

# The Effectiveness of Aerobic and Muscle Strength Training in Patients Receiving Hemodialysis and EPO: A Randomized Controlled Trial

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● **Background:** Individuals with end-stage renal disease on hemodialysis therapy have reduced aerobic exercise capacity and reduced muscle strength. **Methods:** This was a single-blind, randomized, placebo-controlled trial of an exercise intervention in hemodialysis patients administered erythropoietin. The intervention consisted of progressive resisted isotonic quadriceps and hamstrings exercise and training on a cycle ergometer three times weekly for 12 weeks. Individuals in the control group underwent a nonprogressive program of range-of-motion exercises. Both groups were observed for an additional 5 months without intervention. Outcomes were assessed without knowledge of treatment assignment at baseline, 12 weeks, and 5 months. A healthy age- and sex-matched sample provided comparative data. **Results:** Our sample was relatively high functioning, with a mean score on the Physical Function subscale of the Short Form 36 (SF-36) of 76 of 100. At 12 weeks, there were large and statistically significant differences in favor of the experimental group on the submaximal exercise test (14 W; 95% confidence interval, 2 to 26) and muscle strength (45 lb; 95% confidence interval, 9 to 81), but not in the 6-minute walk, symptoms questionnaire, or SF-36. Differences between the intervention and control groups at 12 weeks were not evident on retesting 5 months after the end of the intervention. Compared with the healthy sample, patients were significantly lower functioning on the submaximal exercise test, muscle strength, and 6-minute walk test at baseline. **Conclusion:** In this high-functioning sample, the exercise program improved physical impairment measures, but had no effect on symptoms or health-related quality of life. The impact on patients with a greater degree of physical dysfunction needs to be rigorously studied. *Am J Kidney Dis* 40:1219-1229.

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**INDEX WORDS:** Kidney failure; exercise; physical fitness; program evaluation; quality of life; chronic; hemodialysis (HD); erythropoietin (EPO).

**O**VERALL QUALITY of life in patients with end-stage renal disease (ESRD) is low, and impairments in areas related to physical functioning are particularly prominent.<sup>1,2</sup> Apart from effects on quality of life, poor physical performance, assessed by the Physical Component Scale (PCS) of the Medical Outcomes Survey Short Form 36 (SF-36), has been shown to be a powerful predictor of outcomes: patients with PCS scores below the median were twice as likely to die and 1.5 times more likely to be hospitalized as patients with PCS scores at or above the median in a prospective study of 1,000 hemodialysis patients.<sup>3</sup>

In keeping with low self-reported physical functioning, the aerobic exercise capacity of people treated with maintenance hemodialysis therapy is approximately half the expected value for sedentary healthy individuals.<sup>4</sup> Cardiac disease, alterations in muscle function, metabolic abnormalities, and anemia have been implicated. Cardiac problems include diminished left ventricular functional reserve<sup>5</sup> and increased arrhythmias.<sup>6</sup> Muscle abnormalities include low activity of enzymes, loss of capillaries, fiber atrophy, loss of contractile proteins, and electromyographic

denervation.<sup>7,8</sup> Anemia in hemodialysis patients responds to erythropoietin therapy, and concomitant increases in exercise capacity have been documented. Maximal oxygen uptake ( $VO_2$  max) increased by almost 50% above baseline in some studies (reviewed by Levin<sup>9</sup>). However, Robertson et al<sup>10</sup> found that although mean  $VO_2$  max increased by 17%, none of the 19 patients treated attained the expected value for sedentary healthy individuals. Furthermore, Painter et al<sup>11</sup> found that normalization of hemoglobin level combined with aerobic exercise training does not normalize  $VO_2$  max, suggesting that limitations

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beyond those of anemia and deconditioning are present in hemodialysis patients.

Before the introduction of erythropoietin, a number of studies had examined the response to training in this population (reviewed by Goldberg and Harter<sup>12</sup>). Improvements of 10% to 40% in  $\text{VO}_2$  max and 21% to 46% in physical work capacity compared with controls were observed.<sup>12</sup> Currently, erythropoietin is widely used in dialysis patients, and target hemoglobin levels between 11 and 12 g/dL (110 to 120 g/L) are recommended for patients with ESRD.<sup>13</sup> The clinically relevant question is whether exercise training offers additive benefit to erythropoietin-treated dialysis patients. Previous controlled trials of supervised exercise programs in the erythropoietin era have documented improvements in exercise time,<sup>14</sup> peak muscle strength,<sup>8</sup>  $\text{VO}_2$  max,<sup>11,14-16</sup> left ventricular systolic function,<sup>14</sup> and nerve conduction velocity<sup>8</sup>; normalization of vagal activity<sup>6</sup>; reduced vulnerability to arrhythmias<sup>6</sup>; decreased depression<sup>15</sup>; and reduced fatigue.<sup>17</sup> Improved quality of life by the physical functioning domains of the SF-36 was observed in two studies by Painter et al<sup>11,18</sup> and Kouidi et al<sup>15</sup> using the Quality of Life Index. However, Ridley and Hoey<sup>17</sup> showed no differences in Kidney Disease Questionnaire (KDQ) scores (although other outcomes were affected positively by this intervention in this study). In a nonrandomized controlled trial of supervised exercise that is remarkable for its size and the inclusion of older and more frail patients, Painter et al<sup>18</sup> also documented statistically significant improvements in gait speed, sit-to-stand-to-sit test, role functioning, general health, and bodily pain. Non-supervised coaching interventions have shown inconsistent results.<sup>19,20</sup>

However, interpretation of the controlled studies described is limited by either a nonrandomized design,<sup>16,18</sup> failure to report whether outcome ascertainment was blinded,<sup>6,14-18</sup> and cointervention.<sup>19</sup> None has included a placebo or attention intervention. Only one study included follow-up beyond the intervention period.<sup>19</sup>

We report a randomized controlled trial of the effect of combined aerobic exercise with progressive strengthening exercises on work output in erythropoietin-treated hemodialysis patients, using supervised low-intensity range-of-motion exercises as a placebo intervention. Outcomes were

assessed by a research assistant masked to treatment allocation, both at the end of the 12-week intervention period and after an additional 5 months of follow-up.

