per-protocol analysis without imputation of missing data is the novelty of this study, and the need to understand whether this intervention has potential to modify primary outcomes before the effectiveness of dissemination is assessed. Secondary sensitivity analyses of all outcomes were conducted by using the last-observation-carried-forward method for all missing data at 24 weeks.

Statistical analyses were performed using StatView statistical software package (version 5.0; SAS Institute, Cary, NC). Data distributions were inspected visually and statistically for normality (skewness between −1 and +1). Normally distributed data were described using mean ± SD, and non–normally distributed data, using median and range. Non–normally distributed continuous variables were log-

transformed before use with parametric statistics. Adjusted mean differences and 95% confidence intervals (CIs) were reported between groups at baseline. Analysis of covariance models of absolute and relative change scores (final − baseline/baseline × 100) were constructed to compare 12 versus 24 weeks of PRT, using change score as the dependent variable and baseline score as a covariate. Repeated-measures analyses of variance (ANOVAs) including baseline and 12- and 24-week results in a single model were intentionally not constructed for between-group comparisons because the 12WK group crossed over as planned from usual care to active treatment (PRT) at 12 weeks. However, repeated-measures ANOVA models were constructed for within-group comparisons of rate of change in outcomes during the trial in the 24WK group because they had continuous exercise exposure throughout the trial. Hedge's bias corrected relative effect size and 95% CI were calculated for all outcomes as[20]:

$$\frac{\text{Change in treatment (24WK) group} - \text{Change in control (12WK) group}}{\text{Pooled SD}}$$

Effect sizes were rated according to the conventions of Cohen as small (0.20), moderate (0.50), or large (0.80). Relationships between continuous variables of interest were analyzed by using simple and forward stepwise multiple linear regression models. P less than 0.05 and 95% CI exclusive of zero were accepted as statistically significant. However, as an additional conservative estimate of significance, the Bonferroni correction factor also was applied to the 2 primary outcomes (muscle area and intramuscular lipid content), resulting in an accepted level of significance of $0.05/2 = 0.025$ for these outcomes.

Sample Size Determination

Sample size estimates were calculated by using hypothesized differences between the PRT and usual-care control group in thigh muscle CSA.[11] Based on previous studies,[21] the control group was estimated to have no change, whereas the PRT group was hypothesized to have a +3.5% ± 4.5% change in CSA after 12 weeks. Setting α at 0.05 and β at 0.20, a total of 44 patients were estimated to be required; this was inflated to 49 in anticipation of dropout and/or less than complete adherence to the protocol.

RESULTS

Recruitment

Recruitment flow is shown in Fig 1. Forty-nine medically eligible patients consented, corresponding to 35% of the entire hemodialysis unit (n = 142). Of 65 ineligible patients, only 26 were excluded for medical contraindications to PRT, including unstable cardiac condition (eg, shortness of breath and uncontrolled angina; n = 12), severe aortic stenosis (n = 3), unstable hemodialysis/compliance issues (n = 2), unstable cerebral aneurysms (n = 2), psychological disorder (n = 2), active malignancy (n = 1), multiple hernias (n = 1), emphysema (n = 1), diabetic retinopathy (n = 1), and hemiparesis (n = 1). Of 49 patients randomly assigned, 10 were unavailable for follow-up testing (Fig 1). ANOVA showed that patients who were unavailable for follow-up testing were not different from those who completed all testing procedures with respect to age, hemodialysis vintage, burden of chronic diseases, and baseline measures of 6-minute walk, body weight, intramuscular lipid content, and muscle CSA (all $P > 0.05$).

Baseline Characteristics

Patient characteristics at baseline are listed in Table 1. Patients ranged in age from 30.8 to 80.5 years and had a high burden of comorbid disease, particularly hypertension, depression, and type 2 diabetes. Nutritional risk (body mass index < 22 kg/m^2 and/or Mini-Nutritional Assessment score < 24) was present in 28.6% (14 of 49 patients); whereas 34.7% (17 of 49 patients) were overweight (body mass index > 25 kg/m^2) and 26.5% (13 of 49 patients) were obese (body mass index > 30 kg/m^2). Patients were similar at baseline, with a trend for a greater proportion of patients with diabetes, myocardial infarction, and stroke in the 12WK group and longer hemodialysis vintage in the 24WK group, although differences were not statistically significant (Table 1).

