Kidney Medicine

A Comprehensive Exercise (COMEX) Intervention to Optimize Exercise Participation for Improving Patient-Centered Outcomes and Physical Functioning in Patients Receiving Hemodialysis: Development and Pilot Testing

Manisha Jhamb, Susan M. Devaraj, Maryam Alemairi, Linda-Marie Lavenburg, Sruti Shiva, Jonathan G. Yabes, Daniel E. Forman, and Andrea L. Hergenroeder

Rationale & Objective: To address the need for an intradialytic exercise program that is easily delivered in clinical setting, engaging and scalable, we developed a novel COMprehensive EXercise (COMEX) program based on input from patients receiving hemodialysis (HD), dialysis staff members and nephrologists. The objective of this study was to determine the feasibility, safety, and acceptance of COMEX during HD.

Study Design: Single-arm prospective pilot feasibility study.

Setting & Participants: Seventeen patients receiving in-center HD.

Intervention: Three-month participation in the COMEX program, which included video-based dialysis chair exercises (aerobic and resistance) integrated with educational and motivational components.

Outcomes: Data on recruitment, adherence, safety and acceptability were collected. Additional assessments were performed to evaluate changes in physical functioning, patient-reported symptoms, and objectively measured sleep and physical activity. We also examined the feasibility of obtaining skeletal muscle biopsies and blood samples to explore molecular mechanisms of muscle atrophy and to assess platelet mitochondrial function and adaptation to exercise during HD.

Results: Thirteen of the 17 (76%) participants completed the 3-month intervention. The mean participant age was 63.6 ± 15.1 years. In total, 46% of participants were males, and 55% were White. The mean body mass index was 38.7 ± 11.6 kg/m^2. There were no reported adverse effects, and the adherence rate to exercise sessions was high with 88% of the sessions completed. Patient satisfaction was high, as 100% of the patients would recommend the program to other dialysis patients. It was feasible to collect data on physical functioning, patient-reported symptoms, and objective sleep and physical activity and to obtain muscle biopsies and blood samples.

Limitations: Small sample size, lack of an onsite exercise professional, and technological issues with telemedicine behavioral motivation.

Conclusions: The COMEX intradialytic exercise intervention is safe and acceptable to patients, and outcome measures were feasible to obtain. Future studies should consider including exercise professionals to facilitate progression through a personalized exercise protocol.

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Visual Abstract included

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Correspondence to M. Jhamb (jhambm@upmc.edu)

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Of the 500,000 hemodialysis (HD) patients in the United States (US), the vast majority suffer from fatigue, poor sleep, pain, and poor physical function.[1-4] Additionally, sarcopenia, muscular atrophy and dysfunction are common, predisposing them to frailty, falls and poor health-related quality of life (HRQOL).[5,6] Prior studies in patients receiving dialysis have shown that exercise can improve physical functioning, symptom burden and HRQOL.[7,8] Despite the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guideline recommendations to increase physical activity for all patients with kidney failure, <50% of the HD patients in the US exercise regularly.[8,9]

Exercise during HD (intradialytic) is not only logical but is proven to be safe and effective and addresses many patient-reported barriers to physical activity, such as time and travel constraints, access to equipment and space, and fear of injury.[10,11] Additionally, an intradialytic exercise program is welcomed by patients because it incorporates exercise into their daily life without using up valuable nondialysis time.[12,13] However, it is not part of "standard clinical care" in the US, primarily due to the lack of a program design that meets the needs and preferences of both patients and dialysis unit staff, has long-term acceptance and adherence, and is sustainable within the limited resources of the clinical setting.[14,15] Given the potential for exercise to improve HRQOL, delay functional decline and prevent disability in this vulnerable population, there is a need to develop and test novel exercise programs and evaluate best practices for implementation to bridge the gap between evidence and implementation.

PLAIN-LANGUAGE SUMMARY

We tested a new COMprehensive EXercise (COMEX) program to deliver exercise during dialysis. This 3-month program included video-based dialysis chair exercises (aerobic and resistance) integrated with educational and motivational components. Our study shows COMEX was feasible, had high satisfaction and adherence, and was safe. It was feasible to collect data on physical functioning, patient-reported symptoms, and objective sleep and physical activity and to obtain muscle biopsies and blood samples. Future studies should consider including exercise professionals to facilitate progression through a personalized exercise protocol.

Our prior qualitative study of patients on HD, dialysis staff members and nephrologists identified facilitators, barriers, recommendations and design elements for an intradialytic exercise program, which provided the foundation for current program.[13] Using valuable stakeholder feedback, our multidisciplinary team of experts in nephrology, rehabilitation, and behavioral modification developed a COMprehensive EXercise (COMEX) program. COMEX is a novel video-based intradialytic chair exercise program that primarily targets strength training to improve the sarcopenic and deconditioning effects of kidney disease. It incorporates motivational and educational strategies to promote adherence. It leverages portable technology to simplify delivery of exercise protocols and motivational and educational materials. Video-based delivery of these requires minimal resources as opposed to in-person exercise delivery and overcomes barriers, such as availability of exercise professionals who are willing to travel to dialysis clinics, especially in rural areas, thus facilitating scalability and sustainability.