## METHODS

### *Participants*

Participants were recruited from the Progressive Care Hemodialysis Unit at St Joseph's Hospital (a tertiary care centre) and Bayshore Dialysis Centre (a community dialysis centre) in Hamilton, Ontario, Canada. Patients who undergo dialysis in these units are selected from the total population of the St Joseph's hemodialysis program on the basis of medical stability. Substituted cellulose and polysulfone dialyzers were used, with a target urea reduction ratio of 65% or greater. Target hemoglobin level for each patient was determined by the nephrologist, usually between 10.5 and 12.5 g/dL (105 to 125 g/L); normalization of hemoglobin level was not an aim.

Study inclusion criteria were on hemodialysis therapy for longer than 3 months, administered erythropoietin for the treatment of anemia, hemoglobin level greater than 9.0 g/dL (90 g/L), able to maintain sitting and standing balance without assistance, and ambulatory without assistance. Exclusion criteria were ischemic heart disease, recent myocardial infarction of less than 6 months, uncontrolled hypertension, pericardial or pleural friction rub, aortic stenosis, active musculoskeletal lower-extremity problem, or history of vertebral fracture caused by osteoporosis. Patients also were excluded if they participated in team sports or formal organized exercise programs.

A sample of healthy age- and sex-matched volunteers without renal problems who met none of the exclusion criteria described was drawn from hospital personnel to determine comparative values for the submaximal exercise test, muscle strength, and 6-minute walk test.

### *Design*

Hemodialysis patients were randomly assigned (using concealed assignments generated from a random numbers table and randomizing in blocks of four) to receive an active intervention or a control intervention for a period of 12 weeks and were assessed at the end of the 12-week period and again after an additional 5 months, during which no intervention was provided. The Research Ethics Board of St Joseph's Healthcare approved the protocol. All patients provided informed consent.

### *Interventions*

Participants underwent hemodialysis sitting in a reclining chair. Participants randomized to the experimental group received 20 minutes of aerobic training on a Monark Rehab Trainer (Monark-CrescentAB, Varberg, Sweden) that was positioned and stabilized in front of the participant while sitting in the dialysis chair during hemodialysis. After a 2-minute warm up, resistance was adjusted so that individuals were working at a level of perceived exertion (Borg scale)<sup>21</sup> of "somewhat strong" at approximately 50 rpm. The

exercise was progressed by increasing resistance when the rating fell below "somewhat strong." For safety, heart rate and blood pressure were monitored throughout the session. Training was terminated if the patient exceeded 80% of their maximum heart rate, if heart rate or blood pressure parameters were exceeded (blood pressure > 200/110 or < 110/50 mm Hg), or the patient had chest pain, severe dyspnea, wheezing, leg cramps, confusion, visual symptoms, pallor, or cyanosis.

Either before or after the dialysis session, based on convenience, participants performed strength training for hamstrings and quadriceps muscle groups on a Response Seated Leg Curl Thigh Extension pulley weight system (Brookdale Medical Specialties, Woodbridge, ON, Canada). The highest weight that could be lifted five times and no more (five-repetition maximum [5-RM]) at baseline was determined. Testing was performed at 5-RM rather than 1-RM to minimize undue stress on the cardiovascular system. Week 1 started at 50% of the patient's baseline 5-RM for one set of 10 repetitions, and the number of sets (to a maximum of three) and percentage of 5-RM (to a maximum of 125%) were increased gradually during 12 weeks. Weights were not increased until the patient could complete the number of repetitions prescribed. Patients were withdrawn from the intervention if adverse effects occurred (with the exception of transient muscle soreness).

The control exercise protocol consisted of 30 minutes of nonprogressive, nonresisted, low-intensity, range-of-motion exercises of the lower extremities and free upper extremity, performed sitting during hemodialysis.

Both study interventions were performed three times a week for 12 weeks. Training was performed by kinesiologists. Trainers were instructed to ensure that both groups received equal encouragement.

### Data Collection

Age, sex, time since starting dialysis therapy, time since starting erythropoietin therapy, comorbidity, and employment status were recorded at the start of the study. Each patient's participation in home exercise, hemoglobin level, hematocrit, blood pressure, serum creatinine level, body weight, and urea reduction ratio were noted at the beginning and end of the study.

### Outcomes

Outcomes were assessed by a research assistant masked to treatment allocation at three times: before starting the intervention, after 12 weeks of intervention or control, and after an additional 5 months. The research assistant never attended the dialysis units when subjects might be training, and subjects were instructed not to discuss their study treatment with the research assistant.