Comparisons at 12 Weeks

As noted in our interim report,[11] patients receiving 12 weeks of intradialytic PRT plus usual care significantly improved intramuscular lipid content, strength, CRP level, and indices of body composition and quality of life versus the nonexercising wait-list control group.

Comparisons at 24 Weeks

The 24WK group increased thigh muscle CSA (+1.97%) compared with losses in the 12WK group (−0.74%), with a moderate effect size of 0.59 ($P = 0.04$); however, this finding did not achieve the level of statistical significance required after adjustment for multiple outcomes (Table 2). There was no significant difference in intramuscular lipid content (muscle attenuation) change between groups (Table 2; $P = 0.31$). CRP level decreased in the 24WK group compared with an increase in the 12WK group, again

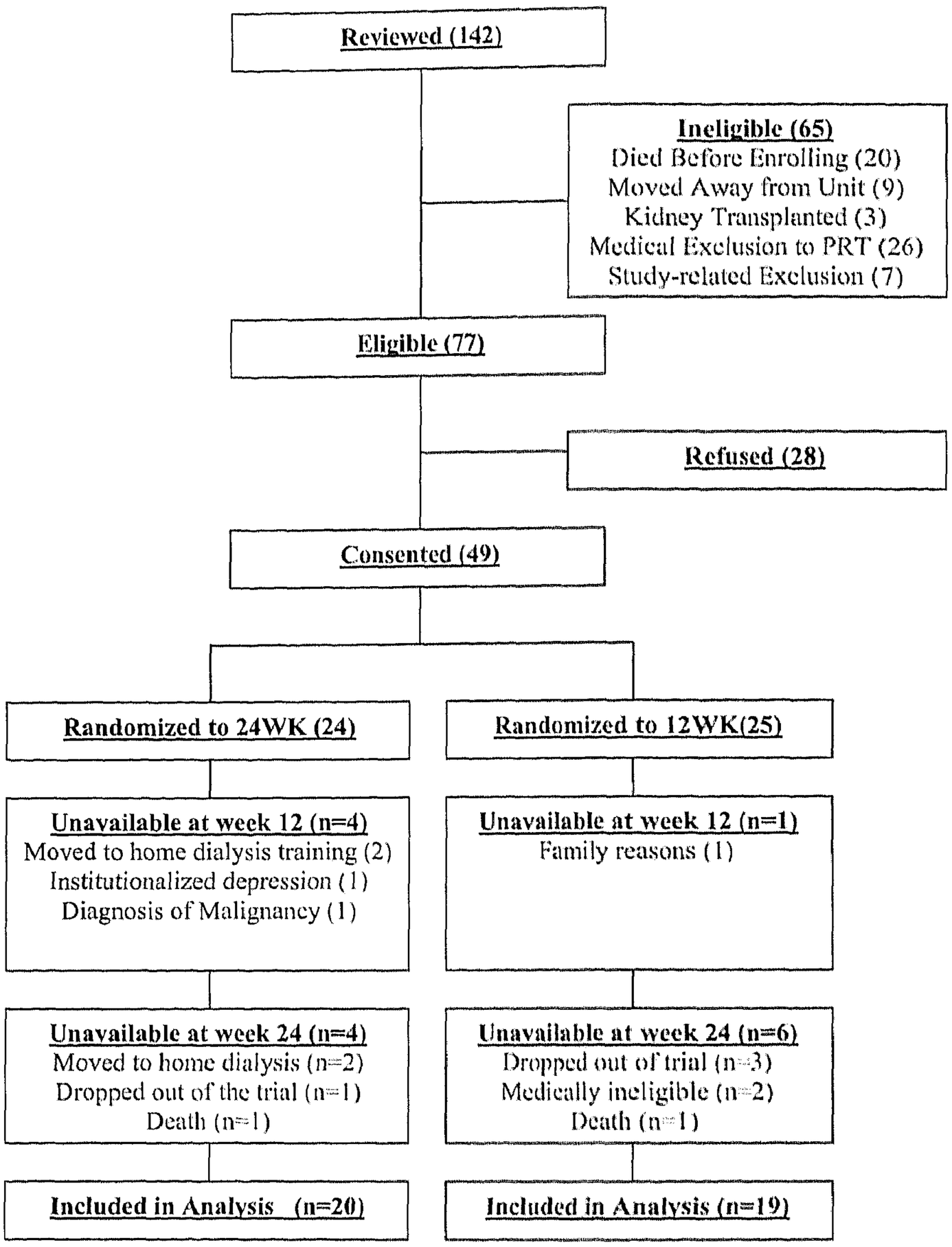

Figure 1. Flow of participants through the Progressive Exercise for Anabolism in Kidney Disease (PEAK) trial.

with a moderate effect size (−0.63); however, this finding did not achieve statistical significance because the CI included zero (Table 2). No other differences between groups were observed (Table 2). Change in muscle CSA and change in CRP level were significantly and inversely related ($P = 0.004$). Clinical covariate data at baseline and after the 24-week intervention are listed in Table 3.

Time Course of Adaptations in the 24WK Group

Repeated-measures ANOVAs were completed within the 24WK group only to assess the time course and relative magnitude of adaptation across 6 months of PRT. The 24WK group significantly increased all measures of strength, specific tension, and exercise capacity (6-minute