The goal of this pilot study was to determine the feasibility, safety and acceptance of a 3-month COMEX program. We also explored changes in key symptoms and physiologic outcomes to inform the design of a future randomized controlled trial. Lastly, we examined feasibility of obtaining skeletal muscle biopsies and platelet respiration measurements to explore molecular mitochondrial mechanisms of muscle atrophy and adaptation to exercise during HD.[16]

METHODS

Study Design and Participants

This is a single-arm prospective pilot feasibility study with a 3-month exercise intervention period. We recruited participants from an outpatient dialysis unit in Pittsburgh, PA from February 2017 to October 2017. Adults (age 18+ years) with kidney failure receiving in-center HD 3 times a week for at least 90 days, able to read and write in English, willing and able to take part in the study, and who had physician (nephrologist and/or primary care provider) approval to participate were eligible. Patients were excluded if they were dialyzed using a tunneled dialysis catheter (because of safety reasons); had significant cognitive impairment or were approaching end of life; had planned a transition to home dialysis or a living donor transplant within 6 months; had severe psychiatric illness, active substance use, or were taking an investigational drug; or were participating in another trial. We also excluded participants who had an acute or chronic medical condition that would preclude moderate intensity exercise, such as uncontrolled hyper- or hypotension, recent myocardial infarction, decompensated heart failure or unstable angina within the last 3 months, unstable diabetes control (hyper- or hypo-glycemia requiring urgent intervention within last 3 months), inadequate dialysis clearance ($spKt/v \leq 1.2$ in the last 2 months) or with complete or partial leg amputation causing inability to walk independently or using assisted device (because the program involves leg exercises). For the muscle biopsy, the only additional exclusion criteria were allergy to lidocaine, bleeding disorder, use of an anticoagulant/antiplatelet that could not be withheld safely, anemia (hemoglobin < 10 gm/dL), or chronic use of oral corticosteroid or other medication that can affect muscle function.

COMEX Intervention

The COMEX program is described in detail in Table 1.[17,18] The chair exercises were designed by a physical therapist (ALH) and nephrologist (MJ), who incorporated feedback from patients and dialysis staff. Given the limitations of chair exercises while doing HD and the inability of participants to move the arm with dialysis access, most exercises focused on the legs. We invited 2 HD patients to try different exercises and equipment (resistance bands, dumbbells, ankle weights) at the University of Pittsburgh Physical Therapy Clinical and Translational Research Center (PT CTRC) and then field-tested these in a dialysis clinic with further modifications based on input from dialysis staff. Some patient-recommended design elements included use of a peer instructor, exercise demonstrations while receiving HD to show safety, and the use of lively background recorded music and motivational phrases ("keep on moving", "don't give up") in the videos to maintain engagement.

COMEX Intervention Implementation

After baseline assessments, patients watched an educational video and were instructed on how to use the exercise video and complete a pretreatment safety checklist and exercise log (Item S1 and S2). Research staff were not exercise professionals but received brief training on how to provide oversight and educate the patients. The first exercise session was supervised by research staff to ensure correct

Table 1. Details of Components of the COMEX Intervention

COMEX Component	Structure	Implementation	Content/Intention
Video-based dialysis chair exercise	45-min video demonstrated exercises performed by a patient on HD alongside a trainer. • Instructions on self-completion of safety checklist, exercise log (record duration of session, difficulty level, amount of weight used), and use of Borg rating of perceived exertion scale (5 min) • Warm-up exercise (5 min) • Aerobic exercise (15 min) • Resistance exercise (15 min) • Cool down exercise (5 min) Additional notable aspects of videos: • Instruction on technique and posture • Lively music • Frequent safety reminders to keep access arm still • Pacing of exercise	Exercise videos were played on small DVD players placed on the chairside arm tables by their dialysis chair and shown every HD session. Equipment: dumbbells (only for the nondialysis access arm), ankle weights and a towel roll, all of which could be used independently with minimal assistance from dialysis staff (except placement of the ankle weights).	Exercise design considerations: • Performed sitting in the regular dialysis chair without moving the access arm • Required minimal assistance from dialysis staff • Scalable intensity according to the patient's ability • Equipment was inexpensive and easy to use, store and sanitize • Incorporated patient and staff feedback
Educational and motivational video	30-min educational video included patient testimonials from 3 dialysis patients who represented different gender and racial backgrounds (one White male, one Black male, one Black female) and educational information from a physical therapist (ALH) and nephrologist (MJ).	Video was shown to patients in the HD unit before starting the exercise program.	Education focused on exercise benefits and safety to address patients' concerns and fears elicited during our qualitative work. Patients discussed the benefits of exercise, lifestyle integration and motivation.
Educational booklet	6-page booklet based on available educational materials[17]	Self-read	Booklet addressed benefits and safety of exercise.
Motivational interviewing	One-time individualized session with communications/patient education expert for goal-oriented, patient-centered counseling for eliciting behavior changes as recommended by the American Heart Association.[18]	Secure online video chat with study tablet set up in the dialysis unit	Intended to resolve ambivalence and increase motivational readiness for exercise.
Motivational video clips	A compilation of 10-15 real-life inspiring video clips from YouTube (5-10 min each) containing testimonials from patients with other chronic illnesses	Watched at home or during HD	Clips addressed barriers, such as poor self-perceived health status and self-efficacy.

Abbreviations: DVD, digital video disk; HD, hemodialysis.

