Resistance Training To Counteract the Catabolism of a Low-Protein Diet in Patients with Chronic Renal Insufficiency

A Randomized, Controlled Trial

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Background: **Chronic renal insufficiency leads to muscle wasting, which may be exacerbated by low-protein diets prescribed to delay disease progression. Resistance training increases protein utilization and muscle mass.**

Objective: **To determine the efficacy of resistance training in improving protein utilization and muscle mass in patients with chronic renal insufficiency treated with a low-protein diet.**

Design: **Randomized, controlled trial.**

Setting: **Tufts University, Boston, Massachusetts.**

Patients: **26 older patients with moderate renal insufficiency (17 men, 9 women) who had achieved stabilization on a low-protein diet.**

Intervention: **During a run-in period of 2 to 8 weeks, patients were instructed and their adherence to the low-protein diet (0.6 g/kg of body weight per day) was evaluated. They were randomly assigned to a low-protein diet plus resistance training ($n = 14$) or a low-protein diet alone ($n = 12$) for 12 weeks.**

Measurements: **Total body potassium, mid-thigh muscle area, type I and II muscle-fiber cross-sectional area, and protein turnover.**

Results: **Mean protein intake was 0.64 ± 0.07 g/kg per day after stabilization. Total body potassium and type I and II muscle-fiber cross-sectional areas increased in patients who performed resistance training by a mean (±SD) of 4% ± 8%, 24% ± 31%, and 22% ± 29%, respectively, compared with those who did not. Leucine oxidation and serum prealbumin levels also improved significantly. Patients assigned to resistance training maintained body weight compared with those who were not. Improvement in muscle strength was significantly greater with resistance training (32% ± 14%) than without (−13% ± 20%) ($P < 0.001$).**

Conclusion: **By improving muscle mass, nutritional status, and function, resistance training seems to be effective against the catabolism of a low-protein diet and uremia in patients with renal failure.**

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See editorial comment on pp 999-1001.

Chronic renal insufficiency, regardless of cause, generally progresses to end-stage renal disease (1). Malnutrition and muscle wasting in chronic uremia often parallel the progression of renal failure (2). They also contribute to excess morbidity and mortality in patients with renal disease (3). Protein-restricted diets delay the progression of renal disease (4, 5) and alleviate uremic symptoms (6). Although nutritional status, as assessed by biochemical and anthropometric indicators, may be maintained during protein restriction (6, 7), studies have shown that deterioration of nutritional status is associated with low energy and protein intake in patients with chronic renal insufficiency (8).

Resistance training increases nitrogen retention (9), protein synthesis (10), and expression of insulin-like growth factor I in skeletal muscle (11); ameliorates losses of muscle mass and function; and enhances quality of life (12) in both healthy and unwell persons. The anabolic potential of resistance training counteracts the catabolism of HIV infection (13) and myopathy secondary to corticosteroid use in cardiac transplantation (14), the loss of lean tissue during energy restriction for obesity (15), and the interleukin-mediated myopathy of chronic heart failure (16). However, its utility as an adjunctive treatment offsetting the catabolism of a low-protein diet in uremic patients is not known (17). We conducted a randomized, controlled trial to determine whether resistance training would preserve lean body mass, nutritional status, and muscle function through alterations in protein turnover (synthesis and oxidation) in patients with moderate chronic renal insufficiency who were consuming a low-protein diet to slow the progression of renal failure.

METHODS

Study Design

Patients older than 50 years of age with chronic renal insufficiency were randomly assigned to a low-

protein diet plus resistance training or a low-protein diet plus sham exercises (referred to as low-protein diet alone). Patients were asked to follow a low-protein diet (0.6 g/kg of body weight per day) for 2 to 8 weeks (run-in period) before randomization. They continued the low-protein diet for an additional 12 weeks after randomization (intervention period) (**Figure 1**). The Human Investigation Review Committee at Tufts University, Boston, Massachusetts, and collaborating hospitals approved the study, and written informed consent was obtained from all patients.

Study Sample

Patients were recruited from the nephrology clinic at New England Medical Center, Saint Elizabeth's and Newton Wellesley Hospitals, and the Lahey Hitchcock Clinic, all in Boston, Massachusetts. Screening procedures took place at the Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging (HNRCA) at Tufts University. These procedures included sociodemographic and health history questionnaires; physical examination; electrocardiography; blood hematology, chemistry, and urine analyses; and a treadmill stress test. Eligibility criteria included serum creatinine concentrations between 133 and 442 μmol/L (1.5 and 5.0 mg/dL) and physician approval to follow a low-protein diet. A nephrologist confirmed renal diagnosis by reviewing renal biochemistry results and clinical records. Exclusion criteria were myocardial infarction (within the past 6 months), any unstable chronic condition, dementia, alcoholism, dialysis or previous renal transplantation, current resistance training, recent involuntary weight change ($\pm$2 kg), albumin level less than 30 g/L, proteinuria greater than 10 g/d, or abnormal stress test results at screening (18). Reasons for early withdrawal from the study included loss of more than 25% of initial body weight; need for dialysis or transplantation; development of any serious condition requiring hospitalization or precluding exercise; and signs of malnutrition, such as a decrease in serum transferrin levels to less than 1.5 g/L or a 15% decrease in hemoglobin or leukocyte count to below baseline levels.