The primary outcome was a submaximal exercise test, usually performed on a dialysis day (but not while patients were undergoing dialysis). For patient convenience and to minimize loss to follow-up, patients were tested after dialysis if they were scheduled for morning dialysis, before dialysis if they were scheduled for afternoon dialysis, and before dialysis if they were scheduled for evening dialysis. The testers, who were blinded to patient group, set up the

appointments. Patients were tested on the Monark Rehab Trainer set up for leg cycle ergometry. Two minutes of warm-up without resistance was followed by 3 minutes at 10 W, increasing every 3 minutes by 10 W until the patient's rating of perceived exertion on the Borg scale reached "somewhat strong." Blood pressure and heart rate were monitored throughout the test. Criteria for stopping were the same as those for intervention training. Maximum workload and duration of testing were recorded. Test-retest reliability was assessed in the first seven subjects on two occasions within 1 week (by the same research assistant).

Muscle strength of the hamstrings and quadriceps was assessed on the Response Seated Leg Curl Thigh Extension system. The 5-RM was determined by starting at 25 lb (11.4 kg) and moving up or down as indicated, with 30 seconds of rest between each trial. For analysis, 5-RM measures were added together for right and left quadriceps and hamstrings. Test-retest reliability was assessed in the healthy comparative sample, with measurements performed by two physiotherapists within 1 week.

*Six-minute walk test.* Patients were instructed to walk as fast as possible in a corridor without compromising their safety for 6 minutes, and the distance walked was measured. The test was standardized to include no encouragement. This test has been shown to be reliable,<sup>22-24</sup> valid,<sup>22,24,25</sup> and responsive<sup>23,26,27</sup> in patients with cardiac failure,<sup>22,23,25,27</sup> respiratory disease,<sup>26</sup> or intermittent claudication<sup>24</sup> and has been used in patients with chronic renal failure.<sup>28,29</sup>

We used the self-administered acute version of the SF-36. This generic health-related quality-of-life instrument has been documented to be reliable and valid in the general population<sup>30</sup> and dialysis patients.<sup>1,3</sup>

*Symptoms questionnaire.* The Laupacis KDQ is a disease-specific quality-of-life instrument shown to be reliable, valid, and responsive in ESRD.<sup>31</sup> The fatigue and physical symptoms dimensions of this instrument were responsive to the change in quality of life associated with the introduction of erythropoietin therapy.<sup>28</sup> To minimize respondent burden, we selected six questions from the KDQ that we believed were most likely to be responsive to the intervention. We added four questions using the same response options (Appendix).

### Analysis Plan

The primary outcome was submaximal workload at 12 weeks. Secondary outcomes were workload at 5 months; and for both the 12-week and 5-month periods, muscle strength (assessed as the sum of the 5-RM for right and left quadriceps and hamstrings), 6-minute walk distance, SF-36 scores, and disease-specific symptoms scores. All outcomes were compared between groups (intervention versus control) by using analysis of covariance to adjust for baseline values. Because each variable was tested twice (12 weeks and 5 months),  $P$  of 0.025 or less is considered statistically significant. Baseline study patients and the intervention group at 12 weeks were compared with the healthy comparative sample by means of  $t$ -tests, considered significant at  $P$  of 0.05. Outcomes were assessed, when possible, in patients who withdrew from the study (with the exception of patients who underwent renal transplantation). Analysis was based on the intention-to-treat principle.

### Sample Size

We estimated that a change of 10 W<sup>32</sup> would represent a clinically significant difference. For an expected SD of 6 W,<sup>7</sup> a two-tailed  $\alpha$  of 0.05, and power of 0.90, 8 subjects per group are required. Eleven patients per group would adjust for an anticipated 25%<sup>33</sup> dropout rate. To improve generalizability, we aimed to recruit 18 patients to each group (36 patients randomized to intervention or control and 18 healthy comparative subjects).

### RESULTS

For reliability of outcome measures, the intraclass correlation coefficient for the submaximal exercise test was 0.75 for watts with a standard error of measurement of 5.3 W. Test-retest reliability of the 5-RM strength determination was assessed in the healthy comparative sample and found to be highly reliable, with an intraclass

correlation coefficient of 0.96 and standard error of measurement of 26 lb.

The flow of participants through each stage of the study is shown in Fig 1. These numbers represent follow-up for the primary outcome measure. In some cases, participants who were not able to undergo the submaximal exercise test were able to complete the SF-36 and symptoms questionnaire. Recruitment occurred from February 1997, and follow-up was finished January 1999. Demographic and clinical characteristics of the experimental and control groups are listed in Table 1. Individuals in the experimental group had a greater incidence of arthritis than those in the control group. Follow-up for the primary outcome at 12 weeks was 76%, and at 5 months, 53%.