walk distance) over time (Table 4). All outcomes except for specific tension ($P = 0.60$) and knee extension strength ($P = 0.62$) continued to improve beyond week 12 (Table 4). Changes in total strength (average, +32.4 kg [+33.1%]; effect size, 1.01; 95% CI, 22.1 to 42.7) during the 24-week trial were robust in magnitude, both clinically and statistically. Changes in 6-minute walk distance also were robust (average, +44.0 m [+7.5%]; 95% CI, 39.5 to 48.5); similar to those typically seen after aerobic exercise in cardiac rehabilitation patients (~50-m improvements).

Table 1. Baseline Characteristics of the Total Cohort and Groups

Characteristic	Total Cohort (n = 49)	24WK Group (n = 24)	12WK Group (n = 25)	*P*
Age (y)	62.6 ± 14.2	60.0 ± 15.3	65.0 ± 12.9	0.23
Men:women	34:15	17:7	17:8	0.83
Hemodialysis vintage (y)	2.2 (0.3-16.7)	3.3 (0.3-16.7)	1.6 (0.6-10.3)	0.08
Body weight (kg)	75.7 ± 18.3	74.9 ± 19.5	76.5 ± 17.4	0.77
Height (cm)	165.6 ± 10.2	166.2 ± 9.1	165.1 ± 11.3	0.69
Body mass index (kg/m^2)	27.5 ± 5.8	27.0 ± 6.0	28.0 ± 5.7	0.54
No. of medications/d	8.6 ± 2.8	8.8 ± 3.2	8.4 ± 5.7	0.63
Tobacco use history	28	11	17	0.12
Chronic diseases*	5.1 ± 1.8	4.9 ± 1.6	5.2 ± 2.0	0.54
Hypertension	49	24	25	1.00
Depression†	17	8	9	0.84
Type 2 diabetes	16	5	11	0.08
Myocardial infarction	11	3	8	0.10
Stroke	6	1	5	0.09
Cause of ESRD				
Glomerulonephritis	12	6	6	
Diabetes	9	3	6	
Hypertension	6	2	4	
Ischemia	4	3	1	
Polycystic kidney disease	4	3	1	
Immunoglobulin A nephropathy	4	3	1	
Analgesic use	3	1	2	
Systemic lupus erythematosus	1	1	0	
Other	6	2	4	

Note: Data reported as mean ± SD for normally distributed variables, median (range) for non–normal distribution, or number of patients.