Diet

Dietary intake of macronutrients and micronutrients and adherence to the low-protein diet were monitored twice per week during the run-in period and weekly during the intervention period by 3-day assisted dietary records (including week and weekend days) and regular meetings with the study dietitian, who was not blinded to group assignment. Dietary data were coded and analyzed by using Nutritionist-IV software (N-Squared Computing, San Bruno, California). Patients collected one 24-hour urine specimen for every 3-day dietary record. Protein intake was also estimated by urea nitrogen levels (19) calculated from urine collections and was used to assess adherence, which was defined as intake within 15% of the prescribed low-protein intake (0.6 g/kg per day).

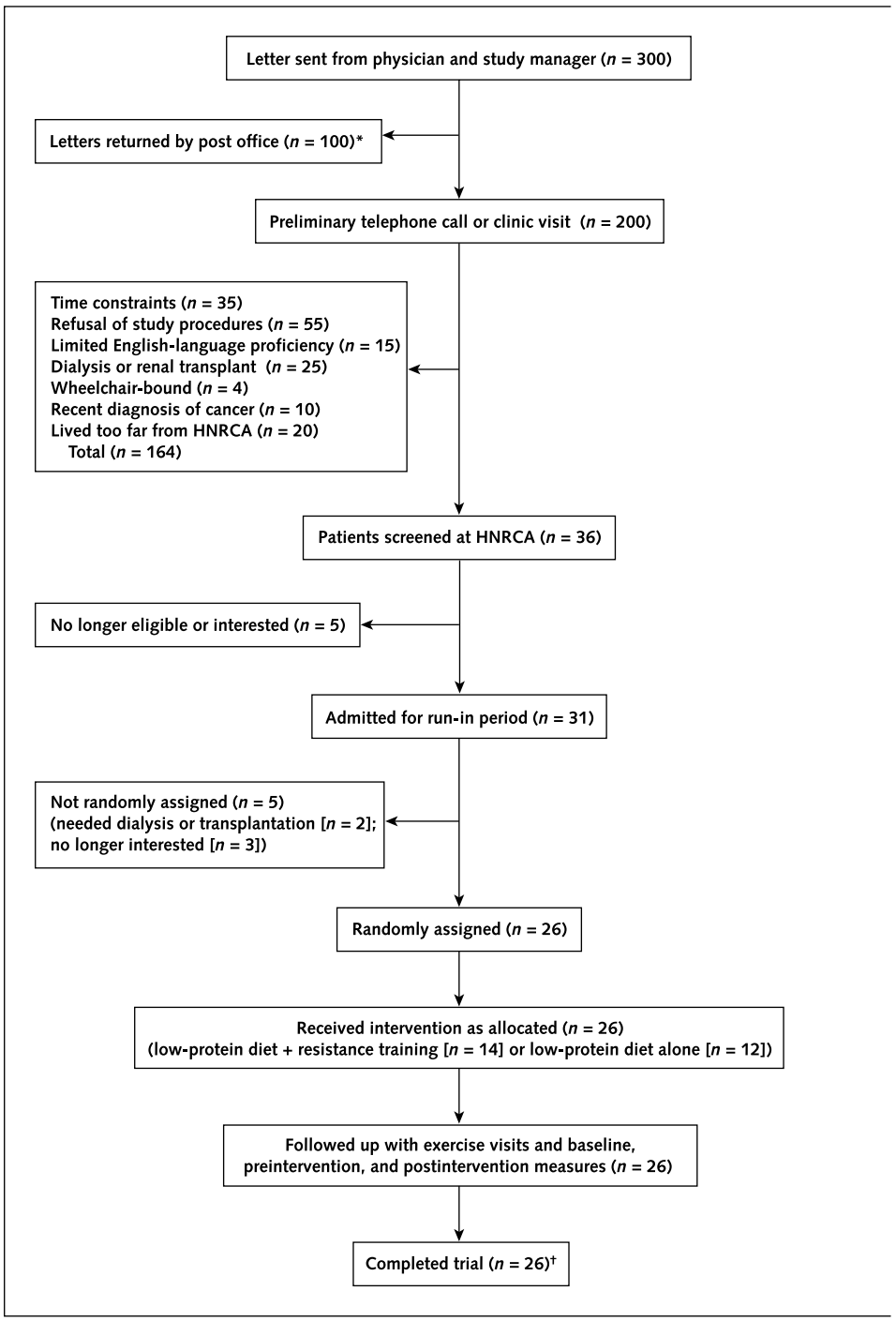
Patients were counseled to reduce their habitual protein intake by eating food sources with less protein or by reducing portion sizes of higher-protein foods. Behavior modification strategies, including tips, recipes, food models, and self-monitoring tools for protein counts, were provided. These strategies were adapted from the Modification of Diet in Renal Disease Study (20).