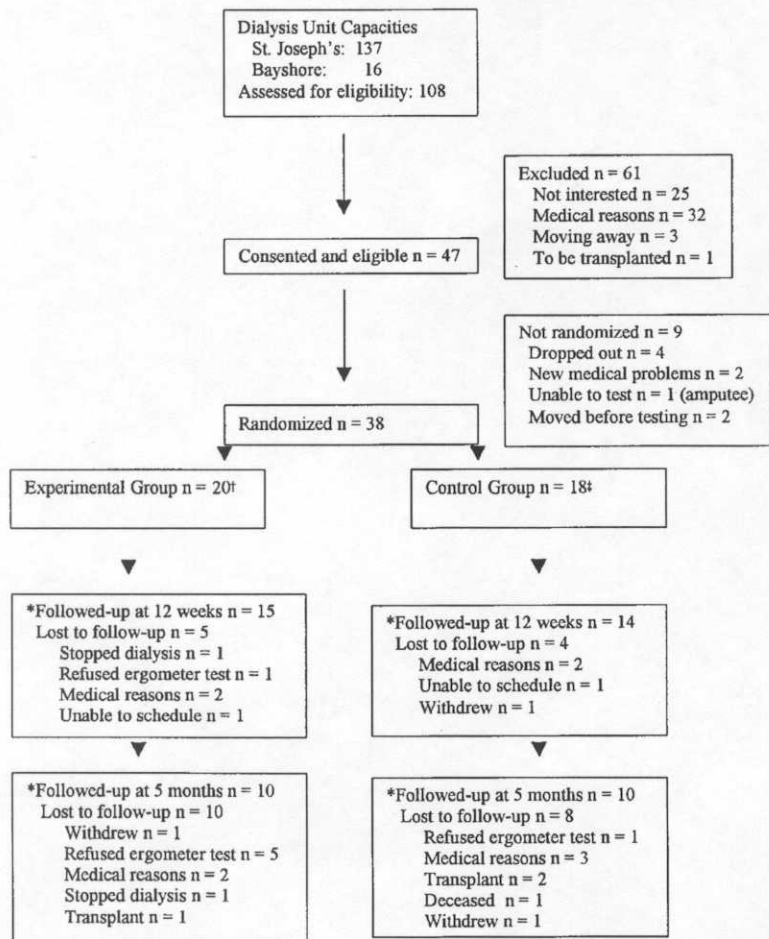


Fig 1. Flow of participants through the study. Follow-up numbers are given for the primary outcome, peak work on the submaximal exercise test. Follow-up for questionnaires was more complete. \*We obtained follow-up outcome measures on as many randomly assigned patients as possible in accordance with the intention-to-treat principle. †Of those randomly assigned to the intervention, 17 patients received the exercise intervention and 3 patients did not because of medical reasons. ‡Of those randomly assigned to the control arm, 18 patients received the placebo intervention and 2 patients did not (1 patient for medical reasons and 1 patient withdrew from the study immediately after randomization).

**Table 1. Demographic and Clinical Characteristics of the Intervention and Control Groups at Baseline**

	Intervention Group	Control Group
Sample size	20	18
Age (y)	55 ± 16	54 ± 14
Sex (men/women)	10/10	13/4
Duration of hemodialysis (y)	4.2 ± 4.8	4.6 ± 4.5
Duration of erythropoietin therapy (y)	2.6 ± 2.5	1.9 ± 1.6
Comorbidity (%)		
Arthritis	45	0
Diabetes	30	35
Cancer	5	0
Cardiovascular	20	35
Stroke	5	6
Employment (%)		
Full-time	10	0
Part-time	5	0
Unemployed/retired/disabled	85	100
Home exercise (%)	50	76

NOTE. Values expressed as mean ± SD, number, or percent.

Results are shown in Table 2 and Fig 2. Table 3 lists change scores to contrast the groups on how much they improved or deteriorated from baseline to 12 weeks and baseline to 5 months. Sample sizes and *P* for analysis of covariance also are listed in Table 3. At 12 weeks, by analysis of covariance, the primary outcome (watts on the submaximal exercise test) showed a statistically significant difference (*P* = 0.02). The difference in change scores between the experimental and control groups was 14 W (95% confidence interval, 2 to 26). At 12 weeks, there also was a significant difference in the combined measure of hamstring and quadriceps muscle strength (*P* = 0.02). The difference in change

scores between the intervention and control groups was 45 lb (95% confidence interval, 9 to 81). For quadriceps, participants improved from 21 to 39 lb, and for hamstrings, from 20 and 37 lb. The 6-minute walk and questionnaires did not show statistically significant or clinically important differences. Also, subscales of the SF-36 were not statistically significantly different. Although at baseline, more participants in the control group performed a home exercise program, at 12 weeks, 71% of the control group and 75% of the experimental group performed home exercise. At the 5-month follow-up, 41% of the control group and 35% of the experimental group reported doing home exercises.

At the 5-month follow-up evaluation, no significant differences between experimental and control groups were noted (Table 3; Fig 2). Between 12 weeks and 5 months, strength and work output declined in the experimental group. Compared with baseline, strength was stable in the experimental and control groups at 5 months, with no statistically significant difference between groups (*P* = 0.18).

The imbalance between groups at baseline in the number of individuals who reported having arthritis was not reflected in baseline differences on the submaximal exercise test or muscle strength test. We explored whether individuals in the intervention group differed in their results based on whether they reported having arthritis. There were no clinically important or statistically significant differences in their response to the intervention.

Patients who did not complete the assessments had worse physical functioning at baseline and greater levels of comorbidity. In the experimen-

**Table 2. Mean Outcome Measures at Baseline and the End of the 12-Week Intervention and the 5-Month Follow-Up Period**

	Intervention Group			Control Group		
	T1 (baseline)	T2 (12 wk)	T3 (5 mon)	T1 (baseline)	T2 (12 wk)	T3 (5 mon)
Ergometer test (W)	21 ± 16	44 ± 19	39 ± 19	22 ± 10	30 ± 10	34 ± 6
Strength (lb)	166 ± 94	228 ± 129	182 ± 55	171 ± 50	173 ± 46	157 ± 45
Six-minute walk (m)	460 ± 136	464 ± 94	476 ± 95	426 ± 131	430 ± 80	458 ± 38
KDQ points	49 ± 10	50 ± 14	47 ± 9	52 ± 7	55 ± 7	47 ± 9
SF-36	100 ± 23	100 ± 21	97 ± 19	100 ± 18	96 ± 16	95 ± 26

NOTE. Values expressed as mean ± SD.