Abbreviation: ESRD, end-stage renal disease.

*Includes diagnosis of ESRD.

†Mild to severe depression diagnosed according to the Geriatric Depression Scale.[22]

One patient in the 24WK group was unavailable for testing at week 12 because of institutionalized depression. However, this patient returned to complete the trial.

Comparison of Intradialytic and Extradialytic Training Efficacy

This study provides for the first time a unique opportunity to compare intradialytic PRT versus PRT outside of dialysis treatment time because the fistula-containing arm was exercised immediately before the patient began dialysis, whereas the nonfistula arm was exercised during the dialysis session. Using data obtained from the total cohort, triceps strength gains (percentage of change) achieved during dialysis were not different from those achieved outside the session after 12 weeks of training (Fig 2; $P = 0.88$), showing the efficacy of our intradialytic training regimen.

Compliance and Adverse Events

Compliance with PRT was not statistically different ($P > 0.05$) between the 24WK and 12WK groups, exclusive (76.5% ± 22.2% and 79.1% ± 15.3%, respectively; $P = 0.67$) or inclusive (58.5% ± 38.0% and 70.4% ± 15.3%, respectively; $P = 0.20$) of the 10 patients unavailable for follow-up testing, suggesting the possibility of long-term adherence to such an exercise regimen in a supervised setting. There were no statistically significant differences between the 24WK and 12WK groups in common dialysis-related symptoms, including headaches, hypotension, fistula/cannulation difficulties, and cramping ($P > 0.05$; data not shown). One rotator cuff tear (supraspinatus) occurred in an elderly woman in the 24WK group during the initial 12 weeks of the trial; however, this patient completed the full trial.[23] There were no other adverse events.

Sensitivity Analyses

Secondary intention-to-treat sensitivity analyses were performed using the last-observation-carried-forward method for the 10 patients who were unavailable for follow-up testing at week

Table 2. Summary of Outcome Measures

	24WK Group			12WK Group			Adjusted Mean Difference* (95% confidence interval)	Effect Size*	*P**
	Baseline	12-Week Change	24-Week Change	Baseline	12-Week Change	24-Week Change			
Primary outcome measures									
Muscle cross-sectional area (cm^2)	103.11 ± 23.81	+1.35 ± 6.23	+1.82 ± 3.25	100.56 ± 20.32	−0.75 ± 7.59	−1.37 ± 6.87	3.19 (−0.27-6.65)	0.59	0.04
Muscle attenuation (Hounsfield unit)	85.56 ± 2.70	−0.10 ± 0.96	+0.19 ± 1.32	87.16 ± 2.3	+0.24 ± 0.63	+0.16 ± 1.69	0.03 (−0.95-1.01)	0.02	0.31
Secondary outcome measures									
Functional measures									
Knee extension strength (kg)	45.1 ± 19.5	+11.6 ± 10.7	+13.8 ± 16.1	48.0 ± 19.2	−2.3 ± 7.5	+9.7 ± 12.7	4.1 (−5.3-13.5)	0.28	0.36
Hip abduction strength (kg)	22.3 ± 8.8	+3.7 ± 4.3	+6.8 ± 3.8	21.8 ± 8.0	+0.4 ± 5.7	+4.1 ± 5.6	2.7 (−0.4-5.8)	0.56	0.09
Triceps strength (kg)	27.8 ± 11.6	+1.8 ± 7.3	+5.6 ± 7.7	25.2 ± 9.9	+0.3 ± 4.0	+3.3 ± 4.5	2.3 (−1.8-6.4)	0.36	0.17
Total strength (kg)	95.2 ± 35.3	+17.2 ± 15.0	+26.2 ± 21.3	95.0 ± 34.0	−1.6 ± 14.7	+17.1 ± 20.2	9.0 (−4.5-22.5)	0.42	0.19
Specific tension (kg/cm^2)	0.22 ± 0.08	+0.06 ± 0.05	+0.07 ± 0.08	0.23 ± 0.09	−0.01 ± 0.05	+0.04 ± 0.07	0.03 (−0.02-0.08)	0.39	0.34
6-Min walk (m)	496.0 ± 138.9	+19.6 ± 44.0	+36.3 ± 50.6	412.6 ± 138.9	+1.5 ± 23.7	+18.6 ± 44.4	17.7 (−13.3-48.7)	0.36	0.53
Nutritional measures									
Body weight (kg)	73.3 ± 15.4	+1.0 ± 1.6	+1.4 ± 2.7	79.2 ± 15.4	0.0 ± 1.5	−0.2 ± 2.3	1.6 (0.0-3.2)	0.62	0.06
Waist circumference (cm)	95.7 ± 19.3	+0.3 ± 2.9	+0.9 ± 3.9	102.6 ± 11.5	0.6 ± 1.7	0.0 ± 1.8	0.9 (−1.1-2.9)	0.29	0.67
Midarm circumference (cm)	29.9 ± 3.8	+0.4 ± 1.5	+0.6 ± 2.0	30.7 ± 3.9	−0.5 ± 0.9	0.0 ± 1.6	0.6 (−0.6-1.8)	0.32	0.36
Midcalf circumference (cm)	35.0 ± 3.8	+0.2 ± 1.3	+0.5 ± 1.0	36.0 ± 3.4	0.0 ± 0.7	+0.1 ± 0.9	0.4 (−0.2-1.0)	0.41	0.34
Mini-Nutritional Assessment[18] (0-30)	26.4 ± 1.5	+0.4 ± 1.3	+0.1 ± 2.9	26.2 ± 2.3	+0.2 ± 2.8	+0.7 ± 2.6	−0.6 (−2.4-1.2)	−0.21	0.44
Inflammatory marker									
Log C-reactive protein	0.71 ± 0.60	−0.09 ± 0.40	−0.13 ± 0.48	0.74 ± 0.54	+0.22 ± 0.39	+0.14 ± 0.34	−0.27 (−0.54-0.00)	−0.63	0.05

