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Original Investigation

Effect of Exercise Training on Estimated GFR, Vascular Health, and Cardiorespiratory Fitness in Patients With CKD: A Pilot Randomized Controlled Trial

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Background: Exercise capacity, which is predictive of all-cause mortality and cardiovascular disease risk, is reduced significantly in patients with non–dialysis-dependent chronic kidney disease. This pilot study examined the effect of moderate-intensity exercise training on kidney function and indexes of cardiovascular risk in patients with progressive chronic kidney disease stages 3 to 4.

Study Design: Single-blind, randomized, controlled, parallel trial.

Setting & Participants: 20 patients (aged 18-80 years; 17 men) randomly assigned to rehabilitation (n = 10) or usual care (n = 10). Participants were included if they were 18 years or older and had evidence of rate of decline in creatinine-based estimated glomerular filtration rate ($eGFR_{cr}$) ≥ 2.9 mL/min/1.73 m^2 per year for 12 months preintervention. Patients were excluded if they had unstable medical conditions or had recently started regular exercise.

Intervention: The rehabilitation group received resistance and aerobic training (3 days per week) for a 12-month period. The usual care group received standard care.

Outcomes: Kidney function assessed by comparing mean rate of change in $eGFR_{cr}$ (mL/min/1.73 m^2 per year) from a 12-month preintervention period against the 12-month intervention period. Pulse wave velocity (PWV), peak oxygen uptake (Vo_{2peak}), and waist circumference assessed at 0, 6, and 12 months.

Measurements: eGFR assessed using creatinine, cystatin C ($eGFR_{cys}$), and a combination of both values ($eGFR_{cr\text{-}cys}$).

Results: 18 participants (rehabilitation, 8; usual care, 10) completed the study. A significant mean difference in rate of change in $eGFR_{cr}$ (+7.8 ± 3.0 [95% CI, 1.1-13.5] mL/min/1.73 m^2 per year; $P = 0.02$) was observed between the rehabilitation and usual care groups, with the rehabilitation group demonstrating a slower decline. No significant between-group mean differences existed in absolute $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, or $eGFR_{cys}$ at 12 months of study intervention. Significant between-group mean differences existed in PWV (−2.30 [95% CI, −3.02 to −1.59] m/s), waist circumference (−7.1 ± 12.8 [95% CI, −12.4 to −3.2] cm), and Vo_{2peak} (5.7 [95% CI, 1.34-10.10] mL/kg/min). Change in $eGFR_{cr}$ was correlated inversely with PWV ($r = -0.5$; $P = 0.04$) at 12 months.

Limitations: Small sample size, inconsistency between primary and secondary measures of kidney function.

Conclusions: The effect of a 1-year exercise intervention on progression of kidney disease is inconclusive. A larger study with longer follow-up may be necessary.

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INDEX WORDS: Rehabilitation; Vo_{2peak}; pulse wave velocity (PWV); cardiovascular risk; physical activity; chronic kidney disease (CKD); exercise; end-stage renal failure; arterial stiffness; cardio-respiratory fitness; kidney disease trajectory; estimated glomerular filtration rate (eGFR).

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD) regardless of whether progression to chronic kidney failure occurs.[1-3] Exercise capacity, which is predictive of all-cause mortality and CVD risk,[4-6] is reduced significantly in CKD.[7] Observational research suggests an association between higher physical activity levels and slower rate of estimated glomerular filtration rate (eGFR) loss in patients with CKD stages 3 and 4.[8] Experimental interventions to improve cardiovascular risk factors or kidney function by increasing exercise capacity in patients

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with non–dialysis-dependent CKD have not been successful despite improved physical function.[9-15] However, studies with animal models in CKD demonstrate that long-term exercise training may preserve kidney function.[16] Recent studies also have demonstrated an improvement in kidney function, measured as a secondary outcome, in human participants.[17-19] Exercise training has the potential to favorably modify indexes of arterial stiffness in hemodialysis patients[10,20] and patients with non–dialysis-dependent CKD,[14] and regular aerobic exercise has been reported to induce numerous positive effects on endothelial function in healthy asymptomatic people,[21] as well as in those with evident cardiometabolic disease pathology.[22] Exercise training has the potential to increase kidney function as a result of a reduction in abdominal visceral fat,[18] which has been shown to be associated with cardiovascular risk factors.[23,24]

The mechanisms associated with the potential improvement, or amelioration in the decline, of kidney function in patients with non–dialysis-dependent CKD as a result of exercise training remains unclear and further investigation in this area is warranted. Hence, this current feasibility pilot study was designed to explore the effects of long-term individually structured pragmatic exercise training and physical behavioral modification on mean rate of change in creatinine-based eGFR ($eGFR_{cr}$) and indexes of cardiovascular function. Access to safe exercise facilities and patient convenience influenced choice of the exercise component used in the rehabilitation intervention. Patients with progressive CKD, rather than stable CKD, were chosen so that the influence of the rehabilitation program on the rate of progression could be studied within the study time frame.