Table 2. Assessment Tools and Measures Conducted Preintervention and Postintervention (Baseline and 3 Months)

Test/Questionnaire	Assessment/Scoring	Properties
Physical Function Tests (Completed at PT CTRC)		
SPPB	Assess standing balance, gait speed and lower extremity strength (time to complete 5 chair rises) Composite scores [0 (worst) to 12 (best)] calculated per protocol[21]	Reliable and valid tool for use in older adults with a range of physical abilities[22]
30-s STS test	Assesses lower body strength Outcome is number of times sit to stand can be performed in 30 seconds	Valid measure of lower extremity strength and balance[23]
Gait speed	Time to walk 4 meters of an 8-meter course at the participant's usual pace	Reliable measure of physical function in clinical settings
6MWT	Distance walked over 6 min as a submaximal test of aerobic capacity/endurance	Standardized, well-validated, objective measure of functional capacity[25]
Measurement of Leg Strength with Biodex System 3 Pro (Biodex Medical Systems, Shirley, NY)	Maximal voluntary isometric contraction of quadriceps muscle (average of 3 sets, ~ 5 s/each)	The intraclass correlation coefficient with 2 raters and the average of 3 measures is 0.92[24]
Patient-Reported Measures (Completed chairside in the dialysis unit)		
FACIT-F	Assesses fatigue Possible score range, 0-52 Higher score indicates lower fatigue	Shown to be a valid and reliable measure of fatigue[26]
BDI	Assesses depressive symptoms Score ≥ 16 in dialysis patients indicates clinically significant depression	Found to be consistent, reliable, and valid[27]
PSQI	Measure of sleep quality and disturbances over a 1-mo time period Possible range 0-21 Higher score indicates worse sleep quality	Found to be valid and reliable with utility in both clinical and research settings[28]
AMPAC Short Form	Measures basic mobility, daily activity, and applied cognitive functions	Found to be reliable for activity outcome measurement[29]
PROMIS Adult Global Health questionnaire	Measures individual physical, mental, and social health	Valid and reliable in measuring health in respective domains[30]
SF-36	Part of the Medical Outcomes Survey that measures quality of life Each domain is scored 0-100 with a higher score indicating more favorable status	Physical and mental health components found to distinguish severity of conditions within respective domains[31]
PASE	Physical activity questionnaire designed for participants age 65 y and older combining measures of leisure, household, and occupational activity Assesses frequency, duration, and intensity of activities completed in the past week Possible score of 0-793 with a higher score indicating more activity	Shown to be valid for use in studies evaluating associations between physical activity and physical health and function in older adults[32]
Objective Sleep and Physical Activity Assessment (worn simultaneously for 7 consecutive days, 24 h a day)		
Actigraph (Actiwatch by Minimitter, Inc.; worn on the wrist of the arm without an active graft or fistula)	Measures sleep and wakefulness by assessing activity through an accelerometer placed on the wrist that records movement Worn for 7 d	Found to be useful in measuring sleep in older adults alongside subjective measures[33]
ActivPAL3 (PAL Technologies, Ltd.; a thigh-worn accelerometer)	Records and classifies activity into time spent in sedentary, standing, and walking behaviors using proprietary	Validated in older adults and individuals with lower physical functioning

(Continued)

Table 2 (Cont'd). Assessment Tools and Measures Conducted Preintervention and Postintervention (Baseline and 3 Months)

Test/Questionnaire	Assessment/Scoring	Properties
	algorithms using a 24-h wear protocol Worn for 7 d	Reliable and valid measure of sedentary and physical activity behaviors and step counts[34]
Sleep and Physical Activity Diary	Patients recorded sleep and wake times and daily leisure activities	Used to confirm monitor-obtained data
Skeletal Muscle Biopsy (UPMC Montefiore CTRC, performed in a subset of 10 patients)		
Biopsy of the vastus lateralis (thigh) muscle in the nondominant leg was performed on a non-HD day using a standard procedure[35]	Muscle specimens were immediately processed, stored in RNA preservation solution, frozen in liquid nitrogen and stored	Future analysis will evaluate muscle mitochondrial function and expression of genes previously defined as induced or suppressed in atrophying skeletal muscle (atrogenes)
Blood samples	Samples obtained to explore utility of platelets to measure mitochondrial function Analysis will be performed at the Center for Metabolism and Mitochondrial Medicine	Evaluate effect of exercise on basal and maximal platelet respiration and platelet nitrite levels

Abbreviations: UP PT CTRC, University of Pittsburgh Physical Therapy Clinical and Translational Research Center; SPPB, Short Physical Performance Battery; 30-s STS, 30-Second Sit to Stand test; 6MWT, 6-Minute Walk Test; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue; BDI, Beck's Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; AMPAC, Activity Measure – Post Acute Care; PROMIS, Patient-Reported Outcomes Measurement Information System; SF-36, Short Form 36; PASE, Physical Activity Scale for the Elderly; UPMC CRTC, University of Pittsburgh Medical Center, Clinical and Translational Research Center.

posture and use of equipment and safety protocols. Hand and leg weights were individualized based on patient's ability with a target intensity of 12-14 (at least moderate)

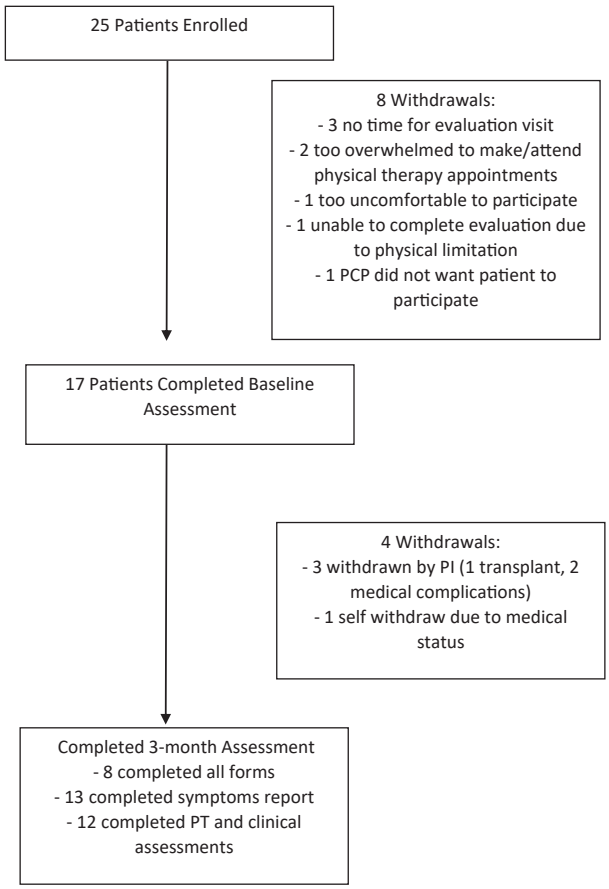

Figure 1. Participant recruitment in COMEX study. Abbreviations: PCP, primary care physician; PI, principal investigator; PT, physical therapy.

