Clinical Kidney Journal, 2023, vol. 16, no. 11, 2003–2010

https://doi.org/10.1093/ckj/sfad192
Advance Access Publication Date: 9 August 2023
Original Article

ORIGINAL ARTICLE

Examining the safety and effectiveness of a 4-week supervised exercise intervention in the treatment of frailty in patients with chronic kidney disease

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ABSTRACT

Background. The optimal duration of antifrailty interventions and how best to deliver them to patients with chronic kidney disease (CKD) is unknown. The aim of this study was to examine the safety, feasibility and preliminary efficacy of a 4-week supervised exercise intervention on frailty in patients with CKD.
Methods. We conducted a prospective feasibility study involving patients with ≥stage 3 CKD (1 patient with stage 3 CKD, 7 patients with stage 4 CKD and 17 patients with stage 5 CKD) who were either frail or prefrail according to the physical frailty phenotype and/or had a Short Physical Performance Battery (SPPB) score ≤10. The exercise intervention consisted of two supervised outpatient sessions per week for 4 weeks (eight total sessions). Frailty and other study measures were assessed at baseline and after 4 weeks of exercise.
Results. Of the 34 participants who completed the baseline assessment and were included in the analyses, 25 (73.5%) completed the 4-week assessment. Overall, 64.0% of patients were on dialysis and 64.0% had diabetes mellitus. After 4 weeks of exercise, frailty prevalence, total SPPB scores and energy/fatigue scores improved. No adverse study-related outcomes were reported.
Conclusions. The 4 weeks of supervised exercise was safe, was associated with an excellent completion rate and improved frailty parameters in CKD patients with CKD. This study provides important preliminary data for a future larger prospective randomized study.
Clinical Trial.gov. registration: NCT03535584

Received: 22.2.2023; Editorial decision: 21.7.2023

LAY SUMMARY

We conducted a prospective, single-center, non-randomized pilot study examining the safety, feasibility and preliminary efficacy of a 4-week supervised exercise intervention on frailty in patients with chronic kidney disease (CKD). We enrolled 25 participants. We found that the intervention was safe, was associated with an excellent completion rate and improved frailty parameters in patients with CKD. This study provides important preliminary data for a future larger prospective randomized study.

Keywords: chronic kidney disease, diabetes, dialysis, exercise, frailty

INTRODUCTION

Frailty is common in patients with chronic kidney disease (CKD) and is associated with numerous adverse health outcomes. The prevalence of frailty increases as kidney function declines. Up to 78% of patients with dialysis-dependent CKD are frail [1]. The prevalence of frailty is also affected by diabetes. Patients with CKD who also have diabetes have nearly twice the rate of frailty as patients without diabetes [2]. Frailty has been associated with significant morbidity in patients with CKD [3]. Patients with CKD who are frail are more likely to experience falls [4], decreased quality of life (QOL) [5], hospitalizations [6–8], decreased access to kidney transplantation (KT) [9] and death [8, 10]. Frailty has also been associated with progression to end-stage kidney disease in patients with diabetes [11].

Fortunately, frailty has been shown to be treatable in non-CKD patients through interventions incorporating exercise [12–14]. The optimal duration of exercise interventions and how best to deliver them to patients with CKD is unknown. Many exercise interventions that have been studied in CKD are not standardized, not supervised, suffer from low completion rates and are intradialytic, meaning they are performed during in-center hemodialysis (HD), and are thus not applicable to patients with non-dialysis-dependent CKD or who receive home dialysis [15].

We previously developed a standardized, supervised 8-week regimen of graduated aerobic and strength conditioning that may be beneficial to patients regardless of CKD stage or dialysis modality [15]. The intervention was first shown to be safe and effective in patients with lung disease [16, 17]. We subsequently adapted the intervention for patients with CKD and demonstrated that it was associated with improved fatigue, walking time and grip strength [15]. We now hypothesize that only 4 weeks of the same intervention might also be beneficial. A shorter version of our intervention might ultimately be associated with better completion rates and serve as an effective prehabilitation strategy in patients undergoing KT. In the current study we conducted a clinical trial to evaluate the feasibility, safety and effectiveness of 4 weeks of supervised exercise in patients with CKD.