Exercise

Muscle strength was determined twice before randomization and once after 12 weeks by measuring one repetition maximum (1 RM) (21) using Keiser resistance training equipment (Keiser Sports Health Equipment, Inc., Fresno, California). One repetition maximum is the heaviest load that can be lifted once in good form through the full range of motion. Five machines (chest and leg press, latissimus pull-down, knee extension, and knee flexion) were used to include functionally large muscle groups. The better of the two baseline measurements of 1 RM was used in analyses and to set initial training loads for patients randomly assigned to resistance training. All exercise sessions were performed at the HNRCA three times per week under the supervision of an exercise physiologist. Vital signs and body weight were recorded before each session.

Patients who performed resistance training had monthly 1 RM testing on each machine. Workload during training was adjusted to reflect 80% of the most recent 1 RM. In addition, patients' workloads were progressively increased as appropriate according to the trainer's objective perception of patients' difficulty with workloads at each session. Patients performed three sets of eight repetitions on each machine per session, which

Figure 1. **Flow of patients through the study.**



* The post office returned letters because addresses were incorrect or persons had relocated. † No patients withdrew, experienced ineffective interventions, or were lost to follow-up. One patient in each group had incomplete postintervention measures because of health-related reasons. HNRCA = Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging.

lasted about 45 minutes (21). Patients assigned to the low-protein diet alone performed five to eight sham exercises (gentle movements while standing, sitting, and bending) for the upper and lower body. These were designed not to have a physiologic impact but to provide trainer contact time similar to that of the resistance training group.

Study Measures

All measures were taken before (week 0) and 12 weeks after randomization. Observers were blinded to study group assignment at all times, except during assessments of postintervention muscle strength.

Main Outcome Measures

Total body potassium is the best single measure of body cell mass closely linked to functional status (22), prognosis, and survival (23). Body cell mass (muscle and viscera) comprises the metabolically active tissues where protein is targeted (24). Potassium-40 represents approximately 0.0118% of total body potassium. Loss of total body potassium occurs in patients following low-protein diets (25) and in patients with renal disease (26), as well as in patients with many other wasting syndromes. Total body potassium was determined in the body composition laboratory at HNRCA, with a coefficient of variation of 5% (24).

Regional body composition of the area involving the mid-thigh muscle was determined by computerized tomography of the nondominant thigh. A Siemens DR3 CT Scanner (Somatom-Siemens, Erlangen, Germany) was used to obtain an 8-mm scan at the midpoint between the inguinal crease and the proximal pole of the patella. Images were digitized and analyzed to the nearest 0.01 cm^2, as described elsewhere (coefficient of variation, 0.5% to 1.5%) (21).

Type I and type II muscle-fiber cross-sectional areas were determined from vastus lateralis muscle biopsies of the nondominant thigh, performed with a 5-mm Bergstrom needle (27). Sections were stained with adenosine triphosphatase (pH, 4.3) to visualize type I and type II fibers. A slide preparation was made for each biopsy specimen, and 50 to 150 fibers per patient were analyzed by light microscopy (coefficient of variation, 3%) (11, 27).

Anthropometry

Body weights were measured to the nearest 0.1 kg on a Toledo Weight-Plate (Bay State Scale & Systems, Inc., Burlington, Massachusetts). Height was measured once to the nearest 0.25 cm, without shoes, by using a wall-mounted stadiometer. Body mass index was determined from body weight and height as kg/m^2.

Biochemical Measures

All measurements were collected in the fasting state in a blinded fashion at the nutrition evaluation laboratory at HNRCA (coefficient of variation, 5% to 10%). Urea nitrogen and creatinine concentrations in serum and urine and levels of plasma insulin-like growth factor I were determined, as described elsewhere (25, 27). In addition, blood cell count; hematocrit; and levels of serum albumin, transferrin, and prealbumin were measured monthly to evaluate nutritional status.

Glomerular Filtration Rate

Glomerular filtration rate was measured as the renal clearance of ^{125}I-iothalamate (Glofil, Cypros Pharmaceutical Corp., Carlsbad, California), with a coefficient of variation of 6.3% (28).

Resting Energy Expenditure

Oxygen consumption and carbon dioxide production rates were determined by indirect calorimetry in a ventilated hood system (Deltatrac Systems, Sensormedics Corp., Yorba Linda, California) and were in turn used to determine resting energy expenditure based on the Weir equation (29).

Peak Oxygen Consumption

Under physician supervision, peak oxygen consumption was measured on a motorized treadmill (Desmo CE-25, Woodway USA, Waukesha, Wisconsin) by using a graded exercise tolerance test with on-line analysis of expired gas (Vmax Series 229, Sensormedics Corp.) (30). The first 2 minutes of the test were performed at 0% grade, and the grade was then increased by 2% every minute until the patient asked to stop or the physician terminated the test for medical reasons (18).

