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Randomized Controlled Trial of Exercise in CKD—The RENEXC Study

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Introduction: Home-based, clinically feasible trials in non–dialysis-dependent patients with chronic kidney disease (CKD) are sparse. We compared the effects of 2 different exercise training programs on physical performance, and measured glomerular filtration rate (mGFR) and albuminuria level in patients with CKD stages 3 to 5.

Methods: This is a single-center, randomized controlled trial (RCT) comprising 151 patients (mGFR: 22 $\pm$ 8 ml/min per 1.73 m^2; age 66 $\pm$ 14 years) randomized to either balance or strength training. Both groups were prescribed 30 minutes of exercise per day for 5 days per week for 12 months, comprising 60 minutes per week of endurance training and 90 minutes per week of either strength or balance exercises. The exercises were individually prescribed, and the intensity was monitored with Borg's rating of perceived exertion (RPE).

Results: There were no treatment differences for any of the primary outcomes measuring physical performance. The strength and balance groups showed significantly increased effect sizes after 12 months for the following: walking (31 m and 24 m, $P < 0.001$) and the 30-second sit-to-stand test (both: 1 time, $P < 0.001$); quadriceps strength (right/left: strength 1.2/0.8 kg*m, $P < 0.003$; balance 0.6/0.9, $P < 0.01$); functional reach (both: 2 cm, $P < 0.01$); and fine motor skills (open/closed eyes, right/left, both: between 0.3 and 4 seconds faster, $P < 0.05$). After 12 months, there was a significant treatment difference for albuminuria ($P < 0.02$), which decreased by 33% in the strength group. In both groups, mGFR declined by 1.8 ml/min per 1.73 m^2.

Conclusion: Our primary hypothesis that strength training was superior to balance training was not confirmed. Within groups, 12 months of exercise training resulted in significant improvements in most measures of physical performance. Measured GFR declined similarly in the 2 groups. The strength group showed a significant decrease in albuminuria.

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KEYWORDS: albuminuria; chronic kidney disease; exercise training; glomerular filtration rate; physical performance; randomized controlled trial

In patients with CKD, as in the general population, a low physical performance level is associated with a higher degree of morbidity and mortality.[1–3] All published studies in patients with CKD, irrespective of stage or treatment modality, show that exercise training increases various aspects of physical performance.[4–19]

In most studies, the intervention has been aerobic exercise training, sometimes in combination with strength training.[4–6,19] In a previous retrospective study, we found that handgrip strength and functional reach predicted survival in patients on renal replacement therapy.[20] Recently, a higher risk of falls in older dialysis patients has been reported,[21] emphasizing the importance of improving balance capacity. To our knowledge, no exercise training study in patients with CKD has focused on balance training. To date, mostly measures of endurance and muscular strength have been studied; few studies have tested for balance, and no studies have tested for fine motor skills.

Most studies have supervised patients' exercise training at a treatment center; few have been home-based.[7–9] One study showed that a home-based exercise training program in patients on hemodialysis resulted in similar adherence and effect size as training during

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hemodialysis.[22] Another study showed similar results in patients on hemodialysis when comparing effects of cycling during hemodialysis with walking at home[18] Recently, a large home-based metronome-guided walking study in dialysis patients, the EXCITE (EXerCise Introduction To Enhance performance in dialysis patients) study, showed significantly improved walking capacity.[7]

As a large proportion of patients with CKD are in stages 3 to 5, and as a decline in glomerular filtration rate (GFR) is associated with a decrease in physical performance,[23] investigating ways of attenuating this decline is of interest. However, only a few studies have targeted this group of patients.[8–10] Moreover, in most studies in non–dialysis-dependent patients, the number of patients is quite small, the intervention period is less than 12 months, most patients are younger than age 60 years, and patients rarely suffer from several comorbidities.[8,11,12] Thus, the populations studied are not entirely representative of the typical patient with CKD, who is often elderly and has several comorbidities.

The RENEXC (RCT of exercise in chronic kidney disease) trial employed a pragmatic approach designed to represent the majority of patients with CKD, thus including patients irrespective of age or number of comorbidities. Moreover, a clinically feasible setup was employed with home-based self-administered exercise training. Another important aspect was having an intervention period of 12 months in order to be able to study patients' ability to persevere and integrate physical activity into their daily lives.

Some studies have analyzed estimated GFR (eGFR) before and after an exercise intervention of 48 to 52 weeks, and most have included between 8 and 14 patients.[8,13,14] Several observational studies have revealed an association between degree of physical activity and progression of renal failure.[24–27] No studies have measured GFR, which would avoid confounding due to exercise-induced increases in muscle mass. No larger long-term studies have studied the effects of exercise training on albuminuria.

Most studies have compared exercise training with a non-exercising control group. In the present RCT, RENEXC, we chose to compare 2 active intervention arms—strength training versus balance training—each in combination with endurance training. An important reason for using this comparison is that exercise training is already an integrated part of our comprehensive care, making a sedentary control group difficult to establish, as there would have been a risk of "uncontrolled" exercise training in accordance with our treatment policy in the group designated to be sedentary.

There are, to our knowledge, no other studies comparing the efficacy of different exercise training programs in this group of non–dialysis-dependent patients, and there is a need to gain knowledge about the optimal form of exercise training. Consequently, our main goal was to test whether strength training is superior to balance training. Our primary objective was to compare the effects of 2 exercise training programs on physical performance. In order to obtain a comprehensive evaluation of physical performance, we used tests that measured overall endurance, muscular endurance and strength, balance, and fine motor skills. Our secondary objectives were to analyze the effects of each program on physical performance, investigate the effects of the strength and balance training over time, and analyze the effects of the programs on kidney function by analyzing mGFR and the urine–albumin–creatinine ratio (U-ACR).

METHODS

Trial Design and Participants

This study was a randomized, controlled, parallel-group, interventional, single-center trial with 2 treatment arms and a 1:1 allocation ratio. The Swedish Nephrological Society and the Swedish Kidney Patients Association recommend physical exercise training to patients with CKD, and it is part of usual care at our department. Thus, the study was designed to include 2 treatment arms. There were no changes to methods after trial commencement.

The inclusion criteria were kept as open as possible in order to allow as many interested patients as possible to participate. They had to be ≥18 years old and have no contraindication for regular exercise training or other barriers to study participation. Any comorbid burden was explicitly accepted if it did not constitute a potential risk to the patient's health, as our aim was to achieve as representative a CKD study population as possible. Exclusion criteria were severe orthopedic or neurologic disorders, unstable cardiovascular disease, uncontrolled hypertension, severe anemia, severe electrolyte disturbances, inability to communicate in Swedish, inability to understand oral instructions, and being expected to start renal replacement therapy within 1 year after recruitment.