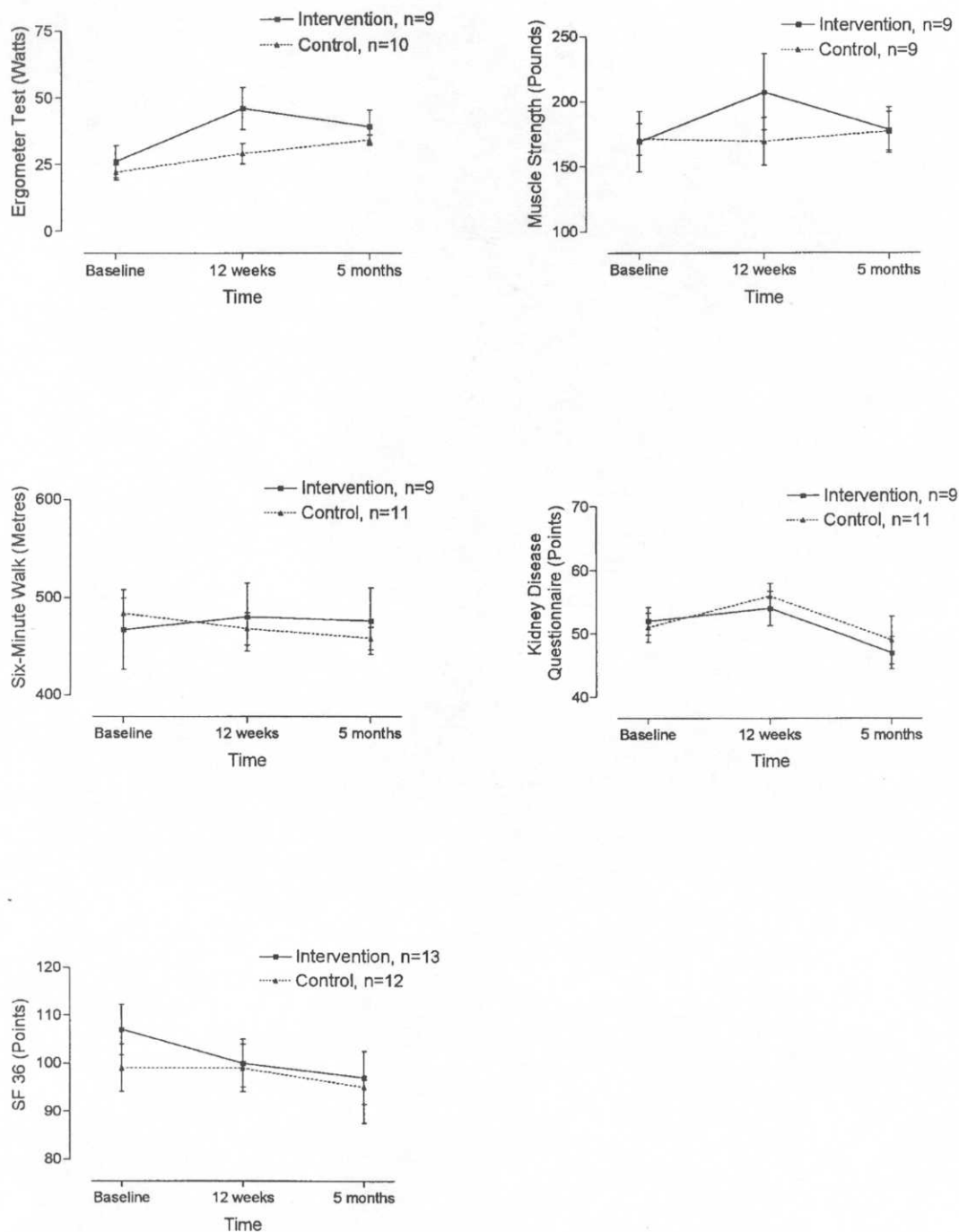


Fig 2. Outcome measures at baseline, 12 weeks (after the intervention), and 5 months (after a period of observation) for the intervention and control groups. The number of patients with complete assessments in each group is shown for each outcome measure, and data represent participants with complete data available at all three times. Error bars are  $\pm$  SD.

**Table 3. Change Scores and Statistical Significance by Analysis of Covariance Adjusting for Baseline Measure, End of the Intervention, and After an Additional 5-Month Follow-Up Period**

	12 Weeks			5 Months		
	Intervention (T2-T1)	Control (T2-T1)	<i>P</i>	Intervention (T3-T1)	Control (T3-T1)	<i>P</i>
Ergometer test (W)	20 ± 18	6 ± 13	0.02	13 ± 18	12 ± 9	0.59
No. of subjects	15	14		10	10	
Strength (lb)	46.7 ± 49.3	1.4 ± 44.7	0.02	8.5 ± 39.9	-14.4 ± 31.7	0.18
No. of subjects	15	14		10	9	
Six-minute walk (m)	3.3 ± 45.7	3.4 ± 86.7	0.52	6.2 ± 47.8	-26.5 ± 43.8	0.10
No. of subjects	15	14		12	9	
KDQ points	1.6 ± 9.1	3.6 ± 6.3	0.39	-4.3 ± 10.0	-2.08 ± 9.6	0.58
No. of subjects	17	15		13	12	
SF-36 points	-1.0 ± 15.9	-1.8 ± 14.1	0.55	-8.4 ± 18.2	-4.3 ± 12.3	0.59
No. of subjects	17	15		14	12	

NOTE. Data shown as mean ± SD. Intention-to-treat sample sizes are given for the analysis of covariance. Abbreviations: T1, baseline; T2, 12 weeks; T3 additional 5-month follow-up.

tal group, subjects for whom 12-week measurements were not available (dropouts) had been treated with dialysis therapy for a shorter period and had a greater incidence of diabetes and lower functioning on baseline outcome measures than those for whom follow-up measures were taken. Those with missing data in the control group were older, had been treated with dialysis therapy for a shorter period, and had a markedly lower 6-minute walk. Similar findings occurred when comparing characteristics of participants with missing data at 5 months with those in whom follow up was achieved. Results of a per-protocol analysis including only patients who completed 75% of training sessions were not different from results of the intention-to-treat analysis.