using the Borg rating of perceived exertion scale. Research staff reviewed the exercise log every 2 weeks and increased the weights to achieve target intensity. Equipment was stored in individual patient-labeled plastic boxes at the dialysis unit, thereby simplifying the logistics of storage and disinfection. Patients were given dumbbells to use at home for the dialysis access arm. The 3-month intervention duration was based on prior successful exercise trials in dialysis and other chronically ill populations showing an improvement in important outcomes after a 2- to 3-month intervention period.[19,20] Patients were followed until intervention completion, death, or loss to follow-up (withdrawal from study, transfer of clinic, change to peritoneal dialysis or transplantation).

Dialysis Staff Education

An important aspect of this program was education of dialysis staff on the benefits and safety of intradialytic exercise. Before starting the program, dialysis staff were provided a brief orientation session and opportunity to ask questions, and staff champions were identified to promote the program and motivate patients.

Study Outcomes

Clinical characteristics, including demographics, comorbidities, medication use, labs, predialysis blood pressures (over the last 6 treatments), and anthropometric measures (height, weight, waist and hip circumference), were collected at baseline from patients and by chart review.

Feasibility Outcome Assessments

The following feasibility outcome assessments were performed: a) Satisfaction: Patient and provider satisfaction on the ease and appropriateness of COMEX was assessed using adapted Client Satisfaction Questionnaires.[21] b) Adherence: Patient-maintained exercise logs were used to calculate exercise attendance rate (number of sessions with

Table 3. Baseline Characteristics of Patients who Completed the 3-month Intervention (n=13)

Characteristics	Mean ± SD or n (%)
Demographics	
Age (y)	63.6 ± 15.1
Males	6 (46)
Race (n=11)	
White	6 (55)
Have caregivers at home	11(85)
Comorbidity and medical history	
Ever smoker	11 (85)
BMI (n=11)	38.7 ± 11.6
ICU admission in the past 1 y	2 (15)
Cardiovascular disease	6 (46)
Diabetes	6 (46)
Diabetic nephropathy	3 (23)
Hypertensive nephrosclerosis	5 (39)
Blood pressure (n=11)	
Systolic pressure	139 ± 16.1
Diastolic pressure	71.0 ± 11.0
Biochemical tests	
Hemoglobin	11.1 ± 0.8
Albumin	4.1 ± 0.3
Creatinine	7.9 ± 2.6
Kt/V	1.8 ± 0.6

Abbreviations: SD, standard deviation; BMI, body mass index; ICU, intensive care unit.

participation/total number of sessions offered) × 100%. Sessions were offered 3 times per week during HD. Participants who reported completing 80% of sessions were considered adherent. c) Adverse events: Patients were monitored weekly for signs and symptoms of 1) hemodynamic stability during and post HD; 2) cardiovascular symptoms; 3) access-related complications; and 4) musculoskeletal injury through review of medical records and patient interviews.

Physical Function/Performance Measures

Study outcomes were assessed in participants at baseline and at 3 months (Table 2).[21–35] Patients completed a range of physical functioning tests on a non-HD day at the PT CTRC with trained physical therapists using standardized protocols. These included the Short Physical Performance Battery (SPPB),[22] 30 Second Sit to Stand (30-s STS) test, gait speed assessment, 6-Minute Walk Test (6MWT)[24] and leg muscle strength assessment.

Patient-Centered Outcomes

To assess patient-reported symptoms (at baseline and 3 months), psychometrically sound questionnaires assessing a wide range of health domains were selected and administered in person by research staff chairside in dialysis units to ensure high rate of data collection and minimal study burden (45-60 min).[26,28,32,36,37] Objective and self-reported sleep and physical activity were also measured.

Translational Measures

To demonstrate feasibility, a biopsy of the vastus lateralis (thigh) muscle in the nondominant leg was performed at baseline and at 3 months on a non-HD day in a subset of 10 patients using a standard procedure at the University of Pittsburgh Montefiore CTRC (Item S3).[35,38] Additionally, blood samples were collected to measure plasma nitrite levels using tri-iodide-based reductive chemiluminescence and mitochondrial function using extracellular flux analysis as previously described (Table 2).[39,40]

Statistical Analysis

The number of patients approached, screened, eligible, and consented were summarized [n(%)] with reasons for nonconsent, exclusion, and drop-out reported at each stage of the study. Descriptive statistics were computed to report baseline characteristics [mean (standard deviation [SD]) and n(%)]. Intervention adherence [n(%)] was calculated for participants who completed both the baseline and 3-month follow-up study visits. Estimates of treatment effect on patient-centered outcomes were calculated using mean estimates of change. Because this is a feasibility study that is not powered to detect differences in outcomes, P values are not reported. All analyses were conducted using R.[41]

RESULTS

Screening and Recruitment Rates

Out of the 40 patients who were screened, 25 (63%) consented, and 17 (43%) completed baseline visits (Figure 1). Among those who completed baseline visits, 4 withdrew due to medical reasons, and the remaining 13 (76%) completed the 3-month intervention. Of participants who completed the intervention, the mean age was age 63.6 ± 15.1 years, 7 (54%) were female, and 6 (55%) were White. The mean body mass index was 38.7 ± 11.6 kg/m^2. In addition, 6 (46%) had diabetes, and 11 (85%) were smokers (Table 3). Of 10 patients eligible and enrolled for muscle biopsy, 7 had baseline muscle biopsies, and 5 had both baseline and 3-month biopsies.