MATERIALS AND METHODS

Patient population

We conducted a prospective study between July 2018 and May 2020 at our center. The study was registered on ClinicalTrials.gov (NCT03535584) and approved by the Mayo Clinic Institutional Review Board (17-009722). Potentially eligible patients ≥18 years of age with CKD stage ≥3 who lived within 70 miles of our center were identified from our medical records and transplant database. Inclusion criteria included frail or prefrail by the physical frailty phenotype and/or a Short Physical Performance Battery (SPPB) score ≤10 (see ‘Study outcomes’ below) [18, 19]. An SPPB score ≤10 was chosen based on published data demonstrating a relationship between scores ≤10 and adverse outcomes in patients with CKD, including decreased access to KT, increased healthcare utilization and increased mortality [20–22]. Exclusion criteria included moderate–severe active cardiopulmonary disease, defined as a history of untreated myocardial ischemia, recent myocardial infarction, heart or lung transplant candidate, left ventricular assist device recipient, known ventricular arrhythmia, significant restrictive or obstructive lung disease or the need for continuous oxygen supplementation.

At enrollment, participants underwent a submaximal exercise test to rule out significant undiagnosed cardiopulmonary disease. We provided parking passes and remuneration to study participants. Demographics were abstracted from the medical records or self-reported by participants. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [23].

Exercise intervention

The exercise intervention was conducted according to previously published methodology [15]. Briefly, participants were asked to complete two ≤60-minute exercise sessions per week for 4 weeks (eight total sessions) according to pulmonary rehabilitation guidelines established by the American Thoracic Society [24]. Exercise sessions were conducted in our outpatient pulmonary rehabilitation unit and supervised by licensed respiratory therapists. Exercise training consisted of endurance, strength and flexibility training and was individualized for each participant. Respiratory therapists adjusted the intensity of endurance training weekly based on target participant Borg scores of 4–6 [moderate to (very) severe] [25]. Study personnel collected vital signs before and after each exercise session; monitored participant oxygen saturation, symptoms and heart rate during exercise; obtained blood pressure during exercise as indicated by participant symptoms and recorded adverse study events.

Study outcomes

The primary study outcome was frailty according to the physical frailty phenotype. We chose the physical frailty phenotype as the primary study outcome because it has been associated with numerous adverse health outcomes in CKD patients, including decreased access to KT and death [3, 8]. The physical frailty phenotype consists of three criteria: wasting (self-reported unintentional weight loss of ≥10 kg over the past year), exhaustion (self-reported using the Center for Epidemiologic Studies Depression

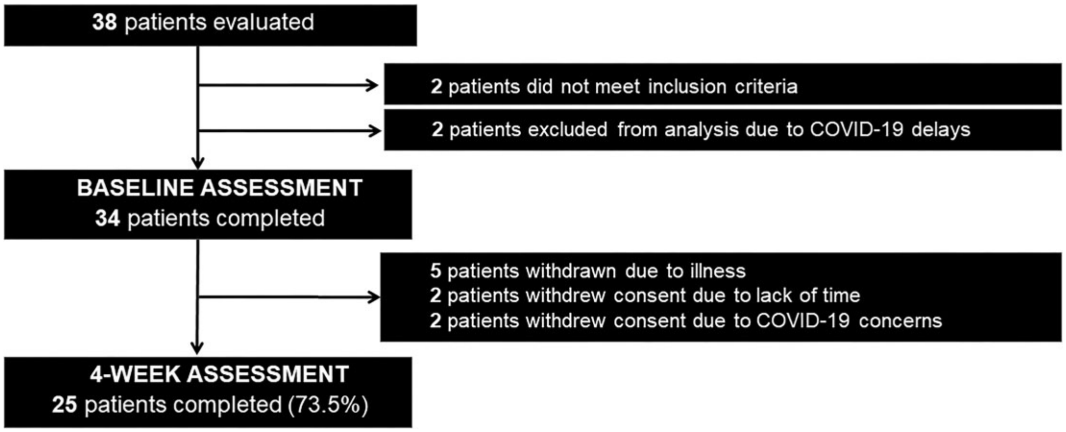

Figure 1: Study flow.

Scale) [26], low physical activity (self-reported using the Minnesota Leisure Time Activity Questionnaire) [27, 28], slow walking speed (assessed via a 15-foot walk) and weakness (assessed via grip strength) [18]. Participants received a score of 0 or 1 for each criterion. Participants with three or more criteria were defined as frail, one to two criteria as prefrail and none of the criteria as not frail. The physical frailty phenotype was assessed at baseline and at 4 weeks. The impact of the intervention on the physical frailty phenotype was analyzed in the subgroup of patients with diabetes, the subgroup of patients on dialysis and among the entire cohort.