There were no statistically significant differences between groups in hemoglobin levels, erythropoietin doses, blood pressures, creatinine levels, body weights, or urea reduction ratios throughout the trial period (Table 4). There also were no clinically important differences between groups. Hemoglobin values were in the range expected based on unit policies: patients were treated adequately to receive expected quality-of-life benefits from erythropoietin, but did not have normalization of hemoglobin levels. Adverse reactions were more common in the experimental group. One participant stopped the exercise because she found the exercise to be fatiguing; one participant, because of sore legs; one participant, because of hypotension; one participant, because of developing an open area on the dorsum of his

**Table 4. Laboratory Values Before and After the 12-Week Intervention**

	Intervention Baseline	Intervention 12 Weeks	Control Baseline	Control 12 Weeks
Hemoglobin				
g/L	116.5 ± 12.2	112.9 ± 20.2	111.1 ± 13.9	112.2 ± 13.5
g/dL	11.6 ± 1.2	11.3 ± 2.0	11.1 ± 1.4	11.2 ± 1.4
Hematocrit	0.35 ± 0.04	.034 ± 0.06	0.33 ± 0.04	0.34 ± 0.04
Mean systolic blood pressure (mm Hg)	143.6 ± 15.9	146.0 ± 19.0	152.0 ± 21.3	153.1 ± 20.2
Mean diastolic blood pressure (mm Hg)	78.9 ± 11.9	81.7 ± 8.6	81.4 ± 14.6	85.2 ± 11.7
Creatinine (μmol/L)	814.9 ± 176.5	871.9 ± 141.8	813.4 ± 200.6	799.0 ± 221.7
Mean body weight (kg)	74.7 ± 23.2	70.4 ± 21.4	72.2 ± 12.1	72.6 ± 12.6
Urea reduction ratio (%)	69.8 ± 6.0	72.2 ± 5.8	70.0 ± 6.7	72.6 ± 7.2

NOTE. Values expressed as mean ± SD.

**Table 5. Outcome Measures for the Healthy Comparative Sample, Total Study Sample at Baseline, and Intervention Sample at 12 Weeks**

	Comparative Sample	Baseline Study Sample	Baseline Percent of Comparative	Intervention Group at 12 Weeks	Intervention Percent of Comparative
Ergometer test (W)	58 ± 18	22 ± 13*	37	44 ± 19*	76
Strength (lb)	249 ± 127	166 ± 75*	67	228 ± 129	92
Six-minute walk test (m)	508 ± 59	417 ± 130*	82	464 ± 94	91

NOTE. Values expressed as mean ± SD or percent.

\* $P < 0.05$ .

foot caused by abrasion from the ergometer; and one participant, because of problems with muscle pain and foot pain caused by the strengthening exercises. In the control group, one participant dropped out because of hypotension during the control exercises.

Table 5 compares the healthy sample with the total study sample at baseline and the intervention sample at 12 weeks. At baseline for all measures, the study sample was lower functioning and statistically significantly different from the comparative sample. At 12 weeks, for strength and the 6-minute walk test, the experimental group approached normal, and differences were no longer statistically significant.

#### DISCUSSION

We have documented improvements in work output and strength resulting from a 12-week exercise program in erythropoietin-treated hemodialysis patients. In contrast to previous studies of similar interventions in dialysis patients, we used an appropriate placebo in the control group. We also report extended follow-up of participants and show that improvements made during the training period were not sustained 5 months after the end of the intervention.

The clinical significance of these improvements in strength and work output might be questioned because we did not observe concomitant changes in quality of life or symptoms. It is possible that these measures were not sufficiently sensitive to the intervention to show differences. It is also arguable that our high-functioning population was sufficiently above their threshold for functional disability that increases in strength did not greatly affect quality of life or symptoms. In lower functioning patients, improvements in exercise capacity and

strength might prevent individuals from dipping below their threshold for clinical disability.

Quality-of-life findings have not been consistently observed in studies of exercise in hemodialysis patients, even in studies in which benefit was observed in objective measures. Kouidi et al,<sup>15</sup> Tawney et al,<sup>20</sup> and Painter et al<sup>18</sup> reported parallel improvements in quality-of-life measures, whereas Ridley et al<sup>17</sup> and Fitts et al<sup>19</sup> did not. It is possible that baseline differences in disability account for these differences, with improvements in aerobic capacity and strength in those who are most disabled having the greatest impact on quality of life. Mean Physical Function scale score of the SF-36 for our sample was 76, whereas Painter et al<sup>18</sup> and Tawney et al<sup>20</sup> studied patients with mean Physical Function scale scores of approximately 49 and 54, respectively. Painter et al<sup>34</sup> reported a subgroup analysis showing that benefit was greatest in low-functioning patients. In our study, a subgroup analysis of participants with baseline SF-36 Physical Function scale scores below the 75th percentile for the sample found no clinically important or statistically significant differences between groups (data not shown), but given our small sample size, this negative finding may be caused by lack of power. However, a positive impact on quality of life for patients with higher baseline function has been reported in one study of a 5-month intervention.<sup>11</sup>

It is not surprising that a difference between groups was not found for the 6-minute walk test because as a whole, subjects at baseline were performing at 82% compared with the healthy sample. Although muscle strength of the quadriceps has been found to be related linearly to walking speed in older adults,<sup>35</sup> this younger group of individuals already may have exceeded

the muscle strength threshold to make a difference in walking speed. A stair-stepping test may have been more challenging and sensitive to the change in muscle strength in the intervention group.