Adherence to COMEX Intervention

The overall adherence rate for the exercise sessions was high with 398 sessions completed of 450 offered (88%), with only 3 of 13 participants comprising 56% of sessions missed. Fifty-two sessions were not complete due to multiple reasons, including staffing or technical issues (1.8%), the patient not feeling well (3.5%), or patient preference (6.7%). The exercise video was used in 91% of completed exercise sessions. Of the 13 participants who completed the program, 7 (53%) increased their dumbbell (arm) weight, 9 (69%) increased their ankle (leg) weight, and the remainder used the same arm or leg weight throughout the program. At initiation, the average arm and

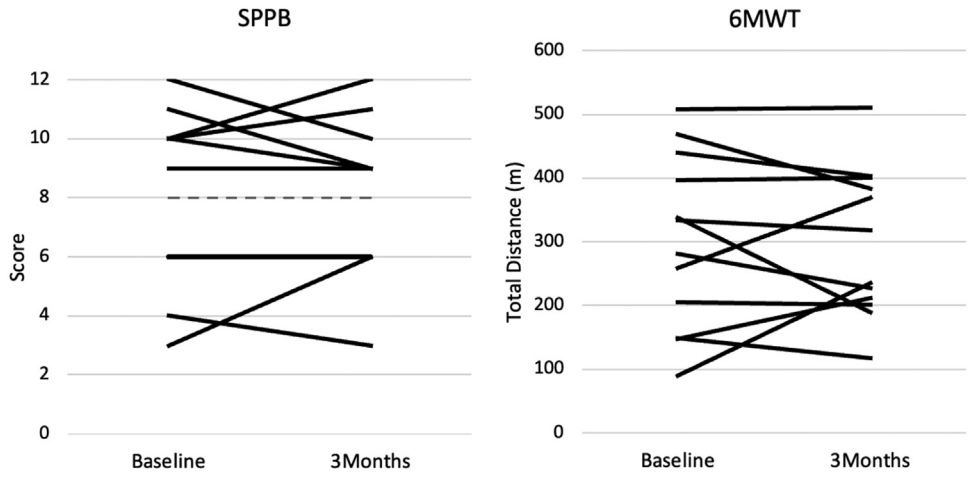

Figure 2. Change in objective physical function tests with the COMEX intervention. Abbreviations: SPPB, Short Performance Physical Battery (composite score range 0-12; lower score indicates worse physical function), 6MWT: Six-Minute Walk Test (shorter distance suggests lower aerobic capacity).

leg weight was 1.7 lb and 1.4 lb, respectively. At 3 months (end of intervention), the average arm and leg weight was 3.2 lb and 3.2 lb, respectively.

The uptake of other components of the COMEX intervention was mixed. Although all patients watched the educational and motivational video before starting the exercise program, <25% were interested in watching the motivational video clips, and none participated in motivational interviewing sessions due to problems with scheduling and connecting to the internet for online video conferencing.

Satisfaction Assessment

Ten of the 13 (77%) participants who completed the program reported they would do the program again, 12 (92%) participants reported they enjoyed doing the exercises, and all 13 (100%) reported they would recommend the program to other dialysis patients. In addition, 4 out of 5 providers who provided feedback reported they were satisfied; however, only 1 provider reported being likely to recommend the program to other dialysis patients (reasons not collected).

Safety Assessment

There were no reported adverse effects with any of the study procedures, including the exercise intervention, measurement of physical function outcomes, Actiwatch and ActivPAL device use, or muscle biopsy. A total of 324 signs and symptoms were recorded throughout the study. Of all 13 participants, the most common symptoms were cold (77%), sleepiness (77%), fatigue (69%), cough (62%), insomnia (62%), and cramps during exercise (62%).

Physical Function/Performance Measures

Objective measures of physical function obtained from the SPPB and 6MWT demonstrated individual changes in scores (Figure 2). Of the 10 participants who completed the preintervention and postintervention SPPB test, 3 (30%) had an increase in SPPB scores, and none of the participants classified as having good physical function at baseline decreased to below the mobility disability cutoff value of 10.[25] Of the 12 participants who completed the 6MWT, 5 (42%) improved.

Patient-Reported Symptoms

Fatigue improved in 8 (62%) patients, and 8 (62%) patients had a decrease in depressive symptoms. No meaningful change in sleep quality was noted over the course of the intervention (Figure 3). Pain improved or remained unchanged in 8 (62%) patients. The Medical Outcomes Survey (MOS) Brief Pain Inventory improved for 3 (23%) patients; however, 7 (54%) patients started at the highest possible score. The MOS Mental Component Score improved for 7 (54%) patients, and the MOS Physical Component Score improved for 4 (31%) patients. The Physical Activity Scale for the Elderly questionnaire indicated an increase in physical activity, with a mean (SD) score increase from 74.9 (61.2) at baseline to 111.5 (68.4) at 3 months.