At the nephrology outpatient clinic at Skåne University Hospital, Lund, all prevalent and incident CKD patients with an eGFR[28] predominantly <30 ml/min per 1.73m^2 are registered on the uremia list. These patients were invited to participate, irrespective of age and comorbidity. Upon being added to the "uremia list," all patients undergo an extensive investigation. They also meet with a renal physiotherapist, who tests their physical performance and prescribes an individualized exercise training program. Patients were recruited consecutively as they were added to the "uremia list." It would not have been practically or ethically feasible to change our routine and deny a control group our standard treatment.

Comorbidity Assessment

Comorbidity was assessed with the Davies Comorbidity Score[29] at the time of visit and physical examination prior to inclusion by MH.

Exercise Intervention

Both groups were prescribed 150 minutes per week of self-administered exercise training for an intervention period of 12 months. In both groups, 60 minutes of endurance training was part of the prescription and was combined with 90 minutes of either strength training (strength group) or balance training (balance group).

An individual training plan based on each patient's physical performance and randomization was provided by a dedicated research physiotherapist (PS). The goal was to achieve 150 minutes of exercise training per week for 12 months, distributed among 3 to 5 sessions per week and preceded by about 10 minutes of warm-up. The training was self-administered at home or at a nearby gym, depending on individual preference. Before starting the study, a bank of predefined exercises was created using exercises from a program called Physiotools[30] used in our department. The physiotherapist designed an exercise training program according to a randomized allotment from the bank of exercises for each patient. For patients training at a gym, the physiotherapist showed each patient, on location at the gym, which exercises to perform and how to perform them. More details of the bank of exercises for endurance training and each treatment arm are provided in Supplementary Appendix S1. Each patient was advised to evaluate his/her training performance according to the RPE using the Borg scale[31] and provide a report by mailing in the training diary. Weekly phone calls by the physiotherapist during the first 3 months, followed by every second week in months 4 to 12, were provided to check progress, encourage patients, and adjust the training plan to maintain the desired level of exertion.

Endurance training should be performed for at least 60 minutes (2 sessions of 30 minutes) per week at an RPE of 13–15 and should consist of walking, jogging, cycling, etc. and be adjusted by increasing speed or distance, or by interval training.

The strength group was prescribed additional strength training for 90 minutes (3 sessions of 30 minutes) per week with a target of 13–17 RPE per exercise set. In all, 4–6 different exercises (e.g., quadriceps extension, squats, biceps curls, pull-ups, etc.) were performed as 2–3 sets of 10 repetitions and adjusted by increasing the weights or the difficulty of the exercises (e.g., adjusting body position regarding angle or leverage).

The balance group was prescribed additional balance training for 90 minutes (3 sessions of 30 minutes) per week at 13–17 RPE per exercise set. In all, 4–6 different exercises (e.g., standing with feet together, on one leg, on balance board or planking, etc.) were performed as 2–3 sets of 10 repetitions and adjusted by increasing the difficulty (e.g., adding arm movements, closing eyes, or changing body position). Initially, some patients were not able to exercise for the prescribed number of minutes. The duration of each session was adjusted according to the patient's RPE and was gradually increased by the physiotherapist.

The primary outcome measures were pre-specified as all the measures of physical performance at baseline, and after 4, 8, and 12 months as treatment differences. The secondary outcomes were pre-specified as the following: treatment and within-group differences in mGFR at baseline and after 12 months; U-ACR at baseline and after 4, 8, and 12 months; and within-group differences of measures of physical performance at baseline, and after 4, 8, and 12 months, and over time. Patients were asked to report training intensity and adherence weekly in their training diaries. There were no changes to trial outcomes after the trial had commenced.

Physical Performance

All physical performance tests have been presented previously in detail.[23] For testing overall endurance, the 6-minute walk test (6-MWT) and stair climbing were used. For testing muscular endurance and fatigability in the proximal leg muscles, the 30-second sit-to-stand test was used; for distal leg muscles, heel rises and toe lifts were used. Neuromuscular function and strength in the lower extremities were tested with isometric quadriceps strength and in the upper extremities with handgrip strength. Balance was tested with functional reach and Berg's balance scale. Fine motor skills were tested using Moberg's picking-up test with open and closed eyes.

The physiotherapist assessed physical performance at baseline, and after 4, 8, and 12 months.

Adherence

Training intensity and adherence during the 12 months of follow-up were evaluated from the self-reported

Table 1. Clinical characteristics at baseline

Characteristic	n	Strength group	n	Balance group
Sex (male/female; n)	76	25/51	75	28/47
Age (yr)	76	67 ± 14	75	65 ± 14
Body mass index (kg/m²)	73	28 ± 6	75	27 ± 5
mGFR (ml/min per 1.73 m²)	73	23 ± 9	75	22 ± 8
eGFR (ml/min per 1.73 m²)	72	19 ± 8	74	20 ± 7
P-cystatin C (mg/l)	72	2.9 ± 0.7	72	2.8 ± 0.7
P-creatinine (μmol/l)	73	263 ± 102	73	246 ± 106
P-urea (mmol/l)	73	16 ± 5	75	16 ± 6
C-reactive protein (mg/l)	73	6 ± 7	75	5 ± 9
P-albumin (g/l)	73	37 ± 4	75	37 ± 3
Hemoglobin (g/l)	73	126 ± 15	74	128 ± 14
Base excess (mmol/l)	68	−1.3 ± 3.3	74	−1.2 ± 2.9
P-potassium (mmol/l)	71	4.3 ± 0.5	75	4.1 ± 0.5
P-calcium (mmol/l)	73	2.3 ± 0.1	74	2.3 ± 0.2
P-phosphate (mmol/l)	73	1.1 ± 0.3	75	1.2 ± 0.3
Parathyroid hormone (ρmol/l)	72	8 - 11 - 21	73	10 - 13 - 18
U-ACR (mg/mmol)	70	4 - 18 - 127	74	4 - 29 - 109
24-hour ambulatory blood pressure (systolic/diastolic; mm Hg)				
Day	67	133/78 ± 15/11	72	134/79 ± 16/10
Night	67	120/66 ± 19/9	69	121/68 ± 18/11
Comorbidity				
Malignancy		16		12
Ischemic heart disease		22		17
Peripheral vascular disease		24		17
Left ventricular dysfunction		8		13
Diabetes mellitus		38		27
Systemic collagen vascular disease		12		9
Other significant pathology		76		76
(e.g., hypertension)				
Medication				
Antihypertensive medication		95		95
Beta blockade		67		67
RAAS blockade		63		57
Central antiadrenergic medication		8		13

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; RAAS, renin–angiotensin–aldosterone system; U-ACR, urine–albumin–creatinine ratio. Values are mean ± SD; 1st - 2nd - 3rd quartiles; or %, unless otherwise indicated. mGFR indicates iohexol clearance, and eGFR = cystatin-C and creatinine-based.

training time and RPE in the training diaries. Cumulative and weekly average values were calculated.