Secondary outcomes included SPPB scores, health-related quality of life (HRQOL), body weight and body composition. The SPPB is a composite measure of lower extremity function involving tests of balance, gait speed and chair stands. Participants received a score ranging from 0 to 4 for each of the three tests, with higher scores indicating better physical function [19]. Scores for each of the three tests were then summed to provide a total SPPB score ranging from 0 to 12 [19]. HRQOL was assessed using the Kidney Disease Quality of Life Short Form (KDQOL-SF), version 1.3, with scores ranging from 0 to 100 and higher scores indicating better QOL [29–31]. Body composition was determined by electrical impedance using the InBody 770 body composition analyzer (InBody USA, Cerritos, CA, USA). Analyzed body composition measures included intracellular water, extracellular water and percent body fat. In addition, we calculated indices for fat mass, skeletal muscle mass and appendicular skeletal muscle mass (sum of muscle mass in both arms and legs) by dividing fat mass, skeletal muscle mass and appendicular muscle mass, respectively, by the square of height. The SPPB, KDQOL-SF, body weight and body composition were assessed at baseline and at 4 weeks.

Statistical analysis

We summarized continuous data as medians with ranges and interquartile ranges (IQRs). We summarized categorical data as counts and percentages. We performed pre- and postintervention comparisons using the paired samples Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. The primary endpoint was frailty at 4 weeks. Secondary outcomes included the change in the physical frailty phenotype, SPPB, HRQOL and body weight at 4 weeks. For exploratory purposes, the impact of the intervention was also examined in the subgroup of patients with diabetes and the subgroup of patients on dialysis. P-values $\leq$.05 were considered statistically significant. Analyses were conducted with JMP version 16.0 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

Study flow is described in Fig. 1. Overall, 38 patients were screened, 2 of whom (5%) did not meet the inclusion criteria, so 36 participants were enrolled in the study. Two participants were excluded from the analysis because they experienced significant interruptions in their exercise intervention due to coronavirus disease 2019 (COVID-19)-related closures at our center and required $>$12 weeks to complete the 4-week assessment. Of the remaining 34 participants who enrolled, 9 (26.5%) withdrew prior to the 4-week assessment due to illness, lack of time and concerns regarding COVID-19. No serious adverse events occurred. One participant experienced a mild adverse event possibly related to the intervention consisting of an episode of desaturation during exercise requiring temporary administration of supplemental oxygen. The participant was subsequently withdrawn from the study prior to completion of the 4-week assessment. The 25 remaining participants (73.5%) completed the 4-week assessment.

Baseline characteristics of the 25 participants who completed the 4-week assessment are outlined in Table 1. The median age was 62 years (IQR 52.5–67), 56.0% were male, 88.0% were non-Hispanic White, 64.0% were on dialysis [4 patients on peritoneal dialysis (PD) and 12 patients on HD], 64.0% had diabetes mellitus and 24.0% had a history of smoking. At baseline, 36.0% ($n = 9$) were frail and the median SPPB score was 9 (IQR 7–10).

Change in study outcomes from baseline to 4 weeks

After 4 weeks of exercise, we observed a decrease in frailty prevalence (Fig. 2). The proportion of patients with diabetes who were frail decreased significantly (43.8% to 12.5%, $P = .03$), as did the proportion of patients on dialysis who were frail (42.9% to 18.8%, $P = .03$). A numerical decrease in frailty prevalence among the entire cohort was also observed (36.0% to 20.0%, $P = .10$). The improvement in frailty appeared to reflect improvements in multiple frailty parameters, including wasting, exhaustion, low

Table 1: Baseline demographics of participants completing the 4-week assessment ($N = 25$).