Objective Physical Activity and Sleep Outcomes

Compliant patient use (ie, wearing the devices for at least 5 out of 7 days) of ActivPAL and Actiwatch was high at baseline [12 (92%) and 13 (100%), respectively] and at 3-months [11 (85%) and 10 (77%), respectively]. Objective measures of activity obtained from the ActivPAL suggest a favorable, but minimal increase in total step count and daily sit to stand transitions [median (25th, 75th percentile) change: 132 (72, 576) steps; 9 (4, 12) sit to stand transitions]. An estimated value for total waking time spent sitting or lying indicated a decrease in these sedentary behaviors after the program [median (25th, 75th

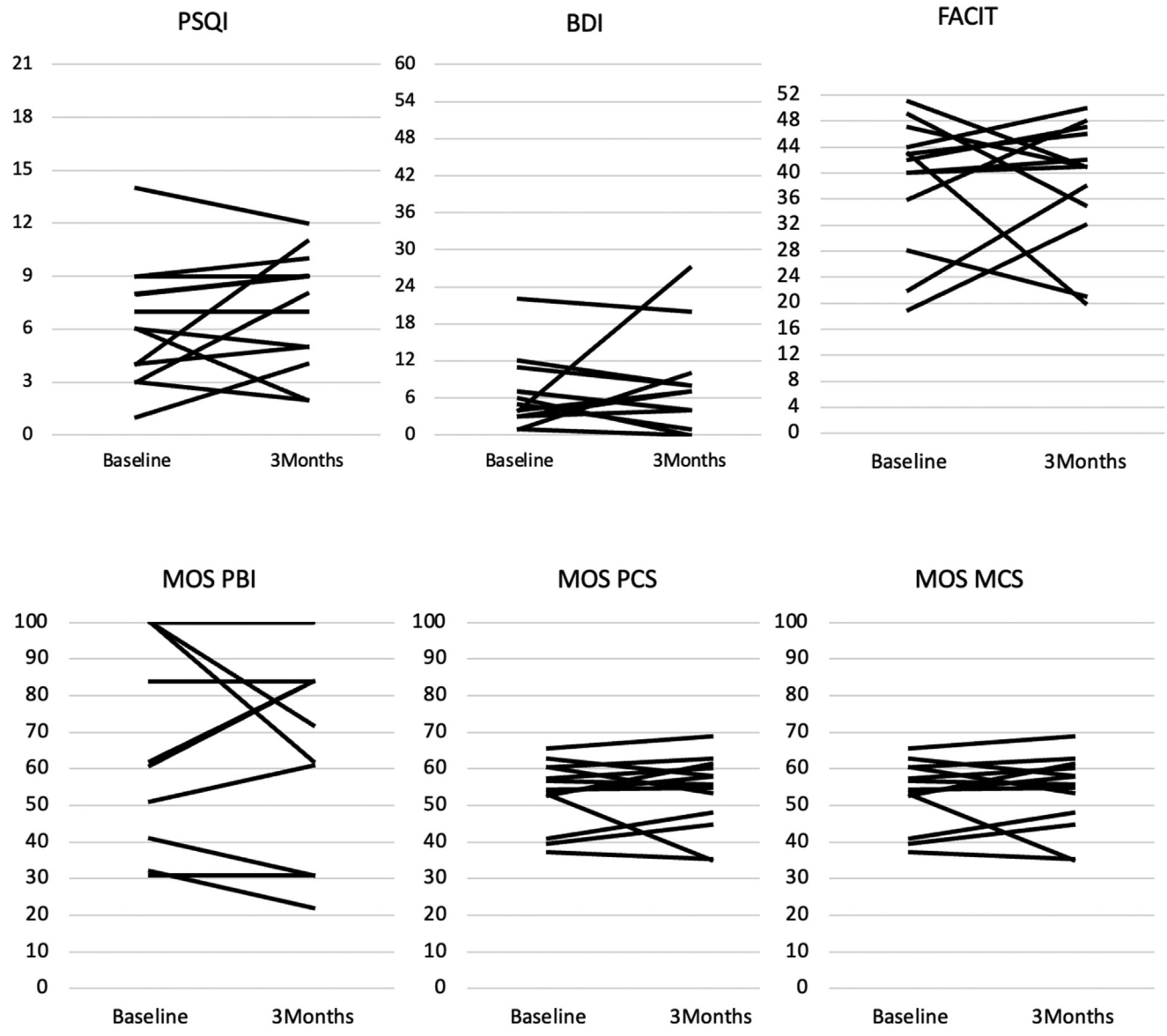

Figure 3. Changes in patient-reported symptoms with the COMEX intervention. Abbreviations: PSQI, Pittsburgh Sleep Quality Index (possible score range 0-21, higher score indicates worse sleep quality); BDI-II, Beck Depression Inventory Second Edition (possible score range 0-63, higher score indicates worse depression); FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue (possible score range 0-52, lower score indicates worse fatigue); MOS BPI, Medical Outcomes Survey Bodily Pain Index (possible score range 0-100, lower score indicates more severe or limiting pain); MOS PCS, Medical Outcomes Survey Physical Component Score (possible score range 0-100, lower score indicates worse composite of factors contributing to physical health); MOS MCS, Medical Outcomes Survey Mental Component Score (possible score range 0-100, lower score indicates worse composite of factors contributing to overall mental health).

percentile) change: -137 (-181, -18) reported sedentary minutes per day]. There were technical issues affecting the validity of Actiwatch data, so no objective measures of sleep are presented here.

Translational Measures

Platelet mitochondrial respiration was measured as a marker of systemic mitochondrial function in 6 patients at baseline and 4 patients after the 3-month intervention (Table S1). The mean change in basal respiration and maximal platelet respiration was 4.5 and 13.9 pmol oxygen/min, respectively, indicating a potential enhancement in the capacity for oxidative phosphorylation. Plasma levels of the nitric oxide metabolite nitrite were also increased by 0.2 μM on average post-intervention, suggesting a small increase in vascular nitric oxide bioavailability, which has been associated with improved cardiovascular health.[42,43]

DISCUSSION

This pilot study demonstrated the feasibility, safety, acceptability, and potential benefits of a novel comprehensive exercise intervention integrated with motivational and educational components for improving physical function and symptom burden in patients receiving HD. We had good recruitment and adherence rates and found that the intervention was acceptable to the majority of patients. There were no serious adverse events related to the exercise or outcome data collection. We found staff satisfaction with the program to be acceptable, but only few providers reported they would recommend the program to other patients. The findings of this study are informative to design a full-scale trial, but several important issues were highlighted to increase the appeal and uptake of the intervention.