Note: Data presented as mean ± SD.

*Refers to 24-week comparisons only; values based upon the final model, including baseline assessment value as a covariate.

Table 3. Clinical Covariates

	24WK Group			12WK Group			Adjusted Mean Difference* (95% confidence interval)
	Baseline	12-Week Change	24-Week Change	Baseline	12-Week Change	24-Week Change	
Hemoglobin (g/L)	120 ± 9	+2 ± 17	+2 ± 13	122 ± 12	+4 ± 13	−2 ± 19	4 (−7 to 15)
Hematocrit (%)	0.353 ± 0.080	+0.021 ± 0.037	+0.021 ± 0.100	0.383 ± 0.034	+0.005 ± 0.037	−0.007 ± 0.059	0.029 (−0.030-0.080)
Prealbumin (g/L)	0.36 ± 0.09	−0.00 ± 0.08	+0.01 ± 0.08	0.32 ± 0.10	−0.01 ± 0.08	+0.01 ± 0.06	0.00 (−0.05-0.05)
Albumin (g/L)	35 ± 3	0 ± 3	+1 ± 3	34 ± 3	0 ± 2	0 ± 3	1 (−1-3)
Creatinine (μmol/L)	938 ± 190	−6 ± 99	−3 ± 89	842 ± 199	−29 ± 229	+33 ± 84	−36 (−92-20)
White blood cell count ($\times 10^9$)	6.85 ± 1.65	+0.01 ± 1.55	+0.04 ± 1.32	7.28 ± 2.15	−0.10 ± 1.30	−0.03 ± 1.47	0.07 (−0.84-0.98)
Lymphocytes ($\times 10^9$)	1.50 ± 0.54	0.0 ± 0.3	+0.2 ± 0.4	1.55 ± 0.61	+0.1 ± 0.4	+0.2 ± 0.4	0.00 (0.26-0.26)
Kt/V	1.55 ± 0.35	+0.13 ± 0.46	+0.27 ± 0.70	1.54 ± 0.30	+0.12 ± 0.49	+0.38 ± 1.20	−0.11 (−0.74-0.52)
Protein catabolic rate (g/kg/d)	1.08 ± 0.17	+0.01 ± 0.32	+0.08 ± 0.26	1.08 ± 0.20	−0.03 ± 0.18	+0.04 ± 0.23	0.04 (−0.12-0.20)