Variable	Values
Age (years), median (IQR)	62 (52.5–67)
Male, *n* (%)	14 (56.0)
Race/ethnicity, *n* (%)	
White non-Hispanic	22 (88.0)
Black non-Hispanic	1 (4.0)
White Hispanic	1 (4.0)
Other	1 (4.0)
CKD stage, *n* (%)	
3B	1 (4.0)
4	7 (28.0)
5 (non-dialysis)	1 (4.0)
5 (dialysis dependent)	16 (64.0)
Dialysis modality, *n* (%)	
HD	12 (48.0)
PD	4 (16.0)
Time on dialysis (years), median (IQR)	3.0 (0.6–6.0)
Diabetes, *n* (%)	16 (64.0)
History of smoking, *n* (%)	6 (24.0)
BMI (kg/m^2), median (IQR)	30.5 (27.1–34.5)
Evaluated for kidney transplant, *n* (%)	21 (84.0)
Physical frailty phenotype score, *n* (%)	9 (36.0)
SPPB score, median (IQR)	9 (7–10)

physical activity and slow gait speed, which decreased numerically in patients with diabetes (Table 2), patients on dialysis (Table 3) and among the entire cohort (Table 4). The only frailty parameter that did not numerically decrease across groups was grip strength.

After 4 weeks of exercise we also observed improvements in total SPPB scores (Fig. 3). The largest improvement was observed in patients with diabetes, who experienced a significant increase in their total SPPB score from 7.5 (IQR 7.0–9.8) to 9 (IQR 8.0–10.0, $P = .03$). Likewise, patients on dialysis and the entire cohort experienced a significant increase in their total SPPB score [9.0 (IQR 7.0–10.0) to 9 (IQR 9.0–10.0), $P = .03$ and 9.0 (IQR 7.0–10.0) to 9.0 (IQR 9.0–10.5), $P = .002$, respectively]. The improvement in total SPPB scores appeared to reflect improvements mainly in balance and chair stand scores. The most significant improvements in balance and chair stand scores occurred among the entire cohort, where each score improved by 1 point ($P = .05$ and $P = .04$, respectively). Median gait speed scores in patients with diabetes (Table 2), patients on dialysis (Table 3) and the entire cohort (Table 4) were already 4.0 at baseline, which represents the highest possible score, with no room for improvement.

When examining HRQOL, no improvements in the physical or mental composite scores of the KDQOL were observed in the subset of patients with diabetes, those who were on dialysis or among the entire cohort (data not shown). However, scores on the energy/fatigue scale of the KDQOL improved across all groups. In patients with diabetes, energy/fatigue scores numerically improved from 35.0 (IQR 20.0–50.0) to 50.0 (IQR 38.8–62.5, $P = .07$), while in patients on dialysis, energy/fatigue scores improved significantly from 42.5 (IQR 21.3–50.0) to 50.0 (IQR 40.0–60.0, $P = .008$). Energy/fatigue scores among the entire cohort also improved significantly from 42.5 (IQR 26.3–50.0) to 50.0 (IQR 40.0–61.3, $P = .02$). The intervention was not associated with body weight or body composition in patients with diabetes, patients on dialysis or among the entire cohort (data not shown).

DISCUSSION

In this study we conducted a clinical trial examining the safety, feasibility and efficacy of a 4-week supervised exercise intervention on frailty in patients with CKD. We found that the intervention was feasible and safe, with no serious adverse events. Nearly 75.0% of the cohort completed the 4-week intervention. After 4 weeks of exercise we observed a 31.0% decrease in frailty prevalence in the subset of patients with diabetes ($P = .03$) and a 24.1% decrease in frailty prevalence in the subset of patients on dialysis ($P = .03$). We also observed statistically significant improvements in total SPPB scores, with the largest increase occurring in patients with diabetes [7.5 (IQR 7.0–9.8) to 9 (IQR 8.0–10.0), $P = .03$]. Improvements in energy/fatigue as measured by the KDQOL were also noted. No study-related adverse events occurred.