METHODS

Participants

Participants were identified from a renal patient database and approached during predialysis clinics or by telephone. They were included if they were 18 years or older, were patients with CKD stages 3 to 4 (GFR, 20-60 mL/min/1.73 m^2), and had evidence of progressive decline in kidney function (≥2.9 mL/min/1.73 m^2 per year in the 12 months prior to the study start date). Patients were excluded if they were pregnant, required support for ambulation for a distance < 50 m, had unstable medical conditions (eg, uncontrolled hypertension [blood pressure > 160/100 mm Hg], congestive heart failure, active myocarditis/pericarditis, or cardiac arrhythmias), had participated in structured exercise programs within the prior 6 months, or had comorbid catabolic conditions, a known neuromuscular disorder, uncontrolled diabetes, severe orthopedic conditions, psychiatric illnesses (including anxiety and untreated eating disorder), or infection or course of antibiotics within the prior month.

Study Procedure

Ethics committee approval was granted by the South West London Ethics Committee (11/LO/0154). Eligible patients were provided with patient information sheets. Following a 2-week period, patients were contacted to see if they were willing to take part. Interested patients were consented and baseline assessments were conducted before a member of the rehabilitation team randomly assigned patients (using a computerized randomization procedure produced by lead investigator) to either rehabilitation or usual care. A researcher blinded to patient group allocation conducted all assessments and patients were asked not to reveal their group allocation (Fig 1).

Patients attended King's College Hospital Renal Department for 0-, 6-, and 12-month assessments. These were early-morning appointments after an overnight fast. Data collection included blood, urine, anthropometrics, blood pressure, heart rate, pulse wave velocity (PWV), and peak oxygen uptake (Vo_{2peak}). All assessments were performed during the same visit.

Primary Outcome: Kidney Function

$eGFR_{cr}$ (milliliters per minute per 1.73 m^2) was calculated using the 2009 CKD-EPI (CKD Epidemiology Collaboration) creatinine equation[25] with serum creatinine level, age, ethnicity, and sex. Mean rate of change in $eGFR_{cr}$ (milliliters per minute per 1.73 m^2 per year) then was calculated for each participant for the 12-month preintervention and 12-month intervention periods. The difference in mean rate of change in $eGFR_{cr}$ (milliliters per minute per 1.73 m^2 per year) between the preintervention and intervention 12-month periods then was calculated for the rehabilitation and usual care groups.

Secondary Outcomes

Kidney Function

Because cystatin C was measured during the intervention period, absolute eGFR (milliliters per minute per 1.73 m^2) values were calculated using the 2012 CKD-EPI cystatin C ($eGFR_{cys}$) and CKD-EPI creatinine–cystatin C ($eGFR_{cr\text{-}cys}$) equations for the 0-, 6-, and 12-month time points of the intervention period.

Cardiorespiratory Fitness

Vo_{2peak} was determined during an incremental recumbent cycling exercise tolerance protocol. Breath-by-breath gas exchange was measured using the MetaLyzer 3B cardiopulmonary exercise testing system (Cortex) calibrated prior to each patient assessment. The exercise protocol started from a 3-minute unloaded cycle and increased by 15 W/min until one of the following occurred: (1) a plateau in oxygen uptake, (2) attainment of a respiratory exchange ratio of 1.15 or greater, or (3) the patient request to stop. Average oxygen uptake of the final 20 seconds of the test was recorded as Vo_{2peak}. Electrocardiogram monitoring, blood pressure, and heart rate were recorded continuously throughout the incremental test.

Pulse Wave Velocity

PWV was measured using the Vicorder system (Skidmore Medical Ltd) at 0, 6, and 12 months. Arterial stiffness was assessed at the systemic region (carotid-femoral PWV), the gold-standard method.[26] Conditions for assessment, as stated by expert consensus statement by Laurent et al,[26] were adhered to for measurements. The measurement protocol by Hickson et al[27] was used, mathematically removing an additional femoral segment from the Vicorder standard protocol, to correct for any inherent bias at high arterial PWV. An average of 3 measurements (of 20 consecutive signals) was recorded at each time point.

Anthropometric Measures

Waist circumference was measured with a cloth medical tape measure horizontally at the umbilicus by the same investigator. Body weight was recorded, and height was measured using a calibrated stadiometer.