Although Ridley et al<sup>17</sup> found a significant improvement in some domains related to fatigue, the two measures we used did not identify a difference. They used a 42-item scale, whereas we used only one subscale on the SF-36 and one KDQ item, which may have been less responsive to change. At all three measurement points, mean response in our sample was a feeling of low energy "some of the time." Detailed measurement of fatigue is warranted in future studies.

Patients tolerated the resistance training aspect of the program well. Based on prescribing progressive resistance from their 5-RM performance, they nearly doubled the amount of weight they were pressing by the end of the 12-week intervention. Our findings on improved muscle strength are consistent with those of Kouidi et al,<sup>15</sup> who observed increased quadriceps strength despite using only low-weight resistance exercises. No studies of isolated muscle strength training in this population have been reported; whether the strength training, aerobic training, or combination causes the observed increase in strength is not known. The resistance component of our exercise program strengthened only hamstrings and quadriceps. Studying a more extensive program of muscle strength training rigorously in hemodialysis patients would be of interest, but poses practical problems. It would be difficult to devise a progressive resisted program that could be performed while the patient is undergoing dialysis. Such a program could be completed outside dialysis time, but patients who were sufficiently motivated to participate would likely be fitter and higher functioning, limiting their potential improvement in quality of life from any such intervention.

The duration of our program (12 weeks) may have limited the effects we were able to show. Other studies<sup>15,20</sup> of 6 months' duration have shown improvements in quality of life and activities of daily living. However, in these studies, lack of an attention or placebo intervention in the control groups and positive effects of social interaction in intervention groups may have exaggerated the difference between groups. In our

sample, percentage of normal work output was found to be lower (37%) than in other studies.<sup>4</sup> This may be caused by our use of a submaximal exercise test, which enabled lower functioning individuals to participate who might have been excluded from other studies that required performance on a maximal exercise test.

We achieved only 76% follow-up at 12 weeks, similar to other studies. Dropouts were older, more disabled, and less than 4 years since starting dialysis therapy. It is possible that those more severely affected may not tolerate this kind of program. This emphasizes the importance of structuring individual patient exercise prescriptions according to baseline level of functioning.

The intervention studied, although effective, was resource intensive: a trained kinesiologist directly supervised each exercise session. Exercise coaching and rehabilitation counseling without supervision have not been shown to be effective in this population,<sup>19</sup> but patient-specific goal-oriented exercise programs with direct supervision have not been studied and warrant further research. In light of our finding that fitness and strength gains were not maintained after the end of the program, methods of enhancing participation in and long-term compliance with exercise programs also deserves formal study.

In conclusion, in a relatively high-functioning group of hemodialysis patients, aerobic and strength training resulted in large changes in exercise capacity and muscle strength. Improvement in quality of life was not evident. Five months after cessation of the program, gains in the intervention group had been lost. Further randomized controlled studies with adequate placebo intervention and blinded outcome evaluation are needed to define optimal exercise regimens that are feasible for long-term implementation in different subpopulations of hemodialysis patients.

#### APPENDIX: SYMPTOMS QUESTIONNAIRE

During the past 2 weeks, how often have you felt weak?

How often during the past 2 weeks have you felt low in energy?

How often in the past 2 weeks have you felt down in the dumps?

Response options: All of the time, Most of the

time, A good bit of the time, Some of the time, A little of the time, Hardly any of the time, None of the time.

During the past 2 weeks, how much trouble or difficulty have you had because of very little strength?

During the past 2 weeks, how much trouble or difficulty have you had running up and down two flights of stairs?

During the past 2 weeks, how much trouble or difficulty have you had with your health?

During the last 2 weeks, how much trouble or distress have you had with restless legs?

During the last 2 weeks, how much trouble or distress have you had with muscle cramps?

During the last 2 weeks, how much trouble or distress have you had with feelings of anxiety?

Response options: A very great deal of trouble or distress/difficulty, A great deal of trouble or distress/difficulty, A good deal of trouble or distress/difficulty, A moderate amount of trouble or distress/difficulty, Some trouble or distress/difficulty, Very little trouble or distress/difficulty, No trouble or distress.

Please indicate how you feel about your overall health.

Response options: Excellent, Very good, Good, Medium, Fair, Poor, Very poor.