Note: Data expressed as mean ± SD. To convert hemoglobin in g/L to g/dL, divide by 10; albumin in g/L to g/dL, divide by 10; creatinine in μmol/L to mg/dL, divide by 88.4.
*Refers to 24-week comparisons only; values based upon the final model including baseline assessment value as a covariate.

24. The statistical significance of the primary and secondary outcomes did not change from the primary analyses with the exception that body weight significantly increased (+1.2 kg) in the 24WK group versus the 12WK group (−0.4 kg; $P = 0.02$).

DISCUSSION

The PEAK trial was conducted to evaluate the myogenic effects of a novel intradialytic PRT regimen[10] in patients with ESRD. We previously reported that 12 weeks of intradialytic PRT significantly improved intramuscular lipid content, strength, CRP level, and indices of body composition and quality of life compared with usual care.[11] We now report that dialysis patients randomly assigned to prolonged intradialytic PRT (24WK group) tend to increase muscle CSA, evaluated by means of computed tomography, compared with patients randomly assigned to a shorter duration of training (12WK; $P = 0.04$). However, although the effect size is moderate, this difference is not statistically significant when adjusted for multiple outcomes testing, suggesting the possibility of type II error. Prolonged training did not significantly improve intramuscular lipid content estimates relative to shorter duration training.

The powerful association between muscle wasting and mortality in patients with ESRD[7] provides support for continued investigation in this area. Even in relatively healthy older adults, leg lean mass decreased by approximately 1% per year.[24] Thus, the 1.97% relative improvement in muscle CSA that we observed in our 24WK group equates to a reversal of approximately 2 years of age-related muscle wasting. The relative improvement in muscle mass likely is even more pronounced in our cohort given that loss of muscle mass is accelerated in hemodialysis patients versus healthy sedentary counterparts.[25] However, we acknowledge that the difference in muscle CSA between 12 and 24 weeks of PRT did not reach statistical significance after adjustment for multiple comparisons, and our trial therefore requires confirmation in a larger cohort. Although it is likely that an untreated control group would have had significant losses of muscle area compared with the gains evaluated in the 24WK group, our study design precluded this comparison.

To date, 4 uncontrolled trials[26-29] evaluated muscle CSA adaptations in response to exercise

Table 4. Time Course of Functional Adaptations in the 24WK Group

Outcome Measure	Week 0	Week 12	Week 24	*P**	*P*† Week 0 *v* 12	*P*† Week 0 *v* 24	*P*† Week 12 *v* 24
Total strength (kg)	97.0 ± 26.3	116.8 ± 33.7	129.4 ± 35.6	<0.001	<0.001	<0.001	0.02
Total knee extension strength (kg)	47.2 ± 20.0	60.1 ± 23.9	61.8 ± 23.8	<0.001	<0.001	<0.001	0.62
Total hip abduction strength (kg)	23.7 ± 8.6	27.4 ± 8.2	30.7 ± 9.7	<0.001	0.001	<0.001	0.003
Total triceps strength (kg)	27.2 ± 10.2	29.8 ± 9.3	34.6 ± 9.4	0.002	0.17	<0.001	0.01
6-Minute walk (m)	503.6 ± 144.8	526.2 ± 159.6	547.6 ± 163.8	<0.001	0.03	<0.001	0.04
Specific tension (kg/cm^2)	0.23 ± 0.09	0.28 ± 0.11	0.29 ± 0.12	0.003	0.005	0.001	0.60

Note: Data expressed as mean ± SD.

**P* corresponds to change over time within the 24WK experimental group, calculated using repeated-measures analysis of variance.