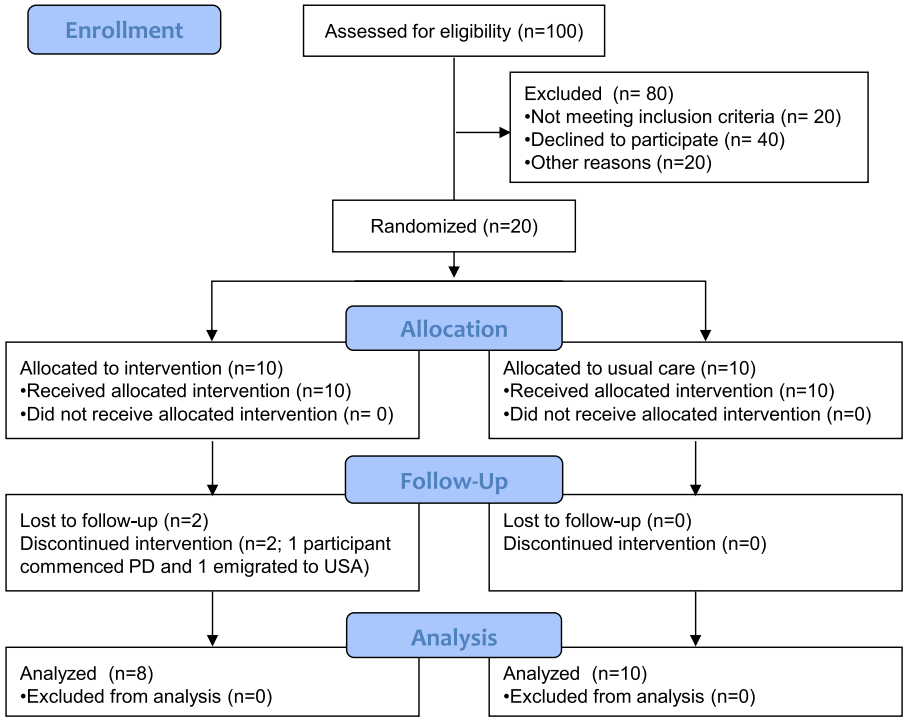

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. Abbreviations: PD, peritoneal dialysis; USA, United States of America.

Blood Tests

Venous blood was collected after an overnight fast at each time during the intervention. Serum creatinine (traceable to a calibrator tested with a reference method [isotope-dilution mass spectrometry), cystatin C (traceable to international reference preparation ERM-DA471), lipids profile, hemoglobin A1c, and high-sensitivity C-reactive protein were analyzed in the biochemistry department at King's College Hospital.

Blood Pressure and Heart Rate at Rest

After sitting quietly for 5 minutes, blood pressure and heart rate at rest were recorded in triplicate, with a 1-minute interval between measurements, using an automated sphygmomanometer (Tango; SunTech Medical). The average of 3 recordings is reported.

Exercise Intervention

Patients in the rehabilitation group were inducted into a gymnasium setting in a community hospital and an individualized program was developed taking into account patient choice and aiming for a combination of aerobic and resistance exercises. Aerobic exercise was performed predominantly on recumbent stationary exercise cycles at an intensity corresponding to 80% heart rate reserve, with maximum heart rate as derived from incremental exercise testing. Patients wore heart rate monitors and were asked to modulate resistance on bikes to keep heart rate close to the defined target range. Patients were shown how to use the rate of perceived exertion (RPE) scale[28] as a visual aid to assist with progression and were asked to rate perception of effort at the prescribed exercise intensity. Exercise wattage was increased upon patients reporting a consistent reduction in RPE of 1 unit. Patients participated in a warm up and cool down of a minimum of 5 minutes on stationary exercise cycles, RPE of approximately 11, followed by gentle stretching. Patients worked toward two 20-minute sessions and eventually one 40-minute session 3 times per week (twice supervised; once as a home exercise program). Resistance training was prescribed at 80% of 1 repetition maximum, the maximum amount of weight an individual can lift or press once but not twice,[29] for a variety of upper- and lower-body muscle groups (eg, bench press, latissimus pull-down, bicep curl, triceps pull-down, leg press, knee extension, hamstring curl, and calf raises). Patients were instructed to use a starting point of 1 to 2 sets × 10 repetitions (based on 80% one-repetition maximum and tolerance) with the aim to progressively increase to 3 sets and 8 to 10 repetitions. One repetition maximum was reassessed monthly, and the program was adjusted accordingly. Patients attended free supervised structured exercise classes twice per week for 12 months and were provided with a static cycle, Theraband (The Hygenic Corp), and free weights for home exercise once per week for 12 months.

Patients in the rehabilitation group met with a senior renal physiotherapist for an additional 40-minute individual session at baseline, at which both exercise and personal goals were discussed using motivational interviewing.[30] Each patient completed an exercise diary after each home exercise session to maintain motivation and assess adherence. Patients were telephoned weekly to encourage self-managed exercise at home and assess RPE.

Usual Care Group

The usual care group was seen in the nephrology clinic but not referred for exercise rehabilitation or exercise advice because this is not offered as part of usual care for this patient population. They were assessed at 0, 6, and 12 months.

Power Analyses

Using a 2-group *t* test with a 0.05 two-sided significance level, a sample size of 11 in each group will have 80% power to detect a difference in $eGFR_{cr}$ slope mean values of 10.63 mL/min/1.73 m^2 per year assuming that the common standard deviation is 8.4. Adjusting this for the analysis of covariance (ANCOVA) under an assumed pre-post correlation of approximately 0.6 yields an

overall target sample size of 16. Inflating this for an estimated attrition rate of 25%, we aimed to recruit 20 participants.

Statistical Analyses

Data are presented as mean ± standard deviation. Individual rate of change in $eGFR_{cr}$ (milliliters per minute per 1.73 m^2 per year) was calculated for each participant for the 12-month pre-intervention and 12-month intervention phases using linear regression. ANCOVA analyses with mean pre 12-month slope as covariate and post 12-month slope as dependent variable were used to test for between-group differences in mean rate of change in $eGFR_{cr}$. ANCOVA analyses with baseline value (0 months) of intervention period as covariate were used to assess for between-group mean differences at 12 months for all secondary outcomes. Paired *t* tests on change scores with Bonferroni correction were used to compare within-group changes over time. Pearson correlations were performed between change in main outcome measure and change scores of other secondary outcome measures. All tests were 2 sided and assessed at the $P < 0.05$ level of significance. SPSS, version 20 (SPSS Inc), with PASW (Predictive Analytics SoftWare) was used for all analyses.