Table 1. **Baseline Characteristics of the Study Sample***

Characteristic	Low-Protein Diet plus Resistance Training (*n* = 14)	Low-Protein Diet Alone (*n* = 12)
Age, *y*	65 ± 9	64 ± 13
Sex (women/men), *n/n*	6/8	3/9
Ethnicity, *n*		
White	11	9
African American	3	2
Hispanic/Latino	0	1
Education, *y*	14 ± 4	12 ± 4
Body weight, *kg*	86.4 ± 16.9	77.3 ± 13.6
Body mass index, *kg/m²*	29.3 ± 6.6	26.8 ± 2.7
GFR, *mL/min per 1.73 m²*†	24.76	27.53
Serum creatinine concentration, *μmol/L (mg/dL)*†	187.41 (2.12)	202.44 (2.29)
Serum urea nitrogen concentration, *mmol/L (mg/dL)*†	13.33 (37.35)	16.40 (45.95)
Hematocrit, %†	31.60	32.10
Serum albumin level, *g/L*†	37	37
Peak oxygen consumption, *mL/kg per minute*	16.0 ± 5.1	18.5 ± 7.1
Protein intake, *g/kg of body weight per day*‡	0.84 ± 0.19	0.85 ± 0.22
Energy intake, *J/kg per day*‡	68.7 ± 30.9	86.6 ± 28.5
Cause of renal disease, *n*		
Renovascular hypertension	5	5
Type 2 diabetes mellitus	5	5
Polycystic kidney disease	1	0
Goodpasture disease	1	0
Lupus erythematosus	0	1
Lithium therapy	2	1
Diagnosed hypertension, %	64	83
Chronic conditions, *n*	5.5 ± 1.5	6.4 ± 1.7
Medications, *n*	5.6 ± 2.4	6.4 ± 1.6

* Unless otherwise noted, values are the mean ± SD. Groups did not differ significantly in any of these characteristics, as assessed by independent sample *t*-test comparisons for continuous variables, the chi-square test for categorical variables, and the Wilcoxon rank test for non-normally distributed continuous variables. GFR = glomerular filtration rate.
† Non-normally distributed variables, for which medians are shown.
‡ Protein intake was estimated from urea nitrogen appearance by using the Maroni method (19), and energy intake was estimated from 3-day assisted dietary records.

Whole-Body Leucine Kinetics

Protein turnover was assessed by using a primed-constant infusion of L-[1-^{13}C]-leucine. Leucine is an essential amino acid that is metabolized solely in skeletal muscle. Once metabolized, it permits determination of protein turnover by isotopic enrichment of ^{13}C-α-ketoisocaproic acid (KIC), resulting from leucine transamination. We conducted a 4-hour intravenous constant infusion of leucine following priming doses of $NaH^{13}CO_2$ and L-[1-^{13}C]-leucine, using a calibrated pump (Harvard Apparatus, Natick, Massachusetts) (31). Arterialized venous blood and breath samples were taken at 0, 120, 180, 190, 200, 210, 220, 230, and 240 minutes to determine the enrichment of KIC and $^{13}CO_2$ (coefficient of variation, 5%), from which leucine synthesis and oxidation, respectively, were calculated (31).

Statistical Analysis

Data are presented as the mean (±SD), except for non-normally distributed variables (glomerular filtration rate, serum albumin level, creatinine and urea nitrogen concentrations, hematocrit, and insulin-like growth factor I concentrations), for which medians are shown. The non-normally distributed variables were log-transformed, checked for normal distribution after log transformation, and used as log-transformed variables for analyses. Baseline comparisons of the randomly assigned groups were made by using independent sample *t*-test comparisons for continuous variables, the chi-square test for categorical variables, and the Wilcoxon rank test for non-normally distributed continuous variables. Regression models were performed by using general linear models to test the treatment effect on main outcomes (total body potassium, mid-thigh muscle area, and type I and II muscle-fiber cross-sectional areas) and secondary outcomes (biochemical, metabolic, and dietary variables). The change in each outcome was the dependent variable, and the covariates were group assignment, any variable that differed between groups at baseline, and sex. Sex was selected as a covariate a priori because of its