†Fisher's least significant difference post hoc *t*-test.

training in patients with ESRD. One of these trials prescribed 6 months of cycle ergometer training on nondialysis days in continuous ambulatory peritoneal dialysis patients and during dialysis in hemodialysis patients and reported significant muscle hypertrophy in 9 patients undergoing muscle biopsy.[28] Another small uncontrolled trial[27] reported significant muscle fiber hypertrophy in 7 patients after participation in a 6-month exercise regimen involving aerobic exercise and low-intensity strengthening on nondialysis days. Conversely, 2 trials prescribing intradialytic cycling for 12 weeks did not show significant muscle hypertrophy evaluated by means of muscle biopsy[29] and dual-energy x-ray absorptiometry.[26] Thus, according to the findings of these 4 uncontrolled trials, a longer training duration (ie, 6 months) may be more favorable for eliciting muscle hypertrophy versus a shorter training duration (ie, 12 weeks). Unfortunately, the small sample size and lack of a control group in these trials limits the robustness of these data, particularly with regard to the development of clinical exercise guidelines for this cohort. Moreover, none of these studies implemented high-intensity PRT, now well recognized as the preferred exercise modality for inducing muscular adaptations.[8] To date, only 1 other randomized controlled trial prescribed PRT in patients with ESRD.[30] Johansen et al[30] reported a significant increase in muscle CSA, evaluated by means of magnetic resonance imaging, in patients performing 12 weeks of moderate-intensity lower-body intradialytic PRT combined with a nandrolone placebo injection.

We previously reported that systemic inflammation, indicated by increased CRP level, de-