RESULTS

Participants

Eighteen participants completed the study. Two participants from the rehabilitation group dropped out before the 6-month study visit (1 started peritoneal dialysis therapy and 1 emigrated to the United States). Consequently, we were able to analyze data from 8 participants (6 men) in the rehabilitation group and 10 participants (9 men) from the usual care group (Fig 1). Participant demographic and clinical characteristics are described in Table 1. Participant adherence to the program, defined as total number of exercise sessions (including home-based sessions) completed as proportion of total possible number of sessions (147 sessions) during the 12-month period, was 79.2% ± 13.2%. There were no reported adverse events, cardiovascular events, or hospitalizations as a result of the intervention.

Primary Outcome

Mean change in $eGFR_{cr}$ was −9.7 ± 7.2 mL/min/1.73 m^2 per year in the 12-month preintervention period and −3.8 ± 2.8 mL/min/1.73 m^2 per year in the 12-month intervention period in the rehabilitation group. During the same period, the usual care group had a change from −6.6 ± 4.7 to −8.5 ± 6.4 mL/min/1.73 m^2 per year (Table 2). By the end of the 12-month exercise intervention period, mean difference in $eGFR_{cr}$ change slopes between the rehabilitation and usual care groups was statistically significant (+7.8 ± 3.0 [95% confidence interval (CI), 1.1-13.5] mL/min/1.73 m^2 per year; $P = 0.02$; Table 2).

Secondary Outcomes

ANCOVA analyses with baseline value (0 months) of the intervention period as covariate revealed no significant between-group mean differences in absolute eGFRs at 12 months for any of the 3 different equations ($eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$) used (Table 3; Figs 2 and 3D and E). A significant mean difference in PWV (−2.3; 95% CI, −3.02 to −1.59 m/s; $P < 0.001$) was observed between the rehabilitation and usual care groups at the 12-month post-intervention period (Fig 3A). There was a significant correlation between mean rate of change in $eGFR_{cr}$ and change in PWV following the intervention ($r = -0.5$; $P = 0.04$). Significant mean differences between the rehabilitation and usual care groups at 12

Table 1. Baseline Demographics, Causes of Kidney Disease, and Medication Use of Randomly Assigned Participants

Variable	Rehab (n = 8)	Usual Care (n = 10)	*P*
Age	53.8 ± 13.5	53.3 ± 12.9	0.9
Male sex	6 (75)	9 (90)	0.4
Ethnicity			0.7
White	4 (50)	2 (20)	
Black	3 (37)	7 (70)	
Asian	1 (13)	1 (10)	
$eGFR_{cr}$ (mL/min/1.73 m^2)	36.6 ± 10.1	46.5 ± 20.6	0.2
$eGFR_{cys}$ (mL/min/1.73 m^2)	45.6 ± 14.0	48.4 ± 26.1	0.1
$eGFR_{cr\text{-}cys}$ (mL/min/1.73 m^2)	40.1 ± 11.6	46.7 ± 19.6	0.4
Serum creatinine (μmol)	184.3 ± 42.9	175.5 ± 58.3	0.7
Cystatin C (mg/L)	1.6 ± 0.3	1.6 ± 0.6	0.8
Kidney disease cause			
Diabetic nephropathy	0 (0)	2 (20)	0.2
Hypertensive nephrosclerosis	3 (36)	4 (40)	0.9
IgA nephropathy	0 (0)	1 (10)	0.4
Tubulointerstitial nephritis	0 (0)	1 (10)	0.4
Polycystic kidney disease	1 (13)	0 (0)	0.3
Obstructive nephropathy	1 (13)	0 (0)	0.3
Medullary sponge kidney disease	1 (13)	0 (0)	0.3
Unknown	2 (25)	2 (20)	0.8
Medications			
ARB	5 (63)	6 (60)	0.8
ACE inhibitor	5 (63)	4 (40)	0.6
β-Blocker	1 (13)	3 (30)	0.2
α-Blocker	2 (25)	4 (40)	0.3
Diuretic	4 (50)	5 (50)	0.7
Insulin	0 (0)	1 (10)	0.4
Statin	2 (25)	3 (30)	0.8
Oral antidiabetic	0 (0)	1 (10)	0.4
Anticoagulant therapy	0 (0)	1 (10)	0.4
Antiarrhythmic therapy	0 (0)	1 (10)	0.4

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation. There were no significant ($P < 0.05$) differences between groups for any baseline parameters.

Abbreviations and definitions: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$, estimated glomerular filtration rates calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine, creatinine–cystatin C, and cystatin C equations, respectively; Rehab, rehabilitation.

Table 2. Result of ANCOVA to Test for Differences in Mean $eGFR_{cr}$ Rate-of-Change Slope From Preintervention and Intervention 12-Month Periods

	Rehab (n = 8)		Usual Care (n = 10)		Between-Group Differences ANCOVA		
Factor	Preintervention	Postintervention	Preintervention	Postintervention	Mean ± SD	*F*	*P*
$eGFR_{cr}$ (mL/min/1.73 m^2 per y)	−9.7 ± 7.2	−3.8 ± 2.8	−6.6 ± 4.7	−8.5 ± 6.4	+7.8 ± 3.0	6.3	0.02

Note: $eGFR_{cr}$ values are given as mean ± standard deviation.