Table 2. **Biochemical, Metabolic, and Dietary Variables***

Variable	Low-Protein Diet plus Resistance Training (n = 14)		Low-Protein Diet Alone (n = 12)		*P* Value
	Value	Change, Absolute	Value	Change, Absolute	
Body weight, *kg*					
Week 0	84.6 ± 15.8		76.1 ± 13.5		
Week 12	84.8 ± 16.2	0.46 ± 2.6	72.5 ± 9.0	−3.21 ± 1.5	0.049
Insulin-like growth factor I level, *nmol/L*†					
Week 0	15.5		16.1		
Week 12	18.3	2.5	17.4	1.0	0.125
Serum prealbumin level, *mg/L*					
Week 0	253 ± 46		232 ± 60		
Week 12	276 ± 46	17 ± 31	234 ± 50	3 ± 31	0.050
Leucine synthesis, *μmol/kg of body weight per minute*‡					
Week 0	61.1 ± 14.8		59.8 ± 14.8		
Week 12	61.4 ± 14.7	0.30 ± 7.0	60.6 ± 15.7	0.8 ± 5.9	>0.2
Leucine oxidation, *μmol/kg per minute*‡					
Week 0	9.8 ± 2.5		9.2 ± 1.5		
Week 12	10.4 ± 2.2	0.7 ± 2.2	8.1 ± 1.9	−1.1 ± 2.1	0.046
Urinary creatinine concentration, *mmol/d (g/d)*					
Week 0	0.113 ± 0.03 (1.13 ± 0.03)		0.102 ± 0.02 (1.02 ± 0.02)		
Week 12	0.104 ± 0.03 (1.04 ± 0.03)	−0.01 ± 0.1	0.103 ± 0.02 (1.03 ± 0.02)	0.001 ± 0.07	0.074
GFR, *mL/min per 1.73 m²*†					
Week 0	24.76		30.01		
Week 12	26.35	1.18	28.03	−1.62	0.048
Hematocrit, *%*†					
Week 0	31.55		32.10		
Week 12	32.75	0.99	32.70	−0.37	>0.2
Serum urea nitrogen level, *mmol/L (mg/dL)*†					
Week 0	8.6 (24.0)		10.4 (29.1)		
Week 12	9.3 (26.0)	0.5	10.6 (29.6)	0.1	>0.2
Serum creatinine concentration, *μmol/L (mg/dL)*†					
Week 0	187.41 (2.12)		202.44 (2.29)		
Week 12	163.54 (1.85)	0.003	182.10 (2.06)	0.01	>0.2
Resting energy expenditure, *mJ/d*§					
Week 0	5.86 ± 0.80		5.82 ± 1.00		
Week 12	6.06 ± 0.71	0.19 ± 0.46	5.63 ± 0.84	−0.12 ± 0.77	>0.2
Protein intake, *g/kg of body weight per day*‖					
Week 0	0.64 ± 0.08		0.65 ± 0.09		
Week 12	0.60 ± 0.08	−0.02 ± 0.06	0.60 ± 0.11	−0.01 ± 0.05	>0.2
Energy intake, *J/kg per day*‖					
Week 0	67.7 ± 26.9		87.1 ± 28.4		
Week 12	76.4 ± 32.2	8.8 ± 17.6	98.3 ± 24.9	7.2 ± 14.1	>0.2

* Unless otherwise noted, values are the mean ± SD. Regression analysis by general linear models was performed to compare the treatment group effect on the change in each variable adjusted for sex. GFR = glomerular filtration rate.
† Non-normally distributed variables, for which medians are shown. Log-transformed variables were used for analysis.
‡ Determined from leucine kinetics on a 4-hour constant infusion of L-[1-^{13}C]-leucine, as described elsewhere (31).
§ Resting energy expenditure was estimated from indirect calorimetry.
‖ Protein intake was estimated from appearance of urea nitrogen in a 48-hour urine collection by using the Maroni method (19), and energy intake was estimated from two 3-day assisted dietary records.

known association with the main outcomes. Secondary, model-building stepwise regression analyses of the difference between postintervention and preintervention outcomes were carried out to determine the predictive potential of selected covariates. Independent predictive variables were chosen on the basis of their statistically significant association with the main outcomes at baseline (as determined by univariate analysis using the Pearson correlation coefficient). Thus, separate models were constructed with the change in each main outcome as the dependent variable and baseline protein and energy intakes, baseline body weight, and sex as the independent variables. Group assignment was forced into each model. Statistical results were considered significant if

Table 3. **Muscle Strength***

Variable	Low-Protein Diet plus Resistance Training (n = 14)			Low-Protein Diet Alone (n = 12)			*P* Value
	Week 0	Week 12	Change	Week 0	Week 12	Change	
	kg		%	*kg*		%	
Upper body strength							
Chest press	24.0 ± 10.4	31.8 ± 12.9	34 ± 12	28.4 ± 5.8	26.2 ± 6.4	−7 ± 8	<0.001
Latissimus pull-down	26.4 ± 7.5	33.9 ± 10.0	29 ± 14	29.5 ± 8.0	27.6 ± 10.0	−9 ± 19	<0.001
Lower body strength							
Leg press	167.4 ± 102.3	210.9 ± 129.0	29 ± 15	135.0 ± 26.7	134.3 ± 36.3	−1 ± 12	0.001
Knee extension	39.9 ± 17.8	55.9 ± 22.4	47 ± 24	36.7 ± 9.8	38.8 ± 14.0	2 ± 4	<0.001
Knee flexion	39.8 ± 13.6	55.8 ± 13.6	44 ± 22	43.4 ± 16.0	39.5 ± 9.4	−3 ± 24	<0.001

* Values are the mean ± SD. Regression analysis by general linear models was performed to compare the treatment group effect on the change in muscle strength for each machine, adjusted for sex.

the two-tailed *P* value was less than 0.05. The package used for analysis was SPSS 10.0 for Windows (SPSS, Inc., Evanston, Illinois).

Role of the Funding Sources

The funding sources had no role in the design of the study but oversaw aspects of its conduct and reporting.

RESULTS

Thirty-six of 200 persons contacted were screened, and 26 completed the study (**Figure 1**). One patient in each group did not complete all postintervention measures because of medical reasons. Groups did not differ at baseline in sociodemographic, body composition, biochemical, or health variables (**Table 1**).