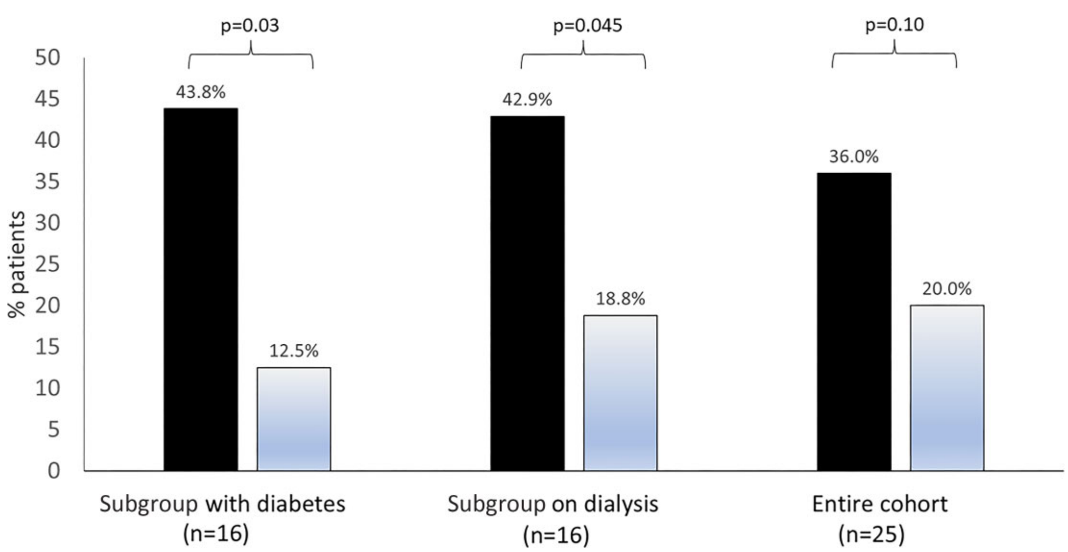

Figure 2: Change in the physical frailty phenotype from baseline to 4 weeks different patient groups. Baseline results displayed in black and 4-week results in gray.

Table 2: Change in frailty among subgroup of patients with diabetes.

Outcome	Baseline ($n = 16$)	4 weeks ($n = 16$)	P-value[a]
Physical frailty phenotype			
Frail, *n* (%)	7 (43.8)	2 (12.5)	.03
Wasting, *n* (%)	4 (25.0)	3 (18.8)	.56
Exhaustion, *n* (%)	7 (43.8)	5 (31.3)	.41
Low physical activity, *n* (%)	6 (37.5)	2 (12.5)	.10
Slow walking speed	3 (18.8)	1 (6.3)	.16
Walking time (sec), median (IQR)	5.2 (4.6–5.6)	4.0 (3.4–4.6)	<.0001
Weakness, *n* (%)	12 (75.0)	10 (62.5)	.32
Grip strength (kg), median (IQR)	22.3 (14.8–29.6)	21.2 (19.9–32.8)	.35
SPPB			
Total score, median (IQR)	7.5 (7.0–9.8)	9.0 (8.0–10.0)	.03
Total score ≤10, *n* (%)	15 (93.8)	13 (81.3)	.32
Balance score, median (IQR)	3.0 (2.0–4.0)	3.5 (3.0–4.0)	.23
Gait speed score, median (IQR)	4.0 (4.0–4.0)	4.0 (4.0–4.0)	.10
Gait speed test time (sec), median (IQR)	4.5 (3.9–4.8)	3.7 (3.2–4.4)	.01
Chair stand score, median (IQR)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	.16
Chair stand test time (sec), median (IQR)	14.7 (13.1–20.3)	19.5 (15.1–25.4)	.07

[a]Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables.

Table 3: Change in frailty among subgroup of patients on dialysis.

Outcome	Baseline ($n = 16$)	4 weeks ($n = 16$)	P-value[a]
Physical frailty phenotype			
Frail, *n* (%)	7 (42.9)	3 (18.8)	.045
Wasting, *n* (%)	5 (31.3)	4 (25.0)	.32
Exhaustion, *n* (%)	9 (56.3)	5 (31.3)	.32
Low physical activity, *n* (%)	6 (37.5)	3 (18.8)	.18
Slow walking speed, *n* (%)	3 (18.8)	2 (12.5)	.32
Walking time (sec), median (IQR)	5.2 (4.7–5.7)	4.0 (3.4–4.5)	<.0001
Weakness, *n* (%)	11 (68.8)	11 (68.8)	1.00
Grip strength (kg), median (IQR)	21.4 (16.9–27.3)	20.4 (17.8–27.6)	.67
SPPB			
Total score, median (IQR)	9.0 (7.0–10.0)	9.0 (9.0–10.0)	.03
Total score ≤10, *n* (%)	14 (87.5)	13 (81.3)	.56
Balance score, median (IQR)	3.0 (2.3–4.0)	4.0 (3.0–4.0)	.11
Gait speed score, median (IQR)	4.0 (3.0–4.0)	4.0 (4.0–4.0)	.50
Gait speed test time (sec), median (IQR)	4.2 (3.8–4.7)	3.8 (3.1–4.2)	.03
Chair stand score, median (IQR)	1.5 (1.0–2.8)	2.0 (1.0–3.0)	.62
Chair stand test time (sec), median (IQR)	16.6 (14.7–25.6)	15.4 (13.1–20.2)	.15

[a]Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables.