Kidney Function

Iohexol Clearance

Kidney function was assessed with mGFR, measured with iohexol clearance,[32] at baseline and after 12 months. An up-to-date body weight and P-creatinine (not older than 1 month) for estimation of GFR was obtained. The patient was given an i.v. injection of 5 ml iohexol (300 mg iodine/ml, 647 mg iohexol/ml). GFR was calculated based on the amount of iohexol injected, the estimated distribution volume of iohexol (calculated on the basis of body weight), and the concentration of iohexol in the blood sample taken. In CKD, the blood sample was taken according to the estimated GFR: between 20 and 50 ml/min per 1.73 m² at 7 hours after iohexol injection, and for <20 ml/min per 1.73 m² at 24 hours after injection. Iohexol concentration was measured by high-performance liquid chromatography.

P-creatinine, P-cystatin-C, and eGFR were estimated with the cystatin-C– and P-creatinine–based equation.[28] Albuminuria was analyzed using a morning sample of urine with the U-ACR.[33] The U-ACR, along with other laboratory analyses, was measured at baseline, and after 4, 8, and 12 months. All laboratory analyses were measured with routine methods at the Department of Clinical Chemistry, Laboratory Medicine Skåne, which is accredited by the Swedish Board of Accreditation and Conformity Assessment according to the international standards ISO 15189:2012. There were no changes to trial outcomes after the trial commenced.

Determination of Sample Size

This study was powered to detect at least a 10% improvement in endurance, measured by the 6-MWT and at least a 10% improvement in muscular strength and endurance, measured as quadriceps strength and the 30-second sit-to-stand test. This approach was based on the results from an earlier study of ours in which we had a similar group of elderly patients with CKD 4 to 5 undergo exercise training.[34] Cohen's d was used to indicate the standardized difference between 2 means.[35] We assumed a medium-to-large effect size. In order to detect 60% differences at an SD of 5% and 80% of power, we calculated that we needed to include 75 patients in each group to achieve complete data for 50 patients at the end of the intervention.

Randomization

Sequence Generation

Patients were randomized using ProcPlan in SAS (SAS Institute, Cary NC). The permutation of the blocks and the size of each block were known by only one person (PH), who had no contact with the patients, and who designed the randomization so that it was not possible to guess which treatment would be allocated to a specific patient.

Allocation Concealment Mechanism

Patients were included and allocated sequential treatment according to a list that only the research physiotherapist could access. No other member of the group had access to this information while the study was ongoing.

Implementation

PH generated the random allocation sequence, the nephrologist enrolled patients, and the physiotherapist assigned participants to an intervention.

Table 2. Physical performance in strength and balance groups at baseline

	Observations					
	Strength group			Balance group		
Measure	n	Absolute	% Exp norm	n	Absolute	% Exp norm
Endurance (overall)						
Walking capacity (6-MWT, m)	73	405 ± 138	75 ± 25	74	425 ± 133	82 ± 21
Climbing capacity (number of flights of stairs)	72	4 - 6 - 12	NA	75	5 - 7 - 13	NA
Muscular endurance and fatigability						
Proximal leg muscles (30-STS, n)	73	11 ± 6	64 ± 36	74	12 ± 6	73 ± 36
Distal leg muscles						
Heel rise (n)						
Right	70	0 - 7 - 20	0 - 28 - 80	72	0 - 9 - 21	0 - 34 - 84
Left	71	0 - 7 - 20	0 - 28 - 80	72	0 - 8 - 21	0 - 32 - 85
Toe lifts (n)						
Right	69	0 - 0 - 13	0 - 0 - 65	73	0 - 3 - 16	0 - 15 - 80
Left	70	0 - 1 - 10	0 - 5 - 50	73	0 - 3 - 15	0 - 15 - 75
Neuromuscular exercise function/strength						
Lower extremity						
Isometric quadriceps strength (kg*m)						
Right	71	11 ± 4	91 ± 28	73	11 ± 4	91 ± 25
Left	71	12 ± 4	92 ± 27	73	11 ± 4	88 ± 24
Upper extremity						
Hand grip strength (kg)						
Right	73	32 ± 10	84 ± 19	75	31 ± 11	84 ± 22
Left	73	30 ± 10	84 ± 21	74	29 ± 11	83 ± 24
Balance						
Functional reach (cm)	72	32 ± 9	95 ± 24	74	34 ± 9	99 ± 25
Berg's balance scale	72	50 ± 9	NA	73	52 ± 6	NA
Fine motor skills						
Moberg's picking-up test						
With open eyes (s)						
Right	73	9 ± 2	NA	73	8 ± 2	NA
Left	73	9 ± 3	NA	72	8 ± 2	NA
With closed eyes (s)						
Right	73	24 ± 18	NA	73	22 ± 7	NA
Left	73	23 ± 9	NA	72	23 ± 9	NA

% exp norm, % of expected norm; 6-MWT, 6-minute walk test; 30-STS, 30-second sit-to-stand test; NA, not available.
Values are mean ± SD or 1st - 2nd - 3rd quartiles, unless otherwise indicated.

Blinding

The only people who knew which intervention was used were the research physiotherapist and the patient. All other members of the team were blinded. Both interventions comprised endurance training. The difference between the treatment arms was that one group was allocated strength training and one group balance training. The research physiotherapist performed all assessments of physical performance.

Statistical Methods

Continuous variables are presented as means ± SDs or as 1st , 2nd, and 3rd quartiles; categorical variables are presented as percentages and frequencies. Intention-to-treat analysis was used to compare the 2 exercise groups, and all randomized patients were included. To address missing data, we chose the mixed-model analysis. Physical performance and U-ACR were evaluated at baseline and after 4, 8, and 12 months; mGFR was measured at baseline and after 12 months, using the main effects of time and treatment, with their interaction as a fixed effect, and subjects as a random effect. Effects are presented as estimates with 95% confidence intervals. A P value <0.05 was considered statistically significant. Data were analyzed using the R-software (www.r-project.org).

Ethical Approval

The RENEXC study was approved by the Regional Ethical Review Board in Lund (2011/369) and adhered to the Helsinki declaration. All participants gave written informed consent.

Trial Registration

This study was part of the RENEXC trial, registered as NCT02041156 at www.ClinicalTrials@gov.