The recruitment rate for our pilot study was high compared to other exercise studies in this population, and only 25% of eligible participants refused to participate.[44-47] The most common reason for refusal was the travel time required to complete physical function tests outside of the dialysis unit. The logistical barriers of scheduling tests on non-HD day, the need for travel to an off-site research location and limitations of performing physical tasks in a dialysis units due to space and liability/safety concerns are important considerations. These highlight the need to explore other feasible testing locations to make it more convenient for patients. Some potential solutions include performing tests within the patients' home via an in-person visit or through a virtual platform used by other studies during the COVID-19 pandemic when in-person testing was not possible.[48]

Our study had several strengths. Once patients completed the baseline assessments, the attrition rate was low (only 4 of 17 did not complete the study). Importantly, our study included an older population with a mean age of 63 years and achieved a high adherence rate with 88% of the offered exercise sessions completed. Our study included several enablers, which may have contributed to higher patient satisfaction. These included our use of unit champions to encourage participation in the intervention, selection of appropriate exercise equipment located onsite for individual participant use, minimal burden on dialysis staff to facilitate use of exercise equipment, real-life video testimonials of individuals who shared their positive experience with exercise and acted as role models, and use of engaging exercise videos that offered a variety of exercises and allowed individualization of intensity and pace of exercise. The study also had a dedicated nephrologist (MJ) involved in the recruitment of participants and regular research staff presence in dialysis units, which reduced the possibility of eligibility misconceptions and provided ongoing education and motivation. Additionally, the feasibility and safety of obtaining muscle biopsy preintervention and postintervention in sarcopenic kidney failure patients is encouraging, and future trials can explore molecular mechanisms of symptoms, such as fatigue, and the impact of training on muscle structure and mitochondrial respiration.[49-51]

Our small sample of patients had a range of functional abilities at baseline and mixed responses to intradialytic exercise. The preintervention and postintervention physical function assessments showed some patients improving, others not changing, and still others declining in function on the SPPB and 6MWT. Our exercise prescription included a target intensity of moderate for the aerobic exercise and moderate to vigorous for the strengthening exercise. However, participants may have had difficulty reaching these targets while simultaneously receiving dialysis and adhering to restrictions imposed by dialysis equipment and lines. Additionally, although research staff adjusted the exercise prescription intensity according to patient exercise logs, this was probably insufficient. Given varying levels of physical function and ability of participants at baseline, an exercise professional may have been better able to assess patients and guide progression to the optimal duration and intensity of exercise, help reinforce importance and safety, and facilitate accountability.[52,53]

Moreover, as previously suggested, participation in supplemental exercise and physical activity outside of dialysis is equally, if not more important, to promote overall physical fitness in the kidney failure population.[54] This is especially true with the limitations of chair exercise while doing dialysis and the inability to involve the dialysis access arm or engage in significant aerobic exercise. Patients in our study were provided dumbbells for use at home and encouraged to engage in any form of physical activity. We showed that use of ActivPAL to monitor physical activity was feasible and safe and had a high compliance rate; thus, this device shows promise for use in a larger study. The physical activity level was generally stable, indicating that an exercise intervention may help to offset declines in physical activity that may be experienced in patients on HD.

Castillo et al[52] conducted a theory-informed qualitative study of health care providers and patients to identify potential barriers and enablers to intradialytic exercise interventions. Although our program incorporated many of the feasibility checklist items mentioned in the study, additional findings from this study can inform the redesign of our program to improve provider satisfaction. Low staff satisfaction with the intervention may be due to inadequate knowledge about intradialytic exercise or an increase in dialysis staff responsibilities. Because our study included an orientation session for the dialysis staff, we did not develop specific training modules or provide ongoing education to support staff involvement in the program. Additionally, our program likely did not include sufficient community enhancement strategies to build support for physical activity and restructuring of the social environment in the dialysis unit. Future programs should include

more targeted training for dialysis staff. Sharing participant progress reports throughout the intervention may better demonstrate the real-life effects of intradialytic exercise and enhance staff beliefs about the benefits of an exercise program. Additionally, incorporating an onsite or remote exercise professional to manage the intradialytic exercise program/prescription development, engage and educate staff and promote social culture of physical activity in the dialysis unit may be a worthwhile added resource to address several program limitations.

Our study had several limitations, including a small sample size; selection bias due to strict eligibility criteria and patient withdrawals; the lack of close supervision by an exercise professional, which limited participant progression and exercise prescription individualization; and technological issues with the telemedicine behavioral motivation. Future studies would benefit from considering these issues and must balance the need for more individualization of the exercise program in a scalable and resource efficient manner. The use of telehealth, including a virtual exercise professional, may be a promising consideration for such programs.

In conclusion, our pilot study showed that an intradialytic comprehensive exercise program was acceptable and safe, and outcome measures, including muscle biopsy, were feasible and safe to collect. Our study also highlighted important issues related to barriers to recruitment, inability to achieve targeted intensity of exercise, and less than optimal dialysis staff satisfaction with the program. Before initiating a full-scale trial, strategies to minimize the burden of physical function testing, provide a dedicated exercise professional, and reduce the responsibility of program delivery on clinic staff will need to be considered. In addition, staff education on the benefit of exercise programs and creating a supportive social dynamic in dialysis unit may improve the credibility of such programs and lend to greater staff support for program delivery.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Exercise checklist.