Abbreviations: ANCOVA, analysis of covariance; $eGFR_{cr}$, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation; Rehab, rehabilitation; SD, standard deviation.

months were observed for body mass index (−3.3 [95% CI, −5.66 to −0.89] kg/m^2; $P = 0.01$), weight (−5.6 [95% CI, −10.1 to −1.2] kg; $P = 0.02$), and waist circumference (−7.1 [95% CI, −12.44 to −3.17] cm; $P = 0.003$; Fig 3C). Change in waist circumference was associated significantly with mean rate of change in $eGFR_{cr}$ ($r = -0.6$; $P = 0.004$) following the intervention. An observed significant mean difference in relative Vo_{2peak} of 5.7 [95% CI, 1.34-10.10] mL/kg/min ($P = 0.01$; Fig 3B) and a nonsignificant mean difference in absolute Vo_{2peak} of 0.3 (95% CI, −0.1 to 0.6) L/min ($P = 0.2$) was shown when comparing the rehabilitation and usual care groups at 12 months. The intervention had no

Table 3. Effect of the 12-Month Exercise Intervention on Associated Clinical Outcomes

	Baseline		6 mo		12 mo		12-mo ANCOVAs		
Variable	Rehab	Usual Care	Rehab	Usual Care	Rehab	Usual Care	Between-Group Differences	*F*	*P*
$eGFR_{cr}$	36.6 ± 10.1	46.5 ± 20.6	36.9 ± 13.8	44.5 ± 20.9	40.3 ± 18.7[a]	41.7 ± 18.2	+7.3 ± 5.2	2.0	0.2
$eGFR_{cys}$	45.6 ± 14.0	48.4 ± 26.1	46.8 ± 19.2	48.2 ± 24.6	47.3 ± 19.3	46.3 ± 20.1	+1.1 ± 4.7	0.6	0.08
$eGFR_{cr\text{-}cys}$	40.1 ± 11.6	46.7 ± 19.6	40.8 ± 15.7	44.1 ± 18.4	42.4 ± 18.4	43.5 ± 15.9	+2.9 ± 4.7	0.38	0.5
Scr (μmol)	184.3 ± 42.9	175.5 ± 58.3	191.0 ± 56.0	187.3 ± 72.4	187.3 ± 61.6	203.6 ± 100.5	−28.0 ± 24.8	1.27	0.3
Scys (mg/L)	1.6 ± 0.3	1.6 ± 0.6	1.6 ± 0.4	1.7 ± 0.6	1.4 ± 0.8	1.6 ± 0.4	+0.3 ± 0.2	1.46	0.2
PWV (m/s)	9.5 ± 2.2	8.1 ± 2.4	8.7 ± 1.7[a]	8.2 ± 2.1	7.9 ± 2.0[a]	9.1 ± 2.0[a]	−2.3 ± 0.3	47.1	0.001
Vo_{2peak} (L/min)	1.5 ± 0.6	1.5 ± 0.4	1.6 ± 0.5	1.4 ± 0.4	1.7 ± 0.5	1.4 ± 0.5	+0.3 ± 0.2	2.2	0.2
Vo_{2peak} (mL/kg/min)	20.1 ± 5.8	18.3 ± 4.6	20.9 ± 5.7	16.1 ± 4.0[a]	23.0 ± 5.3[a]	16.2 ± 5.0	+5.7 ± 2.1	7.8	0.01
Body weight (kg)	76.5 ± 15.2	83.6 ± 12.3	75.5 ± 16.3	84.5 ± 12.7	72.9 ± 16.1	85.6 ± 12.7	−5.6 ± 12.1	7.33	0.02
BMI (kg/m^2)	27.40 ± 3.52	28.44 ± 4.24	25.85 ± 3.83[a]	28.78 ± 4.42	24.91 ± 3.47[a]	29.00 ± 4.09	−3.3 ± 1.4	7.61	0.01
Waist girth (cm)	94.6 ± 11.8	97.1 ± 10.2	91.0 ± 9.1[a]	98.0 ± 9.0	89.5 ± 8.8[a]	99.2 ± 9.8[a]	−7.1 ± 12.8	12.86	0.003
Heart rate (beats/min)[b]	70.9 ± 14.3	73.2 ± 15.8	77.7 ± 14.9	74.2 ± 11.9	73.8 ± 13.2	73.8 ± 16.9	+1.6 ± 5.5	0.93	0.8
SBP (mm Hg)[b]	135.8 ± 17.4	134.3 ± 20.7	131.3 ± 10.9	132.3 ± 23.2	133.2 ± 14.6	127.1 ± 17.0	+5.1 ± 4.1	1.51	0.2
DBP (mm Hg)[b]	86.5 ± 15.8	86.5 ± 12.7	85.5 ± 10.6	85.5 ± 13.3	84.4 ± 14.7	78.9 ± 6.9	+5.4 ± 2.8	3.65	0.07
CRP (mg/L)	2.0 [5.0]	1.5 [2]	2.0 [3.7]	2.0 [3.7]	3.0 [3.7]	1.5 [5.5]	−1.3 ± 1.3	1.06	0.3
Cholesterol									
Total (mg/dL)	5.0 ± 0.5	4.7 ± 1.6	4.8 ± 0.5	4.8 ± 1.7	5.0 ± 0.9	4.3 ± 1.2	+0.6 ± 0.4	1.64	0.2
LDL (mg/dL)	3.1 ± 0.8	2.6 ± 1.2	2.6 ± 0.7	2.7 ± 1.3	3.3 ± 3.5	2.5 ± 0.9	+0.5 ± 0.3	2.62	0.1
HDL (mg/dL)	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	1.5 ± 0.5	1.1 ± 0.6	+0.4 ± 0.2	3.0	0.1

Note: Rehab group, n = 8; Usual Care group, n = 10. Values are given as mean ± standard deviation or median [interquartile range]. eGFRs expressed as mL/min/1.73 m^2.