Complete baseline data from the RENEXC trial have been presented previously but were analyzed with

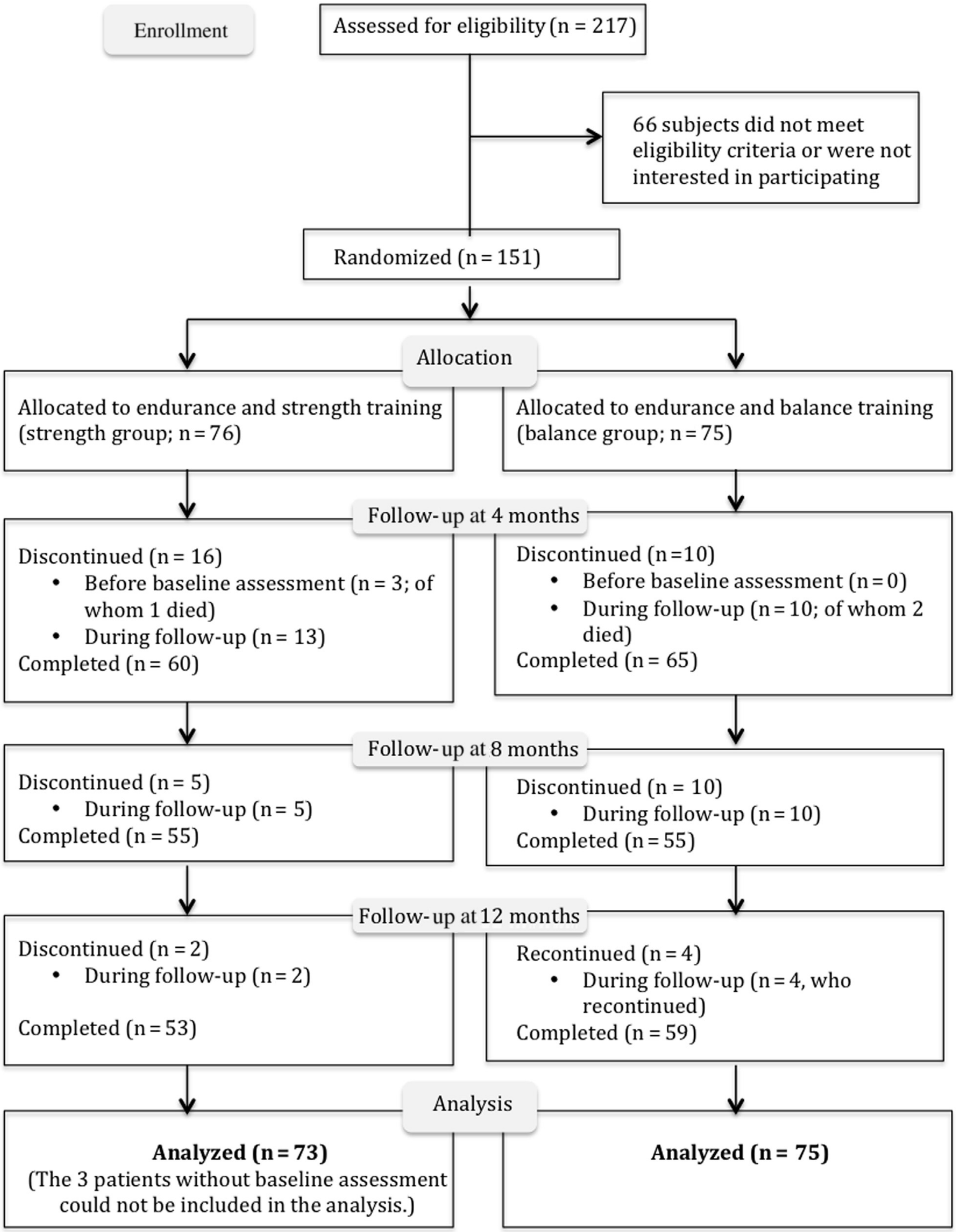

Figure 1. CONSORT flow diagram for RENEXC, 12 months. Three patients dropped out shortly after randomization and before baseline assessment because of bone fracture, terminal illness, and recurring retinal hemorrhage. Three patients died for reasons unrelated to the study. Other reasons for lack of data after 4, 8, and 12 months were concomitant illness, travel, moving to another town, or no motivation to continue.

Table 3. Effects of 12 months of exercise on physical performance—a comparison between the strength group and the balance group

	Δ Est. effects after 12 months of training			
Measure	Absolute	*P*	% exp norm	*P*
Endurance (overall)				
Walking capacity (6-MWT; m)	7 [−13, 27]	0.5	2 [−2, 6]	0.3
Climbing capacity (number of flights of stairs)	1 [−2, 4]	0.6	NA	NA
Muscular endurance and fatigability				
Proximal leg muscles (30-STS; n)	0 [−1, 1]	0.5	3 [−3, 9]	0.3
Distal leg muscles				
Heel rises (n)				
Right	−1 [−4, 2]	0.5	−4 [−16, 8]	0.5
Left	0 [−4, 3]	0.8	0 [−16, 12]	0.8
Toe lifts (n)				
Right	−2 [−5, 2]	0.3	−10 [−25, 10]	0.3
Left	−2 [−4, 1]	0.3	−10 [−20, 5]	0.3
Neuromuscular exercise function/strength				
Lower extremity				
Isometric quadriceps strength (kg*m)				
Right	0.1 [0, 0.1]	0.1	5 [−1, 10]	0.1
Left	0 [−0.1, 0.1]	0.9	0 [−6, 6]	0.9
Upper extremity				
Handgrip strength (kg)				
Right	0 [−1, 1]	0.9	0 [−3, 4]	0.8
Left	0 [−1, 2]	0.6	2 [−2, 6]	0.3
Balance				
Functional reach (cm)	0 [−2, 2]	0.7	1 [−5, 6]	0.8
Berg's balance scale	0 [−1, 1]	0.9	NA	NA
Fine motor skills				
Moberg's picking-up test				
With open eyes (s)				
Right	−0.4 [−0.8, 0.1]	0.1	NA	NA
Left	−0.1 [−0.5, 0.3]	0.7	NA	NA
With closed eyes (s)				
Right	−1.6 [−4.8, 1.7]	0.3	NA	NA
Left	−0.4 [−2.6, 1.9]	0.8	NA	NA

6-MWT, 6-minute walk test; 30-STS, 30-second sit-to-stand test;
% exp norm, % of expected norm; NA, not available.
Δ est. effects = differences of the estimated effects by mixed-model analysis in the strength group compared with the balance group; 95% confidence interval is shown in square brackets.

different scientific questions.[36] In order to facilitate understanding of the present study, some information is repeated in the Methods and Results sections.

RESULTS

Recruitment and Baseline Assessment

A total of 217 patients were screened; 53 women and 98 men (151 participants) were included (mean age 66 ± 14 years; mean mGFR 22 ± 8 ml/min per 1.73 m^2). The recruitment period started in October 2011 and ended in May 2016. The follow-up ended in May 2017. The trial ended after the final patient had completed 12 months of exercise training. The causes of kidney disease were hypertension (41%; n = 62), diabetes mellitus (16%; n = 24), interstitial nephritis (15%; n = 22), glomerulonephritis (15%; n = 23), polycystic kidney disease (6%; n = 9), and others (7%; n = 11). A total of 76 patients were randomly assigned to the strength group, and 75 to the balance group. For each group, baseline clinical characteristics are presented in Table 1, and baseline physical performance measures are presented in Table 2. The patients were at CKD stage 3 (n = 14), stage 4 (n = 93), and stage 5 (n = 41). The CONSORT flow diagram (Figure 1 and Supplementary Figure S1) shows that during the 12 months of the intervention, 23 patients discontinued in the strength group and 16 in the balance group. All analyses are performed on the originally assigned groups.