Our exercise intervention is a promising method of delivering exercise to KT candidates and patients with CKD. First, the intervention is standardized, potentially reimbursable and able to be disseminated across pulmonary rehabilitation centers throughout the country. Second, we found preliminary efficacy after only 4 weeks of exercise. Exercise interventions that are brief yet efficacious might be associated with better completion rates and easier to implement as part of a prehabilitation strategy prior to surgical procedures such as KT. Third, the intervention was supervised. Supervised exercise may be safer and more efficacious than home-based programs and allow for real-time feedback, encouragement, teaching and personalization of the program [32]. Fourth, our intervention appeared to be effective at reducing frailty prevalence in patients with diabetes. Patients with CKD who have diabetes and frailty are at especially high risk of mortality, highlighting the importance of developing effective interventions in this vulnerable subgroup [33]. Lastly, our intervention applies to all patients with CKD regardless of dialysis status or modality. Our cohort consisted of patients who were not on dialysis, patients who were on HD and patients who were on PD. Most previously published studies have involved intradialytic exercise or exercise administered during an in-center HD session, which does not generalize well to patients not on dialysis or to patients receiving home dialysis [34].

Table 4: Change in frailty among the entire cohort.

Outcome	Baseline ($n = 25$)	4 weeks ($n = 25$)	P-value[a]
Physical frailty phenotype			
Frail, n (%)	9 (36.0)	5 (20.0)	.10
Wasting, n (%)	8 (32.0)	6 (24.0)	.32
Exhaustion, n (%)	10 (40.0)	9 (36.0)	.74
Low physical activity, n (%)	9 (36.0)	4 (16.0)	.06
Slow walking speed, n (%)	4 (16.0)	2 (8.0)	.16
Walking time (sec), median (IQR)	5.1 (4.5–5.6)	4.1 (3.4–4.5)	<.0001
Weakness, n (%)	14 (56.0)	15 (60.0)	.71
Grip strength (kg), median (IQR)	24.5 (17.0–38.7)	23.1 (19.2–37.9)	.59
SPPB			
Total score, median (IQR)	9 (7–10)	9 (9–10.5)	.002
Total score ≤10, n (%)	23 (92.0)	76.0% (n = 19)	.10
Balance score, median (IQR)	3 [2–4]	4 (3–4)	.05
Gait speed score, median (IQR)	4 [4–4]	4 (4–4)	.19
Gait speed test time (sec), median (IQR)	4.2 [3.8–4.7]	3.9 (3.2–4.5)	.006
Chair stand score, median (IQR)	1 [1–2]	2 (1–3)	.04
Chair stand test time (sec), median (IQR)	16.8 [14.8–23.4]	15.2 (12.3–20.1)	.03

[a]Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables.