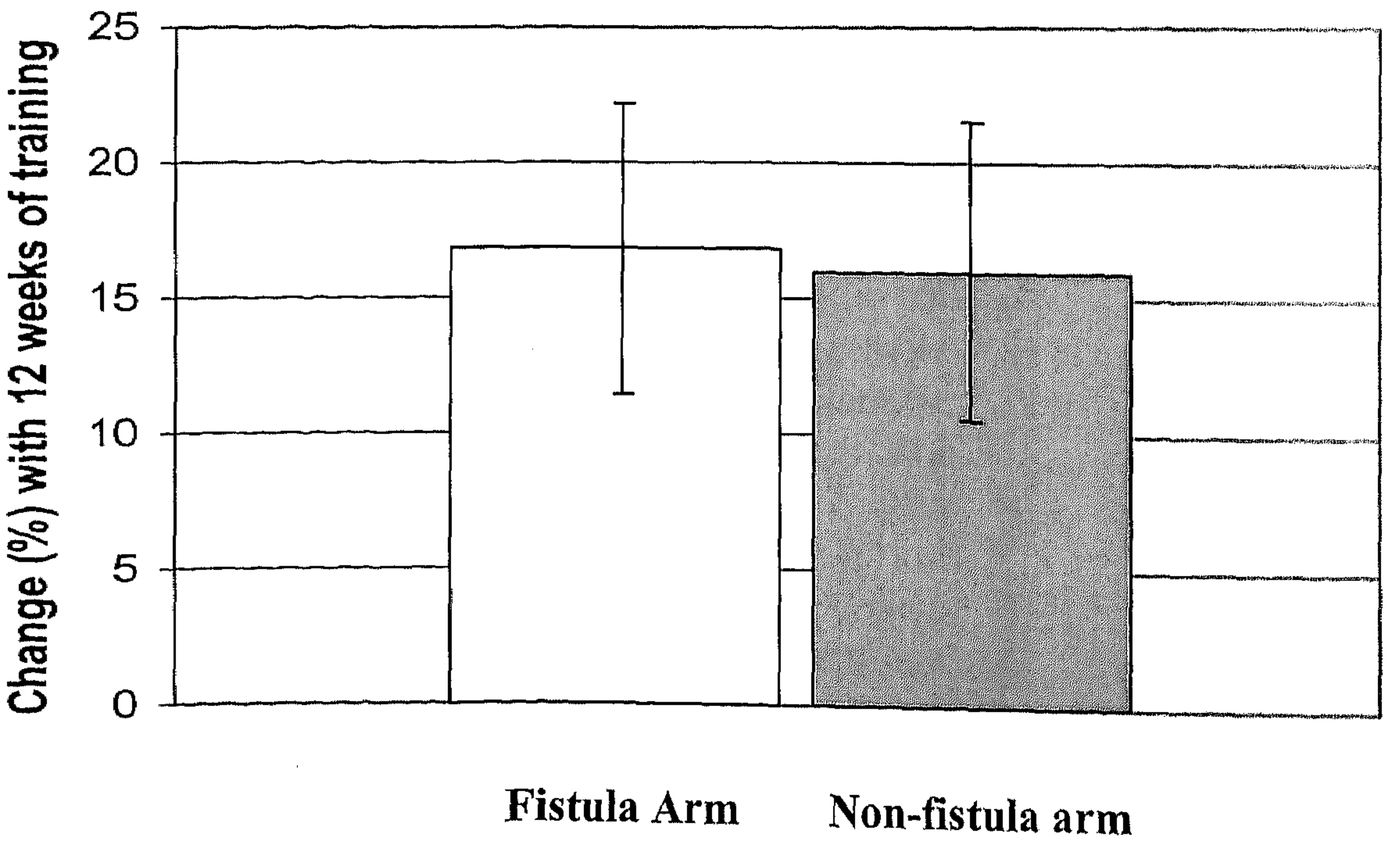

Figure 2. Change in triceps strength in the fistula versus nonfistula arm with 12 weeks of progressive resistance training ($P = 0.88$). Data presented as mean and SD.

creased after 12 weeks of PRT in patients with ESRD[11] and those with predialysis chronic kidney disease.[31] This effect also was noted in 1 small uncontrolled trial that prescribed 12 weeks of PRT on nondialysis days.[32] At present, the mechanism by which CRP level decreases with PRT is not known, and additional research is indicated. However, our present findings, that CRP level tends to decrease further with prolonged training, with a moderate effect size (−0.63), and that the decrease in CRP level is related significantly to gains in muscle size ($P = 0.004$), add support to the clinical utility of our intradialytic intervention, especially in light of robust evidence that increased CRP level is associated with increased cardiovascular morbidity and mortality in patients with ESRD.[33]

Intradialytic exercise is regarded as the most appropriate route by which to foster exercise adoption in patients with ESRD.[34-36] Intradialytic exercise also offers such metabolic benefits as improved amino acid uptake during nutritional supplementation to offset protein losses incurred by undergoing dialysis[37] and can improve dialysis adequacy.[38] Our present report indicates that similar relative enhancement of muscular strength in this cohort can be elicited by prescribing high-intensity PRT during dialysis compared with outside of dialysis (Fig 2). Thus, equipotent anabolic adaptations, enhanced solute removal and protein retention (investigated only with aerobic exercise to date),[37] and environmental/social support for behavioral change[36] favor intradialytic exercise for this cohort.

Although completely novel in this setting, anabolic exercise was well accepted in the dialysis unit, with a high rate of medical eligibility, consent, and adherence. Additional long-term trials are needed to identify barriers to intradialytic anabolic exercise participation and test strategies designed to overcome potentially addressable barriers related to the patient, exercise equipment, staff, dialysis unit design, and health care system itself. At present, intradialytic exercise is not commonly advocated or prescribed,[35] and exercise counseling practices among nephrologists remain extremely low,[39] although exercise has been investigated in this cohort for nearly 3 decades now.[34]

Limitations of our study include the single geographic site used, lack of a control group with no exercise exposure because of ethical considerations, and unblinded assessment of secondary outcomes of physical performance measures (6-minute walk and strength).

In summary, prolonged intradialytic PRT tends to improve muscle wasting and systemic inflammation in patients undergoing maintenance hemodialysis, although these results did not reach statistical significance after adjustment for multiple comparisons. We believe that large-scale randomized controlled trials of the integration and dissemination of PRT into routine hemodialysis care are now warranted to evaluate a broad spectrum of health and clinically relevant outcomes in this cohort.

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