Harms or Unintended Effects

No exercise training–related side effects, unintended effects, or harm were reported by the participants during the intervention period in either group.

Group Comparison

There were no significant interaction effects (treatment*time) between the strength group and the balance group for estimated effects for any of the physical performance measures after 12 months of intervention (Table 3).

Changes in Physical Performance After 12 Months of Exercise Training

All physical performance measures are presented at baseline and after 12 months of intervention, including the estimated effects. The strength group results are shown in Table 4; additional measures at 4 and 8 months are provided in Supplementary Table S1; the balance group results are shown in Table 5 and Supplementary Table S2. In Figures 2, 3, and 4, the within-group changes for measures of physical performance are presented as changes in the percentage of the expected norm. Once significant improvements in physical performance measures were achieved, they consistently remained significant at subsequent assessments in both groups. The one exception was in the balance group, for Moberg's picking-up test with closed eyes and left hand.

Overall endurance, measured with the 6-MWT, increased after 4 months in the strength group and after 12 months in the balance group; stair climbing increased after 12 months in both groups. Muscular endurance in the proximal leg muscles, measured with the 30-second sit-to-stand test, improved after 4 months in the strength group and after 8 months in the balance group. Muscular endurance in the distal leg muscles, measured with heel rises, improved after 4 months in the strength group and after 8 months in the balance group. Heel rises improved in both groups after 8 months. Isometric quadriceps strength increased

Table 4. Physical performance after 12 months of strength and endurance training

	Observations				Est. Effects after 12 months of training				
	Baseline		12 months						
Measure	Absolute	% Exp norm	Absolute	% Exp norm	n	Mean absolute	*P*	Mean % exp norm	*P*
Endurance (overall)									
Walking capacity (6-MWT; m)	379 ± 138	75 ± 25	450 ± 127	89 ± 26	46	31 [16, 46]	**<0.001**	6 [4, 9]	**<0.001**
Climbing capacity (number of flights of stairs)	4 - 6 - 12	NA	5 - 10 - 23	NA	46	6 [3, 8]	**<0.001**	NA	NA
Muscular endurance and fatigability									
Proximal leg muscles (30-STS; n)	11 ± 6	64 ± 36	13 ± 7	88 ± 41	50	1 [1, 2]	**<0.001**	9 [5, 13]	**<0.001**
Distal leg muscles									
Heel rises (n)									
Right	0 - 7 - 20	0 - 28 - 80	5 - 19 - 30	20 - 76 - 128	50	7 [4, 9]	**<0.001**	28 [16, 36]	**<0.001**
Left	0 - 7 - 20	0 - 28 - 80	1 - 17 - 27	4 - 68 - 108	50	6 [4, 8]	**<0.001**	24 [16, 32]	**<0.001**
Toe lifts (n)									
Right	0 - 0 - 13	0 - 0 - 65	0 - 9 - 25	0 - 45 - 125	50	4 [2, 6]	**0.001**	20 [10, 30]	**0.001**
Left	0 - 1 - 10	0 - 5 - 50	0 - 4 - 20	0 - 20 - 100	51	3 [1, 5]	**0.003**	15 [5, 25]	**0.003**
Neuromuscular exercise function/strength									
Lower extremity									
Isometric quadriceps strength (kg*m)									
Right	11.5 ± 4.1	91 ± 28	13.3 ± 4.4	104 ± 28	50	1.2 [0.7, 1.7]	**<0.001**	10 [5, 14]	**<0.001**
Left	11.6 ± 4.3	92 ± 27	13.1 ± 4.9	102 ± 32	51	0.8 [0.3, 1.4]	**0.003**	7 [3, 11]	**0.001**
Upper extremity									
Hand grip strength (kg)									
Right	32 ± 10	84 ± 19	33 ± 10	88 ± 19	52	0 [–1, 1]	0.5	1 [–1, 4]	0.2
Left	30 ± 10	84 ± 21	31 ± 10	88 ± 20	53	1 [0, 2]	0.3	2 [–1, 5]	0.1
Balance									
Functional reach (cm)	32 ± 9	95 ± 24	36 ± 7	105 ± 19	50	2 [1, 4]	**0.003**	7 [2, 11]	**0.002**
Berg's balance scale	50 ± 9	NA	52 ± 9	NA	53	0 [–1, 1]	0.8	NA	NA
Fine motor skills									
Moberg's picking-up test									
With open eyes (s)									
Right	8.6 ± 2.3	NA	7.8 ± 2.0	NA	53	–0.7 [–1.0, –0.3]	**<0.001**	NA	NA
Left	8.6 ± 2.7	NA	8.0 ± 2.3	NA	53	–0.4 [–0.7, –0.1]	**0.01**	NA	NA
With closed eyes (s)									
Right	24.3 ± 18.2	NA	19.5 ± 6.7	NA	53	–4.0 [–6.4, –1.7]	**<0.001**	NA	NA
Left	23.3 ± 8.9	NA	20.9 ± 7.2	NA	53	–1.6 [–3.3, –0.0]	**0.05**	NA	NA

6-MWT, 6-minute walk test; 30-STS, 30-second sit-to-stand test; % exp norm, % of expected norm; Est. effects, estimated effects by mixed model analysis; NA, not available.
Values are mean ± SD, or 1st - 2nd - 3rd quartiles, unless otherwise indicated; 95% confidence intervals are shown in square brackets.
$P < 0.05$ was considered statistically significant and is marked as bold data.

after 4 months in the strength group and after 12 months in the balance group. Handgrip strength did not change in either group. Balance, measured with functional reach, improved after 4 months in the strength group and after 12 months in the balance group. Berg's balance scale was unchanged in both groups. Fine motor skills, measured with Moberg's picking-up test, improved after 4 months in both hands, both with open and closed eyes in the strength group. In the balance group, Moberg's picking-up test with open eyes and the left hand improved after 4 months, but there was no improvement in results using the right hand. The balance group showed an improvement with closed eyes and the right hand after 12 months, and with the left hand after 4 months, but for the left hand, the improvement was not sustained.

Training Intensity and Adherence

Weekly training time was summarized after 4, 8, and 12 months, according to training modality, and is presented in Table 6. Adherence to the training program decreased in both groups during the 12-month observation period. In the strength group, 84% of participants reported training at 4 months, 70% at 8 months, and 62% at 12 months. In the balance group, 89% reported training at 4 months, 76% at 8 months, and 68% at 12 months. The reported RPE ranged between 13 and 15 for the endurance sessions, and between 13 and 17 for the strength and balance sessions, respectively. There were no significant associations between training time or reported RPE levels in terms of estimated effects on physical performance measures or kidney function.