Abbreviations and definitions: ANCOVA, analysis of covariance; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$, estimated glomerular filtration rates calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine, creatinine–cystatin C, and cystatin C equations, respectively; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Vo_{2peak}, peak oxygen uptake; PWV, pulse wave velocity; Rehab, rehabilitation; SBP, systolic blood pressure; Scr, serum creatinine; Scys, serum cystatin C.

[a] $P < 0.05$ indicates significant within-group differences in outcome measures from baseline to that time.

[b] At rest.

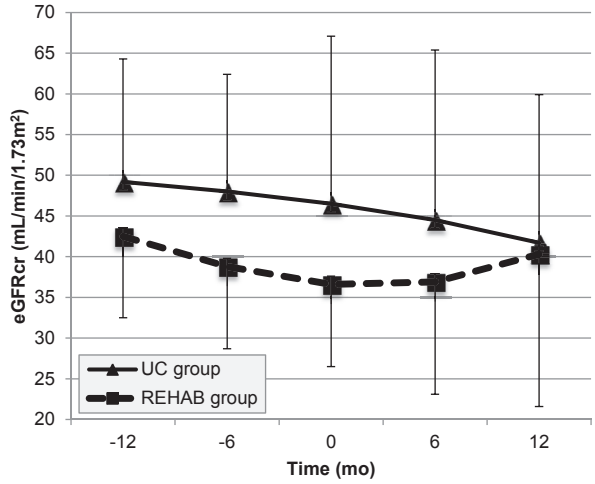

Figure 2. Mean change in creatinine-based estimated glomerular filtration rate ($eGFR_{cr}$) (mL/min/1.73 m^2) comparing the usual care (UC) group with the rehabilitation (REHAB) group for the 12-month period prior to the start of the intervention (−12 to 0 months) and the intervention period (0 to 12 months). The intervention was associated with a significant mean difference in $eGFR_{cr}$ (mL/min/1.73 m^2) (*$P = 0.03$) at 12 months postintervention compared to −12 months of the preintervention period.

significant effect on blood pressure at rest, heart rate, high-sensitivity C-reactive protein level, or lipid levels (Table 3).

DISCUSSION

Our study suggests that 12 months of regular exercise training may be able to retard the progressive deterioration in kidney function of people with CKD stages 3 to 4. Furthermore, regular exercise training was associated with favorable changes in other parameters closely associated with CVD risk (PWV, $V_{O_{2peak}}$, and waist circumference) in people with CKD. This finding is consistent with results published by Toyama et al[17] and Baria et al,[18] who demonstrated a statistically significant improvement in eGFRs in participants who followed an endurance training program.

Other exercise and physical activity studies[9-14] have shown no discernible change in eGFRs between the exercise and control groups; however, the relatively short duration of exercise interventions, as well as small sample sizes, combined with inherent large variability in CKD progression may be responsible for the lack of systematic and consistent effects. Moreover, the total volume of exercise of the various exercise interventions may not have been sufficient to produce significant effects over short periods.[15]

The fact that our study focused on participants with progressive CKD stages 3 to 4, itself associated independently with increased risk of CVD and all-cause mortality,[31] rather than those with more stable kidney function, may have allowed us to demonstrate the potential benefit of exercise on rate of change in $eGFR_{cr}$ and CVD risk factors, in contrast to previous studies.[9,12,13] Although our study has similar limitations, such as small sample size, small exercise dose, and variability in responses, we should emphasize that the aim was to encourage, support, and educate patients to alter their lifestyles to be more physically active and meet current minimum physical activity guidelines[32] for health benefits (150 min/wk of moderate-intensity exercise). We thought that this pragmatic approach may be feasible and deliverable within National Health Service settings while assessing the impact of such a therapeutic intervention on important clinical outcomes.

The primary observations about kidney function are based on rate of change in $eGFR_{cr}$ data across a 24-month period. The secondary outcomes investigate between-group mean differences in absolute eGFRs at the end of the intervention, with the addition of cystatin C level. Although all 3 eGFR equations (yielding $eGFR_{cr}$, $eGFR_{cr\text{-}cys}$, and $eGFR_{cys}$) showed an increase in eGFRs in the rehabilitation group between 0 and 12 months of the intervention (Figs 2 and 3D and E), between-group analysis did not reveal a significant mean difference in these values at the 12-month point. The inconsistency between these results is a limitation of this study and as such, it is suggested that observations about kidney function and exercise therapy be interpreted with caution. Further studies that assess rate of change in eGFR using $eGFR_{cys}$ and $eGFR_{cr\text{-}cys}$ across the same period (24 months) in a larger sample size may yield more conclusive evidence about the renoprotective role of exercise therapy in patients with progressive CKD. The variation seen among the $eGFR_{cr}$, $eGFR_{cys}$, and $eGFR_{cr\text{-}cys}$ equations is likely to be as a result of the relationship between creatinine and muscle mass, which is not likely to be evident with cystatin C.