## REFERENCES

- Chapman MM, Meyer K: Dialysis patients' Short Form 36 health survey norms by age. *J Am Soc Nephrol* 8:188A, 1997 (abstr)
- Khan IH, Garratt AM, Kumar A, et al: Patients' perception of health on renal replacement therapy: Evaluation using a new instrument. *Nephrol Dial Transplant* 10:684-689, 1995
- DeOreo PB: Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *Am J Kidney Dis* 30:204-212, 1997
- Painter P: The importance of exercise training in rehabilitation of patients with end-stage renal disease. *Am J Kidney Dis* 24:S2-S9, 1994 (suppl 1)
- Lundin AP, Akerman MJ, Chesler RM, et al: Exercise in hemodialysis patients after treatment with recombinant human erythropoietin. *Nephron* 58:315-319, 1991
- Deligiannis A, Kouidi E, Tourkantonis A: Effects of physical training on heart rate variability in patients on hemodialysis. *Am J Cardiol* 84:197-202, 1999
- Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH: Uremic myopathy limits aerobic capacity in hemodialysis patients. *Am J Kidney Dis* 22:277-287, 1993
- Kouidi E, Albani M, Natsis K, et al: The effects of exercise training on muscle atrophy in haemodialysis patients. *Nephrol Dial Transplant* 13:685-699, 1998
- Levin NW: Quality of life and hematocrit level. *Am J Kidney Dis* 20:S16-S20, 1992 (suppl 1)
- Robertson HT, Haley NR, Guthrie M, et al: Recombinant erythropoietin improves exercise capacity in anemic hemodialysis patients. *Am J Kidney Dis* 15:325-332, 1990
- Painter P, Moore G, Carlson L, et al: Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. *Am J Kidney Dis* 39:257-265, 2002
- Goldberg AP, Harter HR: Physical activity, fitness, and kidney disease, in Bouchard C, Shephard RJ, Stephens T (eds): *International Proceedings and Consensus Statement*. Champaign, IL, Human Kinetics Publishers, 1994, pp 762-773
- National Kidney Foundation: *K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease*, 2000. *Am J Kidney Dis* 37:S182-S238, 2001 (suppl 1)
- Deligiannis A, Kouidi E, Tassoulas E, Gigis P, Tourkantonis A, Coats A: Cardiac effects of exercise rehabilitation in hemodialysis patients. *Int J Cardiol* 70:253-266, 1999
- Kouidi E, Iacovides A, Iordanidis P, et al: Exercise renal rehabilitation program: Psychosocial effects. *Nephron* 77:152-158, 1997
- Akiba T, Matsui N, Shinohara S, Fujiwara H, Nomura T, Marumo F: Effects of recombinant human erythropoietin and exercise training on exercise capacity in hemodialysis patients. *Artif Organs* 19:1262-1268, 1995
- Ridley J, Hoey K: The exercise-during-hemodialysis program: Report on a pilot study. *J CANNT* 9:20-26, 1999
- Painter P, Carlson L, Carey S, Paul SM, Myll J: Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. *Am J Kidney Dis* 35:482-492, 2000
- Fitts SS, Guthrie MR, Blagg CR: Exercise coaching and rehabilitation counseling improve quality of life for predialysis and dialysis patients. *Nephron* 82:115-121, 1999
- Tawney KW, Tawney PJ, Hladik G, et al: The life readiness program: A physical rehabilitation program for patients on hemodialysis. *Am J Kidney Dis* 36:581-591, 2000
- Borg G: A category scale with ratio properties for intermodal and intraindividual comparisons, in Geissler HG, Petzold P (eds): *Psychophysical Judgment and the Process of Perceptions*. Amsterdam, The Netherlands, North-Holland Publishing Co, 1980, pp 235-242
- Demers C, McKelvie RS, Negassa A, Yusuf S, RESOLVD Pilot Study Investigators: Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. *Am Heart J* 142:698-703, 2001
- O'Keefe ST, Lye M, Donnellan C, Carmichael DN: Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart* 80:377-382, 1998
- Montgomery PS, Gardner AW: The clinical utility of a six-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc* 46:706-711, 1998
- Cahalin LP, Mather MA, Semigran MJ, Dec GW, DiSalvo TG: The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 110:325-332, 1996

26. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH: Interpreting small differences in functional status: The six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 155:1278-1282, 1997

27. Kavanagh T, Myers MG, Baigrie RS, Mertens DJ, Sawyer P, Shephard RJ: Quality of life and cardiorespiratory function in chronic heart failure: Effects of 12 months' aerobic training. *Heart* 76:42-49, 1996

28. Laupacis A, Wong C, Churchill D: The use of generic and specific quality-of-life measures in hemodialysis patients treated with erythropoietin. The Canadian Erythropoietin Study Group. *Control Clin Trials* 12:S168-S179, 1991 (suppl 4)

29. Fitts SS, Guthrie MR: Six-minute walk by people with chronic renal failure. Assessment of effort by perceived exertion. *Am J Phys Med Rehabil* 74:54-58, 1995

30. Ware JEJ: The SF-36 Health Survey, in Spilker B (ed): *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia, PA, Lippincott-Raven, 1996, pp 337-345

31. Laupacis A, Muirhead N, Keown P, Wong C: A disease specific questionnaire for assessing the quality of life in patients on hemodialysis. *Nephron* 60:302-306, 1992

32. Barany P, Freyschuss U, Pettersson E, Bergstrom J: Treatment of anaemia in haemodialysis patients with erythropoietin: Long-term effects on exercise capacity. *Clin Sci* 84:441-447, 1993

33. Ross DL, Grabeau GM, Smith S, Seymour M, Knierim N, Pitetti KH: Efficacy of exercise for end-stage renal disease patients immediately following high-efficiency hemodialysis: A pilot study. *Am J Nephrol* 9:376-383, 1989

34. Painter P, Carlson L, Carey S, Paul SM, Myll J: Low-functioning hemodialysis patients improve with exercise training. *Am J Kidney Dis* 36:600-608, 2000

35. Ferrucci L, Guralnik JM, Buchner D, et al: Departures from linearity in the relationship between measures of muscular strength and physical performance of the lower extremities: The Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci* 52:M275-M285, 1997