Kidney Function

Kidney function measures are presented in Table 7 for both groups, as well as interaction effects, by showing the estimated effects in the strength group compared with the balance group. Once significant within-group changes occurred, they were consistently sustained at

Table 5. Physical performance after 12 months of balance and endurance training

	Observations				Est. effects after 12 months of training				
	Baseline		12 months						
Measure	Absolute	% Exp norm	Absolute	% Exp norm	n	Mean absolute	*P*	Mean % exp norm	*P*
Endurance (overall)									
Walking capacity (6-MWT; m)	425 ± 133	82 ± 21	469 ± 133	89 ± 19	54	24 [10, 37]	**<0.001**	4 [2, 7]	**0.001**
Climbing capacity (number of flights of stairs)	5 - 7 - 13	NA	6 - 9 - 26	NA	51	5 [3, 7]	**<0.001**	NA	NA
Muscular endurance and fatigability									
Proximal leg muscles (30-STS; n)	12 ± 6	73 ± 36	13 ± 8	77 ± 41	59	1 [0, 2]	**0.001**	6 [2, 10]	**0.004**
Distal leg muscles									
Heel rises (n)									
Right	0 - 9 - 21	0 - 36 - 84	3 - 20 - 31	12 - 80 - 124	55	8 [5, 10]	**<0.001**	32 [20, 40]	**<0.001**
Left	0 - 8 - 21	0 - 32 - 84	1 - 17 - 27	4 - 68 - 108	54	6 [4, 9]	**<0.001**	24 [16, 36]	**<0.001**
Toe lifts (n)									
Right	0 - 3 - 16	0 - 15 - 80	0 - 10 - 25	0 - 50 - 125	55	6 [3, 8]	**<0.001**	30 [15, 40]	**<0.001**
Left	0 -3 - 15	0 - 15 - 75	0 - 7 - 25	0 - 35 - 125	55	4 [3, 6]	**<0.001**	20 [15, 30]	**<0.001**
Neuromuscular exercise function/strength									
Lower extremity									
Isometric quadriceps strength (kg*m)									
Right	11.4 ± 4.1	91 ± 25	12.1 ± 4.3	97 ± 25	56	0.6 [0.1, 1.1]	**0.01**	5 [1, 9]	**0.01**
Left	11.1 ± 4.2	88 ± 24	11.9 ± 4.4	95 ± 23	56	0.9 [0.3, 1.4]	**0.001**	7 [3, 11]	**0.001**
Upper extremity									
Handgrip strength (kg)									
Right	31 ± 11	84 ± 22	32 ± 12	86 ± 25	59	0 [−0, 1]	0.3	1 [−1, 3]	0.4
Left	29 ± 11	83 ± 24	29 ± 12	84 ± 27	59	0 [−1, 1]	0.7	0 [−2, 3]	0.9
Balance									
Functional reach (cm)	34 ± 9	99 ± 25	36 ± 8	106 ± 23	57	2 [0, 3]	**0.008**	6 [2, 10]	**0.004**
Berg's balance scale	52 ± 6	NA	52 ± 8	NA	59	0 [−1, 1]	0.9	NA	NA
Fine motor skills									
Moberg's picking-up test									
With open eyes (s)									
Right	8.0 ± 2.0	NA	7.7 ± 2.0	NA	58	−0.3 [−0.6, 0.0]	0.06	NA	NA
Left	8.3 ± 1.9	NA	8.0 ± 1.8	NA	58	−0.3 [−0.6, 0.0]	**0.05**	NA	NA
With closed eyes (s)									
Right	21.7 ± 7.3	NA	19.4 ± 6.2	NA	58	−2.4 [−4.7, −0.2]	**0.04**	NA	NA
Left	23.1 ± 9.3	NA	21.7 ± 9.3	NA	58	−1.3 [−2.8, 0.3]	0.1	NA	NA

6-MWT, 6-minute walk test; 30-STS, 30-second sit-to-stand test; % exp norm, % of expected norm; Est. effects, estimated effects by mixed model analysis; NA, not available.
Values are mean ± SD or 1st - 2nd - 3rd quartiles, unless otherwise indicated; 95% confidence intervals are given in square brackets.
$P < 0.05$ was considered statistically significant and is marked as bold data.

subsequent measurements. There was a significant decrease in mGFR of 1.8 ml/min per 1.73 m^2 in both groups after 12 months, with no interaction effect. U-ACR decreased significantly in the strength group at 12 months and was unchanged in the balance group, with a significant interaction effect.

DISCUSSION

In this RCT, in which we compared the effectiveness of 2 exercise training programs—strength versus balance training, each in combination with endurance training—we did not confirm our primary hypothesis that strength training would result in greater improvements in physical performance compared with balance training. There are several possible explanations. For one, both groups performed endurance training. Secondly, the strength training focuses on muscles in the arms and legs, whereas the balance training focuses on core and leg muscles. The strength group's exercises were mainly dynamic muscle training, whereas the balance group's exercises were predominantly static. This study shows that patients with CKD benefit from either form of muscle training. Thus, balance training emerges as an equally important form of exercise training for patients with CKD. In view of the high risk of falls in elderly patients on dialysis, this study provides important evidence on the efficacy of both strength and balance training to maintain balance function.

In the secondary analyses before and after 12 months of exercise training, we found that 12 months of either strength or balance training combined with endurance training improved or maintained overall endurance, muscular endurance and strength, balance, and fine motor skills. Although there were no significant interaction effects, the strength group improved most measures of physical performance sooner than the

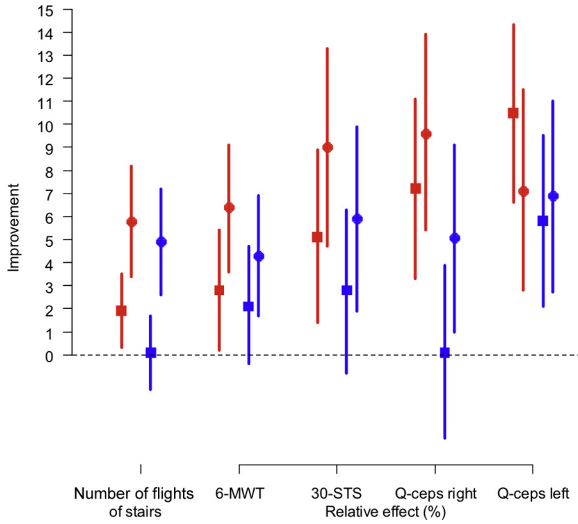

Figure 2. Effects after 4 and 12 months, on stair climbing, walking capacity, chair rises within 30 seconds, and isometric quadriceps strength (Q-ceps). Improvements in stair climbing capacity are presented as numbers of flights of stairs. Improvements in walking capacity were measured with the 6-minute walking test (6-MWT), chair rises within 30 seconds with the 30-second sit-to-stand test (30-STS), and isometric Q-ceps in the right leg and the left leg, presented in relation to the expected norm as relative effects in %. Red, strength group; blue, balance group; square (■), 4 months; circle (•), 12 months.