The correlation of mean rate of change in $eGFR_{cr}$ with change in mean PWV at 12 months is consistent with previously reported links between kidney function and vascular health.[3] Padilla et al[33] suggest that exercise could induce vascular conditioning and local vascular adaptations of the splanchnic and renal vasculatures. The role of hemodynamic forces (ie, shear stress and cyclic strain) and circulating factors discharged from adipose tissue (ie, leptin) and skeletal muscle (ie, interleukin 6) probably are indicators responsible for exercise-induced endothelial adaptations in kidney microvasculature. It is postulated that augmented cardiac output and mean arterial pressure during exercise, along with visceral vasoconstriction, might bring about increases in shear stress notwithstanding the reduction in blood flow to the kidneys during acute exercise.[34] Therefore, the signal for long-term adaptations might be repetitive periods

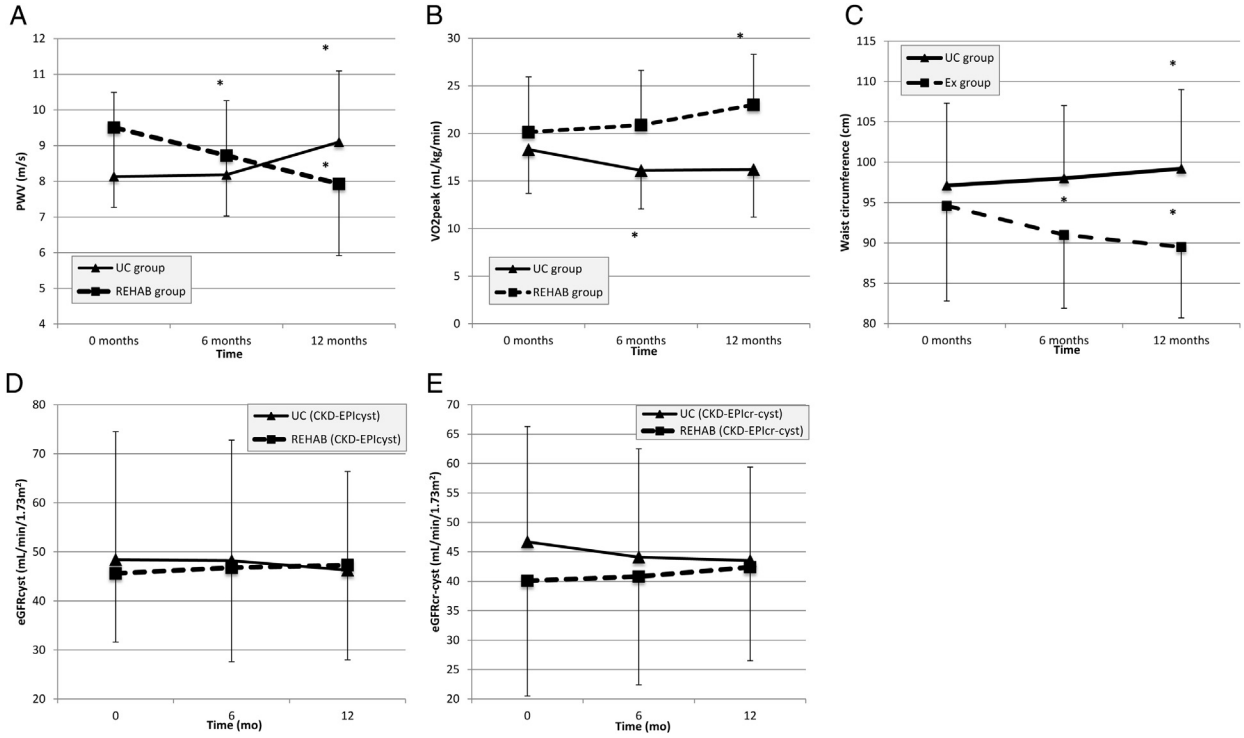

Figure 3. (A) Mean change in pulse wave velocity (PWV) between the rehabilitation (REHAB) and Usual Care (UC) groups from 0 to 6 months and from 0 to 12 months of the intervention period. There was a significant increase in PWV at 6 and 12 months ($^*P < 0.05$) in the REHAB group and a significant increase in PWV at 12 months ($^*P < 0.05$) in the UC group. (B) Mean change in peak oxygen uptake (Vo_{2peak}) between the REHAB and UC groups from 0 to 6 months and from 0 to 12 months of the intervention period. There was a significant improvement in Vo_{2peak} at 12 months ($^*P < 0.05$) in the REHAB group and a significant reduction at 6 months ($^*P < 0.05$) in the UC group. (C) Mean change in waist circumference between the REHAB and UC groups from 0 to 6 months and from 0 to 12 months of the intervention period. There was a significant reduction in waist circumference at 6 and 12 months ($^*P < 0.05$) in the REHAB group and a significant increase at 12 months ($^*P < 0.05$) in the UC group. (D) Mean change in cystatin C–based estimated glomerular filtration rate ($eGFR_{cys}$) comparing the UC group with the REHAB group during the study period (0-12 months). (E) Mean change in creatinine and cystatin C–based eGFR ($eGFR_{cr\text{-}cys}$) comparing the UC group with the REHAB group during the study period (0-12 months).

of increased shear stress during acute exercise. In addition, as a result of training and weight/fat loss, local sympathoinhibitory mechanisms may have been enhanced, influencing renal vascular function and structure.[33]

The exercise prescription was designed to exercise major muscle groups, which may have induced systemic vascular effects such as structural (angiogenesis and remodeling) and functional (involving phenotypic alterations of vascular smooth muscle and endothelial cells) adaptations.[33] These systemic and localized vascular adaptations potentially could have influenced the amelioration in residual kidney function decline in our study, as assessed using rate of change in $eGFR_{cr}$.