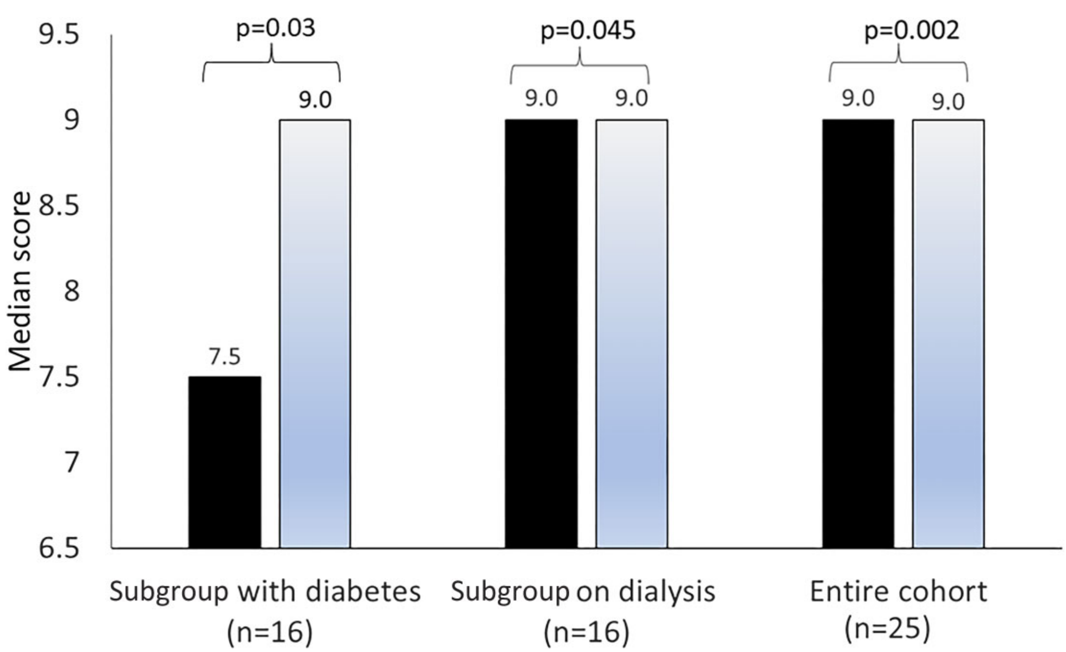

Figure 3: Change in SPPB scores from baseline to 4 weeks different patient groups. Baseline results displayed in black and 4-week results in gray.

An unexpected and noteworthy finding of our study is that our intervention was associated with improvements in energy/fatigue as measured by the KDQOL. Fatigue is a common problem in patients with CKD. Approximately 67% of patients with nondialysis CKD [35] and 89% of patients on dialysis [36] endorse fatigue. Fatigue is associated with subsequent cardiovascular events and death in patients with CKD [37–39]. Our finding that only 4 weeks of supervised exercise improves fatigue, perhaps through improved muscle strength and physical activity, is promising and should be replicated in larger controlled trials.

Our study has important limitations. The study was not randomized and the sample size was small. Participants were mostly White and from a single center. We did not elicit patient perspectives about facilitators and barriers to exercise, including whether a home-based exercise intervention would have been more feasible for them. We do not have data regarding the sustainability of increased physical activity or physical function after completion of the intervention. Our use of the physical frailty phenotype as a study endpoint is limited by the fact that one of the phenotype's criteria is low physical activity—any improvement observed in physical activity might simply reflect study participation rather than true improvement in physiological frailty.

All of the above limitations offer important insights into future study designs. Our findings need to be replicated in a larger, more diverse cohort of patients. Future studies should elicit patient perspectives about exercise using mixed methods approaches. They should involve randomization, potentially not only comparing supervised exercise with usual care but also home-based exercise with supervised exercise. Home-based exercise may also be an effective antifrailty intervention in patients with CKD and be less resource intensive than supervised interventions [40, 41]. Future studies should ideally include other performance-based measures of frailty in addition to the physical frailty phenotype. They should not only examine the sustainability of improvement in frailty over time (especially in patients waitlisted for KT who may need to maintain improved physical function for months to years while they await transplantation), but also the impact of the intervention on outcomes such as hospitalization and access to KT.

In conclusion, 4 weeks of supervised exercise was associated with improved frailty prevalence, SPPB scores and energy/fatigue as measured by the KDQOL in patients with CKD, including subsets of patients with diabetes and patients on different dialysis modalities. Our 4-week intervention was associated with a >70% completion rate and with no study-related adverse events. This study is a step forward in understanding how best to successfully implement exercise interventions in patients with CKD and offers important feasibility data for a future larger randomized study.

ACKNOWLEDGEMENTS

We acknowledge the study coordinators and respiratory therapists, without whom this study could not have been completed, including Renee Weatherly, Karen Thompson, Heidi Walker, Judy Rasmussen, Tara Stewart and Jim Garrett.

FUNDING

C.C.K. is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health (awards HL 128859 and HL 158811). E.C.L. and L.J.H. are supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (awards DK 123313 and DK 109134, respectively). The manuscript's contents are solely the responsibility of the authors and do not necessarily represent the official view of National Institutes of Health. This study was supported by the Center for Translational Science Activities through grant number UL1 TR000135 from the National Center for Advancing Translational Sciences. This study was also supported by the Mayo Clinic Robert and Billie Pirnie Endowment Award for Transplant Research.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Received: 22.2.2023; Editorial decision: 21.7.2023