balance group. By 4 months, the strength group achieved significant improvements in walking distance, muscular endurance in the leg muscles, quadriceps strength, balance, and fine motor skills in contrast to those in the balance group, who in general needed 12 months to achieve significant effects. However, once a

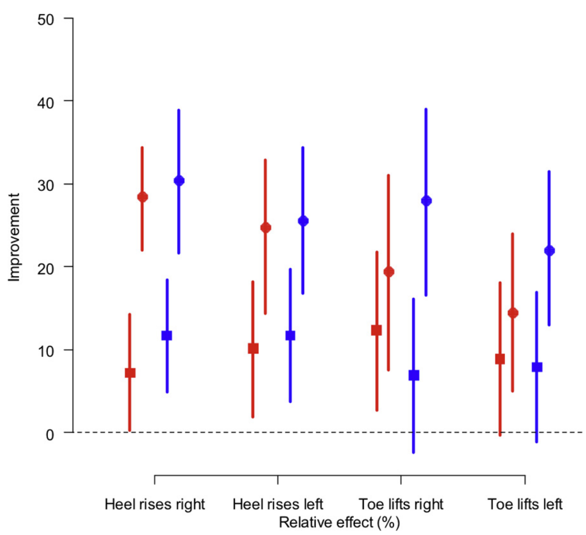

Figure 3. Effects after 4 and 12 months on muscular endurance in the distal legs. Improvements in muscular endurance in the distal leg muscles are presented for right and left heel rises and right and left toe lifts, as relative effects in %, related to the expected norm. Red, strength group; blue, balance group; square (■), 4 months; circle (•), 12 months.

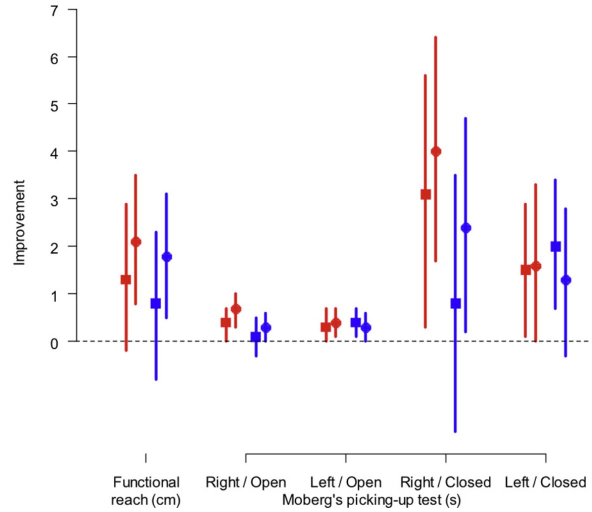

Figure 4. Effects after 4 and 12 months on balance and fine motor skills. Improvements in absolute values on balance measured as functional reach in cm and on fine motor skills with Moberg's picking-up test in the right and left hand with open and closed eyes, respectively, in seconds. Red, strength group; blue, balance group; square (■), 4 months; circle (•), 12 months.

significant improvement was achieved, it was sustained throughout the 12-month intervention period in both groups. The within-group effects were highly significant.

To date, the RENEXC trial is the largest RCT in patients with non–dialysis-dependent CKD, comprising 151 patients, of whom 53 patients completed 12 months of exercise training in the strength group and 59 in the balance group, a total of 112 exercising patients. The EXCITE trial, the largest to date RCT in patients on dialysis, studied the effects of walking exercise in 296 patients, of whom 151 were randomized to the exercise group, with 104 patients completing the 6-month intervention period and showing improved walking distance and sit-to-stand test results.[7]

The Landmark III study is the hitherto largest RCT exercise training study in non–dialysis-dependent patients with CKD, comprising 83 patients, of whom 36 performed strength and endurance exercise training for 12 months and showed an improvement in maximal oxygen uptake and walking distance.[9,15] Similar results have been reported from other smaller RCTs with non–dialysis-dependent patients with CKD after at least 11 months of exercise training.[11,14,16]

We used an extensive battery of measures of physical performance including Moberg's picking-up test, which measures fine motor skills and assesses functional sensibility and motor function in the hand and fingers. This test has been used by our group only in patients with CKD.[23] Previously, we found that a decrease in fine motor skills was related to a decline in mGFR.[23] This association might reflect the development

Table 6. Reported exercise training time

Exercise training time	Months	Strength group n	Training time		Balance group n	Training time	
Total exercise training time (min/wk)							
	4	64	85 - 141 - 182	(145 ± 81)	67	80 - 116 - 173	(160 ± 152)
	8	53	88 - 126 - 214	(152 ± 95)	57	65 - 122 - 207	(167 ± 171)
	12	47	64 - 100 - 187	(140 ± 112)	51	64 - 118 - 161	(173 ± 252)
Endurance exercise training average time (min/wk)							
	4	64	30 - 62 - 98	(74 ± 65)	67	38 - 71 - 108	(106 ± 137)
	8	53	31 - 63 - 120	(85 ± 70)	57	29 - 66 - 125	(112 ± 149)
	12	47	17 - 57 - 91	(75 ± 80)	51	34 - 60 - 109	(104 ± 145)
Strength/balance exercise training average time (min/wk)							
	4	64	40 - 69 - 97	(70 ± 38)	67	28 - 46 - 67	(53 ± 39)
	8	53	30 - 57 - 83	(60 ± 41)	57	21 - 39 - 66	(49 ± 46)
	12	47	34 - 51 - 81	(61 ± 48)	51	23 - 33 - 52	(46 ± 46)

Values are 1st - 2nd - 3rd quartiles, or mean ± SD, unless otherwise indicated.

of neuropathy and could also indicate an increased risk of cognitive impairment in the course of CKD.[23,37–39] Impaired fine motor skills in the hands are often related to loss of functional ability and autonomy. The strength group already had improved their fine motor skills after 4 months, with further improvement after 8 and 12 months. The balance group showed sustained improvement of fine motor skills in the picking-up test with the left hand and open eyes (i.e., the non-dominant side) after 4, 8, and 12 months. We previously reported that the non-dominant side may be more sensitive to changes.[20,23] It is possible that the fact that the strength group had a quicker response to exercise training, after only 4 months, compared with the balance group is reflected in their improved fine motor skills. Another explanation could be that the strength group exercised arm muscles to a greater extent than the balance group.

Previous observational studies in patients without CKD have shown that higher levels of physical activity were associated with reduced risk of both cognitive decline and occurrence of dementia.[40] We did not analyze cognitive ability in RENEXC, but the registered improvement in fine motor skills may be due to a combined effect on cognitive, motor, and sensory function.

The adherence rate in RENEXC was good, with about two-thirds of all participants performing regular exercise training for about 150 minutes/week for 12 months. This result demonstrates that our model, with self-administered home- or gym-based training, is feasible, acceptable, and applicable in clinical routine.