Mean change in waist circumference observed between groups at 12 months was associated with mean rate of change in $eGFR_{cr}$. This finding is in agreement with the study by Baria et al,[18] which demonstrated a significant reduction in visceral fat and waist circumference in patients with CKD following a 12-week supervised aerobic exercise intervention, accompanied by improvement in eGFR. Obesity has been identified as an independent risk factor for the development and progression of CKD.[35,36] A significant association between central adiposity and CVD risk has been reported in published studies.[36,37] Observations of a significant inverse relationship between rate of change in $eGFR_{cr}$ and waist circumference change suggest that ~36% of the improvement noted in rate of change in $eGFR_{cr}$ could be explained by reductions in waist circumference and perhaps associated central adiposity. The moderate weight loss observed in the rehabilitation group was associated with an improvement in rate of change in $eGFR_{cr}$ and PWV and possibly was augmented by the exercise intervention.[38] The patients in this study did not receive dietary intervention and no record was made of dietary intake, so we are unable to tell whether the resulting decrease in weight and waist circumference is due purely to the exercise intervention or the exercise intervention encouraged a more self-efficacious approach to other areas of lifestyle management.

A large proportion of mortality in CKD is attributed to CVD, and interventions that positively affect this risk are warranted. Increased vascular stiffness, measured with aortic PWV index, by 1 m/s has been associated with a 14% increase in both cardiovascular and overall mortality risk in hemodialysis patients.[39] The significant improvement in PWV of 1.58 ± 0.87 m/s, although not corrected for age, blood pressure, heart rate, and sex, observed in our study may equate to reductions in longer-term cardiovascular risk and all-cause mortality. The carotid-femoral PWV increases early in the development of CKD and shows progression with deterioration in kidney function.[40] The observed improvements in PWV support findings by Toussaint et al[41] and possibly may be mediated by lower levels of vascular calcification in these patients with CKD stages 3 to 4.

Studies have identified low self-reported physical activity and fitness as prognostically important for CVD and all-cause mortality in patients with CKD stages 2 to 4.[42,43] In our study, the significant increase in mean relative Vo_{2peak} of ~3 mL/min/kg in the rehabilitation group compared to the usual care group suggests improvements in cardiometabolic efficiency to support high levels of physical stress. However, because absolute Vo_{2peak} did not change in the rehabilitation group (Table 3), it is likely that change in relative Vo_{2peak} is driven mainly by changes in body mass. These data should be viewed in context with nonfavorable observations in the usual care group that showed a 2.1-mL/kg/min decline in cardiorespiratory fitness and no change in body mass. This level of decline in cardiovascular fitness over the 12-month period to reach 16.2 ± 5.0 mL/kg/min is worrying. Sietsema et al[44] suggested an increased risk of all-cause mortality in the 5 years after dialysis therapy initiation for patients with CKD with Vo_{2peak} < 17.5 mL/kg/min at the time they initiated long-term dialysis therapy. Therefore, the potential of rehabilitation interventions such as that presented here may have a significant clinical therapeutic benefit for patients with progressive CKD.

The unusually low dropout rate in the rehabilitation group and the high adherence to the exercise training program, despite the length of the trial, may be attributed to the individually tailored exercise prescription, use of motivational interviewing to enable a patient-centred approach, and the supportive environment of a renal exercise rehabilitation team. This environment and expertise should be considered when designing exercise-related studies in a patient population in which dropout rates are high.

Because this was a pilot study, the sample size is small and results must be interpreted with caution. There was no measure of endothelial function in our pilot study. The link between exercise-induced alterations in endothelial function driving improved kidney function, although plausible, is still speculative at this stage. This pilot study also did not include a measure of vascular calcification for the patients at study entry, which is a limitation when speculating about mechanisms of improvement in PWV. Due to small numbers of female participants in the study, results may not be applicable to female patients with CKD. The lack of assessment of dietary changes is an additional limitation of this study.

This pilot study evaluated the effect of long-term tailored exercise prescription with motivational interviewing compared with usual care in patients with progressive CKD stages 3 to 4. Participants randomly assigned to the intervention exhibited significant improvements in rate of change in $eGFR_{cr}$, PWV, Vo_{2peak}, and waist circumference compared to usual care. Although the question of the benefits of exercise therapy on progression of CKD remains uncertain, the intervention appears to be a feasible approach for rehabilitation in this patient population. Further large randomized controlled trials therefore are warranted to answer this question. The observations on relationships between change in PWV, waist circumference, and rate of change in $eGFR_{cr}$ data suggest that target weight loss initiatives may be an appropriate intervention to develop.

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