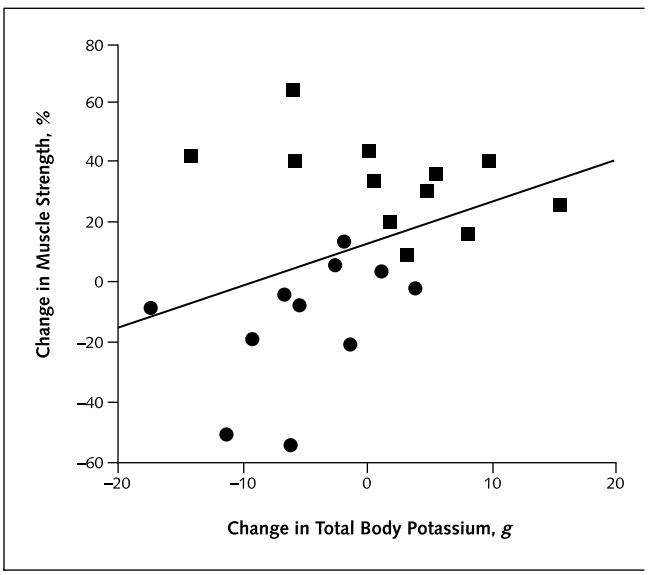
Adherence to resistance training and sham exercise sessions was 91% ± 9% and 90% ± 10%, respectively. These values did not differ significantly. Dietary adherence was achieved in 24 patients during the first 4 weeks of the run-in period. Two patients, one in each group, were permitted an additional 4 weeks to achieve the target protein intake. Dietary counseling from screening to week 12 of the intervention resulted in a 24% reduction in protein intake in each group, while energy intake was maintained and even increased slightly, as shown by baseline and intervention values (**Tables 1** and **2**). Adherence to the low-protein diet, determined by urinary urea nitrogen level, indicated that patients in the resistance training group consumed an average of 108% ± 8% of the target protein level, while patients

Table 4. **Main Outcome Variables***

Variable	Low-Protein Diet plus Resistance Training (n = 14)		Low-Protein Diet Alone (n = 12)		*P* Value
	Value	Change, Absolute	Value	Change, Absolute	
Total body potassium, *kg*					
Week 0	101.6 ± 25.2		104.5 ± 18.7		
Week 12	105.8 ± 23.9	1.9 ± 7.9	97.9 ± 17.9	−5.2 ± 5.9	0.014
Type I muscle-fiber area, μm^2†					
Week 0	3887 ± 1566		4578 ± 1524		
Week 12	4821 ± 1411	934 ± 1486	3960 ± 998	−618 ± 967	0.031
Type II muscle-fiber area, μm^2†					
Week 0	3626 ± 1216		3957 ± 988		
Week 12	4437 ± 1393	811 ± 1479	3399 ± 814	−558 ± 1126	0.045
Mid-thigh muscle area, cm^2‡					
Week 0	108.9 ± 29.5		108.2 ± 20.7		
Week 12	111.3 ± 29.6	2.42 ± 8.35	105.7 ± 18.9	−2.54 ± 6.15	0.113

* Values are the mean ± SD for patients with completed preintervention and postintervention measures. Regression analysis by general linear models was performed to compare the treatment group effect on the change in each main outcome, adjusted for sex.
† Type I and II skeletal muscle-fiber cross-sectional areas of vastus lateralis muscle of the nondominant leg were determined by histochemical analysis.
‡ Measured by computed tomography of the nondominant leg.

Figure 2. **Univariate linear association between the absolute change in total body potassium and the percentage change in muscle strength for each patient following the low-protein diet plus resistance training (*squares*) or the low-protein diet alone (*circles*).**



$r = 0.36$; $P < 0.05$. The solid line indicates linear regression.

following the low-protein diet alone consumed approximately 112% ± 12%. These estimates did not differ significantly between groups. Energy intake, determined as the mean of two self-reported 3-day dietary records, was low in both groups and suggested approximately 20% underreporting compared with measured resting energy expenditure multiplied by an activity factor of 1.2 (32). No exercise-related adverse events or injuries were reported. Nutritional status assessed by biochemical markers of protein nutrition was not adversely affected during the study (**Table 2**). Muscle strength results are shown in **Table 3**. Patients who performed resistance training had significantly larger increases in muscle strength on each machine than patients who followed the low-protein diet alone (overall improvement in muscle strength, 32% ± 14% vs. −13% ± 20%; $P < 0.001$).