Both groups showed a decline in mGFR of 1.8 ml/min per 1.73 m^2 after 12 months of intervention. An observational study in patients with CKD 3–4, with self-reported physical activity of >150 minutes per week, showed a decline in eGFR of 2.6 ml/min per 1.73 m^2 per year compared with 4.0 ml/min per 1.73 m^2 per year in their physically inactive counterparts.[24] A decline of 25 ml/min per 1.73 m^2 during a period of 11 years, which is on average 2.3 ml/min per 1.73 m^2 per year, in middle-aged and older women was associated with self-reported low physical activity in another observational study.[41] The Landmark III study[9,15] did not find a significant change in eGFR after the intervention period of 12 months in either group of patients with CKD stages 3 to 4. Greenwood *et al.*[8] showed an increase in eGFR after 12 months of exercise training in

Table 7. Kidney function, estimated effects, and comparison between estimated effects

	Months	Strength group Observations	n	Mean est. eff.	*P*	Balance group Observations	n	Mean est. eff.	*P*	Group comparison Δ Est. eff.	*P*
mGFR	0	22.6 ± 8.7	70			22.4 ± 7.7	73				
(ml/min per 1.73 m^2)	12	21.9 ± 9.7	50	–1.8 [–3.2, –0.4]	**0.01**	21.2 ± 7.8	55	–1.8 [–3.1, –0.4]	**0.01**	0 [–2.0, 1.9]	0.9
U-ACR	0	867 ± 1239	70			743 ± 1009	73				
(mg/mmol)	4	858 ± 1124	57	–124 [–265, 18]	0.08	637 ± 867	60	–88 [–221, 53]	0.2	–44 [–239, 159]	0.7
	8	770 ± 1142	51	–124 [–265, 27]	0.1	602 ± 788	53	–88 [–230, 62]	0.2	–35 [–239, 177]	0.7
	12	566 ± 867	48	–292 [–442, –142]	**<0.001**	628 ± 876	58	–41 [–186, 97]	0.5	–257 [–460, –44]	**0.02**

est. eff., estimated effects by mixed-model analysis; Δ est. eff., comparison of the est. eff. in the strength group compared with the balance group; mGFR, measured glomerular filtration rate (= iohexol clearance); NA, not available; U-ACR, urine–albumin–creatinine ratio.
Values are mean ± SD, unless otherwise indicated; 95% confidence intervals are given in square brackets.
$P < 0.05$ was considered statistically significant and is marked as bold data.

a group of 8 patients with an initial eGFR of 37 ml/min per 1.73 m^2. Experimental exercise training studies in 5 of 6 nephrectomized rats showed a slowing of uremia progression.[42,43]

In the present RENEXC trial, both groups showed a slower rate of decline in mGFR compared with the results for eGFR in some observational studies.[24,25,41] However, our evidence must be regarded as weak, as we compared 2 active intervention arms and did not have a sedentary control arm. It would have been useful to collect data on kidney function prior to baseline, which would have allowed us to compare the decline in GFR prior to baseline with the decline during intervention. Another important factor is that blood pressure was well controlled in our RENEXC patients.

The strength group showed a significant decrease in U-ACR of 33% after 12 months of exercise training. The interaction effect was significant and favored the strength group, although there was a general trend toward a decrease in albuminuria at 4, 8, and 12 months in both groups. Recently published observational studies showed associations between a decrease in U-ACR and slower progression of CKD.[44,45] Of note is that the etiology of albuminuria is multifactorial.[46–48] Stimulated proximal tubular cells can release inflammatory, vasoactive, and fibrotic substances,[49,50] which have been implicated as a major risk factor for progression of CKD.[51–53] In CKD, albuminuria *per se* is a therapeutic target, when evaluating the effects of renin-angiotensin-aldosterone system inhibitors, improved glucose control, anti-inflammatory agents, or a low-protein diet.[54] Exercise training has been shown to have antiinflammatory effects in patients with CKD.[55–57] Thus, regular exercise training may have wider potential in the treatment of patients with CKD than just its effects on physical performance.

Our study has some limitations. There was no sedentary control group. There is some risk of a learning effect on the tests of physical performance, which cannot be evaluated as we do not have a sedentary control group. There is a similar problem with analyzing the decline in mGFR, which was the same in both groups, as we do not know what the rate of decline in mGFR would have been in a sedentary control group. There is also a risk of a type II statistical error resulting from multiple comparisons.

There are several strengths of the present RENEXC trial: patients of all ages were included; the youngest was 18 and the oldest 87 years old; concomitant comorbidities were permitted; and patients with predominantly CKD stages 4 and 5 participated. The exercise training was at a nearby gym or was home-based, according to each patient's lifestyle and convenience. Thus, this trial endeavored to be as close to real-life conditions as possible. The feasibility of this setup is corroborated by the high adherence rate throughout the 12-month trial.

The "uremia list," comprising patients with an eGFR of approximately 30 ml/min per 1.73 m^2 or lower, at our outpatient clinic enabled us to screen all eligible patients, ensuring a broad selection base. Finally, the fact that we measured GFR is a distinct strength of our RENEXC trial, as an increase in muscle mass would lead to an increase in creatinine and thus a higher eGFR.

In conclusion, we did not find strength training to be superior to balance training in terms of effects on physical performance. However, within each group, we showed that 12 months of individualized self-administered regular strength or balance training, combined with endurance training, improved or maintained overall endurance, muscular endurance and strength, balance, and fine motor skills in a reasonably representative group of non–dialysis-dependent patients with CKD stages 3 to 5. Regarding effects on kidney function, both groups showed a modest decline in mGFR. The strength group had a significant decrease in albuminuria compared with the balance group, for which levels were unchanged. Thus, 12 months of either strength or balance training improved physical performance and might have beneficial effects on the progression of CKD. Moreover, strength training might have other effects with potential positive effects on the glomerular basement membrane.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

Research idea and study design: NC, MH, PH; data acquisition: MH, PS; coordination/management of the intervention period: PS; data analysis/interpretation: MH, PH, NC;

statistical analysis: MH, PH; supervision and mentorship: NC, PH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Appendix S1. Exercise training.

Figure S1. CONSORT statement.

Table S1. Physical performance after 0, 4, 8, and 12 months of endurance and strength training (strength group). Values are 1st - 2nd - 3rd quartiles, or mean ± SD; 95% confidence intervals are given in square brackets. est. eff., estimated effect by mixed-model analysis; NA, not available; relative, % of expected norm.

Table S2. Physical performance after 0, 4, 8, and 12 months of endurance and balance training (balance group). Values are 1st - 2nd - 3rd quartiles, or mean ± SD; 95% confidence intervals are given in square brackets. est. eff., estimated effect by mixed-model analysis; NA, not available; relative, % of expected norm.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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