Main Outcomes

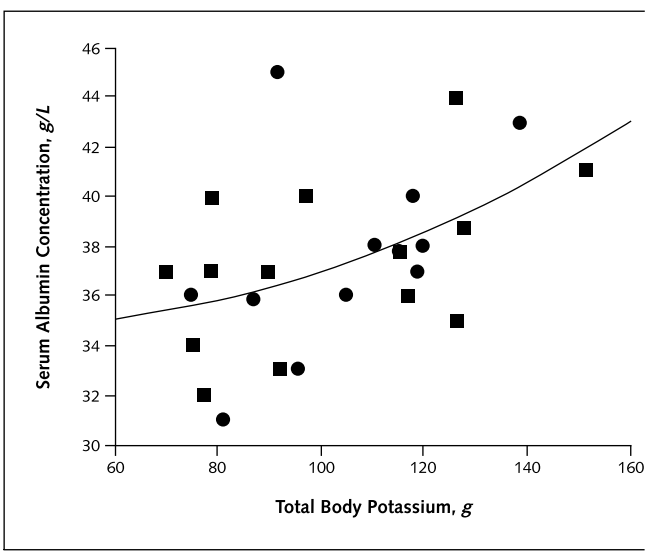
Table 4 shows the results of the main outcomes measured to assess the anabolic effect of resistance training on muscle mass. Completed measurements of total body potassium were available in only 23 of 26 patients (low-protein diet plus resistance training, $n = 12$; low-protein diet alone, $n = 11$) because of technical difficulties ($n = 1$) or medical reasons ($n = 2$). Similarly, results of muscle biopsies were available in only 21 of 26 patients (low-protein diet plus resistance training, $n = 13$; low-protein diet alone, $n = 8$) because of patient refusal to undergo the procedure ($n = 3$) or medical reasons ($n = 2$).

Resistance training significantly increased total body potassium and hypertrophied type I and type II muscle-fiber areas by 4% ± 8%, 24% ± 31%, and 22% ± 29%, respectively, compared with low-protein diet alone. Patients following the low-protein diet alone had mean losses in these variables. There was a trend toward an increase in mid-thigh muscle area in those who performed resistance training compared with those who did not ($P = 0.113$). The change in total body potassium was significantly associated with the change in muscle strength ($r = 0.36$; $P = 0.05$) (**Figure 2**).

Secondary Outcomes

Biochemical, metabolic, and dietary variables are listed in **Table 2**. From screening to the end of the

Figure 3. **Univariate linear association between postintervention total body potassium and postintervention serum albumin concentrations for each patient following the low-protein diet plus resistance training (*squares*) or the low-protein diet alone (*circles*).**



$r = 0.52$; $P = 0.01$. The solid line indicates quadratic regression.

run-in period, patients assigned to the resistance training group lost 2.1 ± 2.8 kg and those assigned to the low-protein diet alone lost 1.1 ± 1.9 kg ($P = 0.02$). During the intervention period, however, those who performed resistance training maintained body weight and those who did not experienced substantial additional loss. Concentrations of insulin-like growth factor I increased by 18% in those who performed resistance training and increased slightly in those who followed the low-protein diet alone ($P = 0.125$). Serum prealbumin level increased significantly in the resistance training group compared with the low-protein diet alone group, and similar trends were seen for serum albumin and transferrin (data not shown). Postintervention total body potassium was significantly correlated with postintervention serum albumin concentrations ($r = 0.52$; $P < 0.01$) (**Figure 3**).

Leucine synthesis did not change in either group. Leucine oxidation increased with resistance training and decreased with low-protein diet alone. Urinary creatinine excretion decreased by 8% in those who performed resistance training and did not change in those who followed the low-protein diet alone. Renal function did not deteriorate, as shown by a small but significant improvement in glomerular filtration rate in those who performed resistance training compared with those who followed a low-protein diet alone. This finding was seen despite a sample of only 18 of 26 patients (resistance training, $n = 8$; low-protein diet alone, $n = 10$) because of shellfish allergies ($n = 4$) and poor intravenous access ($n = 4$). The groups did not differ significantly in hematocrit, serum urea nitrogen level, and creatinine concentration or resting metabolic rate.

Secondary Analysis of Predictors of the Change in Main Outcomes

Univariate correlation analyses at baseline showed that total body potassium was associated with both protein intake ($r = 0.70$; $P < 0.001$) and energy intake ($r = 0.37$; $P = 0.05$), as well as with body weight ($r = 0.57$; $P = 0.003$). Mid-thigh muscle area was associated with protein intake ($r = 0.77$; $P < 0.001$) and body weight ($r = 0.56$; $P = 0.003$). Total body potassium was also significantly associated with concentrations of insulin-like growth factor I ($r = 0.39$; $P = 0.05$) and with leucine oxidation ($r = 0.56$; $P = 0.01$). Given that these variables are a function of protein intake and that this study had a small sample size, baseline protein and energy intake, body weight, sex, and group assignment were the only independent variables used as predictors for each of the models constructed. The change in each main outcome was the dependent variable. Group assignment was found to be the only significant predictor of the change in total body potassium and the change in type I and II muscle-fiber cross-sectional areas, accounting for 47% ($P = 0.02$), 52% ($P = 0.01$), and 61% ($P = 0.03$) of their variances, respectively. None of these factors were independent contributors to the change in mid-thigh muscle area.

DISCUSSION

This study suggests that resistance training is a safe and effective countermeasure to the negative effects of protein restriction on muscle mass accretion, protein utilization, nutritional status, and muscle function in patients with moderate chronic renal insufficiency consuming a low-protein diet. After 12 weeks of resistance training, patients successfully adapted to the low-protein diet. This was evidenced by improved nitrogen retention, as shown by gains in total body potassium; hypertrophy of type I and type II muscle-fiber area; increased prealbumin levels; maintenance of body weight; and increased protein utilization, as measured by leucine oxidation rates. The anabolic effects of resistance training were observed despite patient age, uremia, self-reported low energy intakes, anemia, low aerobic capacity, and comorbid diseases.

The mean protein intake was 0.64 ± 0.07 g/kg per day, a 24% decrease from habitual intake in both groups. Although published evidence suggests that a low-protein diet has a beneficial effect in patients with chronic renal insufficiency (6, 7, 33), it is not commonly prescribed in clinical practice. Nonadherence and the need for intensive dietary counseling are substantial barriers to clinical implementation (34). In addition, concerns exist regarding the possible deleterious effects of accommodation to a low-protein diet on nutritional status, muscle mass, and survival (35). Accommodation takes place when significant losses in important body tissues or functions occur as a result of an environmental stress to maximize protein homeostasis and survival. In contrast, adaptation to a less than adequate protein diet

occurs while body tissues and functions are maintained (36). Findings of accommodation to low-protein diets have been reported in healthy elders with adequate energy intakes (25, 27). In our study, conventional clinical measures of nutritional status, such as serum protein levels, were not affected by the low-protein diet. However, more sensitive indicators of accommodation, such as leucine oxidation rates, body cell mass as measured by total body potassium, mid-thigh muscle area and muscle-fiber cross-sectional area, and muscle strength, were reduced, confirming that a low-protein diet leads to accommodation by altering protein utilization and negatively affecting body composition and function.

Our study provides evidence of increased protein utilization and nitrogen retention (as evidenced by higher rates of leucine oxidation) in patients with chronic renal insufficiency who performed 12 weeks of resistance training while consuming a low-protein diet. Leucine oxidation is likely to reflect increased nitrogen retention and protein accretion, as evidenced by its significant association with total body potassium. This suggests that leucine oxidation may be a good indicator of nitrogen homeostasis.

Protein utilization, however, is also affected by energy intake (36). Our patients reported very low energy intake compared with standard recommendations (37). About 20% of this may be accounted for by underreporting. Even after adjustment for underreporting, however, energy intake was below that recommended for weight maintenance in sedentary persons (32). However, in contrast to patients following the low-protein diet alone, those performing resistance training maintained body weight and gained lean body mass despite marginal energy intakes. This finding confirms the ability of resistance exercise to counteract the catabolic effects of protein restriction and renal disease. Similar gains in lean body mass have been reported in obese patients undergoing weight loss through hypocaloric diets while performing resistance training (15).

We found that measurements of total body potassium were a precise indicator of small but significant changes in body cell mass resulting from successful adaptation and nitrogen retention. Measurement of total body potassium, however, cannot readily be performed in clinical practice, and other measures of protein nutritional status (for example, serum protein levels or measures of functional capacity) are more practical (38). The significant association between total body potassium and serum albumin concentrations (**Figure 3**), as well as the association between the changes in total body potassium and function (muscle strength) we observed (**Figure 2**), suggest that these measures may be useful as surrogates for protein homeostasis and adaptation in this patient population. Our findings support documented associations between serum albumin levels and nutritional status, health (39), and mortality (40) in the general population and in patients with renal failure in whom muscle wasting is the hallmark of disease (2).

Published studies of exercise in renal disease have examined the effects of endurance training as a means to improve the metabolic profile, functional capacity, and quality of life of patients receiving maintenance dialysis (41, 42) or predialysis (43). In our study, the progression and intensity of the exercise regimen led to significant increases in upper and lower muscle strength with no exercise-related injuries or adverse events.

Our study has limitations. First, only a small proportion of the patients invited to participate in the study completed it. However, reasons for not participating were mostly related to time commitment and the invasiveness of the study rather than to medical restrictions on exercise. Second, the sample size was small. However, the measured outcomes agreed with the expected direction of hypothesized changes in all cases that did not achieve statistical significance. Third, the study dietitian was not blinded, and postintervention muscle strength was not measured in a blinded manner. We are confident, however, that dietary counseling, including instruction materials, contact time, and motivational tools, were similar for all patients, as shown by the 24% decrease in protein intake in both groups. To avoid any observer bias, baseline measurements of muscle strength were obtained before randomization by using standard techniques. As for nonblinded postintervention muscle strength testing, even with possible observer bias, blinded measures of body cell mass deposition and muscle hypertrophy support the anabolic effect of resistance training. Fourth, our findings may not apply to patients with chronic renal insufficiency who do not consume low-protein diets.

In conclusion, the anabolic effects of resistance training observed in this study support the usefulness of resistance exercise as a noninvasive, nonpharmacologic intervention capable of offsetting the catabolic effects of

low protein and energy intakes and the wasting syndrome of chronic uremia. If nutritional status cannot be improved by simply increasing protein or energy intake, resistance training may be a central component in the multifactorial therapeutic approach to chronic renal insufficiency and may result in successful adaptation to low-protein diets secondary to prescription or anorexia. Future studies with longer intervention periods, patients with more advanced stages of renal failure, and larger patient samples may confirm and extend our findings.

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