Item S2: Exercise log.

Item S3: Muscle biopsy procedure.

Table S1: Platelet mitochondrial respiration translational measures.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Manisha Jhamb, MD, MPH, Susan M. Devaraj, PhD, RD, Maryam Alemairi, PT, MSc, Linda-Marie Lavenburg, MD, MS, Sruti Shiva, PhD, Jonathan G. Yabes, PhD, Daniel E. Forman, MD, and Andrea L. Hergenroeder, PT, PhD.

Authors' Affiliations: Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh, Pittsburgh, PA (MJ, SMD, LML); School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA (MA, ALH); Kuwait University, Kuwait City, Kuwait (MA);Vascular Medicine Institute, Department of Medicine and Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA (SS); Center for Research on Health Care Data Center, Division of General Internal Medicine, Department of Medicine and Biostatistics, University of Pittsburgh, Pittsburgh, PA (JGY); and Department of Medicine (Divisions of Geriatrics and Cardiology), University of Pittsburgh, and Pittsburgh Geriatrics, Research, Education, and Clinical Center (GRECC), VA Pittsburgh Healthcare System, Pittsburgh, PA (DEF).

Address for Correspondence: Manisha Jhamb, MD, MPH, Renal-Electrolyte Division, University of Pittsburgh School of Medicine, A-915 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 15261, USA. Email: jhambm@upmc.edu

Authors' Contributions: Research idea and study design: MJ, ALH, JGY; data acquisition: MJ, ALH, DEF, SS; data analysis/interpretation: MJ, ALH, SMD, MA, LML, JGY, SS, DEF; statistical analysis: SMD, JGY, MA; supervision or mentorship: MJ, SS, ALH, JGY, DEF. 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.

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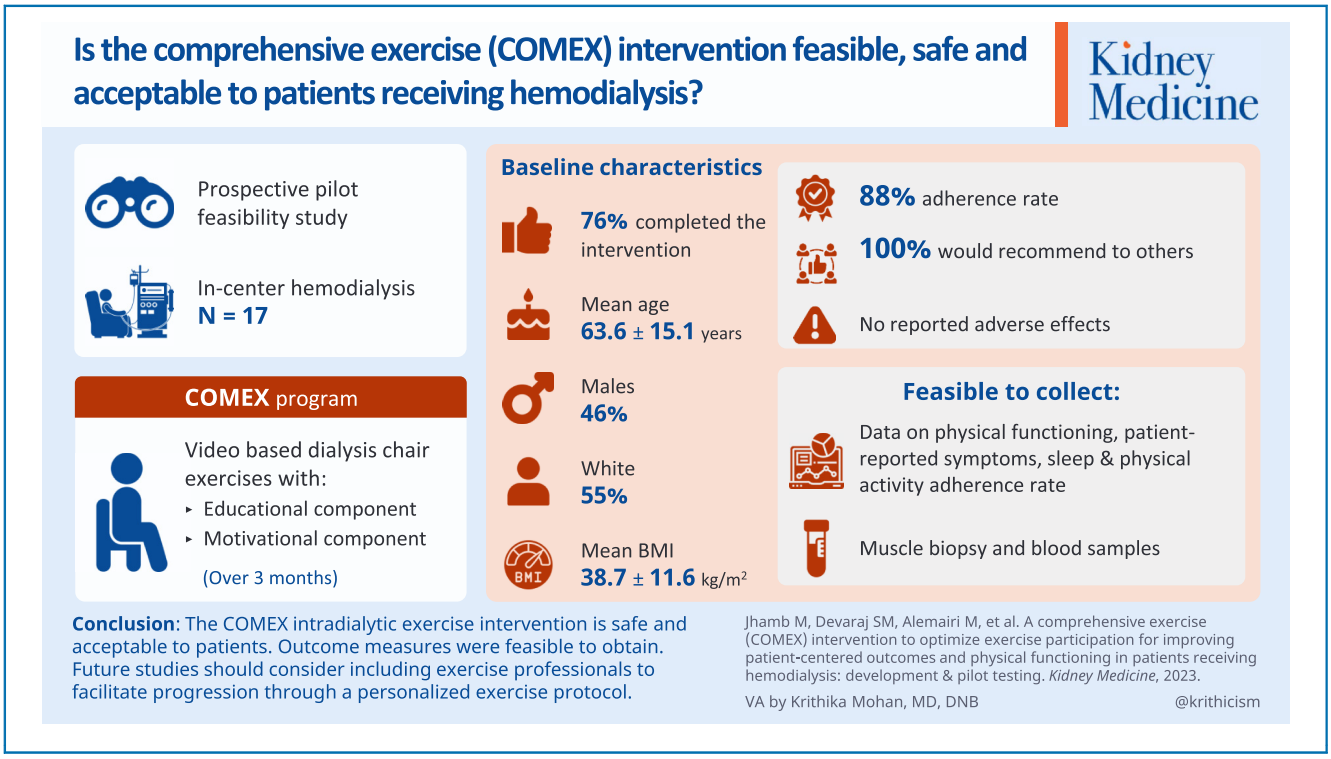
Is the comprehensive exercise (COMEX) intervention feasible, safe and acceptable to patients receiving hemodialysis?
Kidney Medicine
Prospective pilot feasibility study
In-center hemodialysis
N = 17
COMEX program
Video based dialysis chair exercises with:
Educational component
Motivational component
(Over 3 months)
Baseline characteristics
76% completed the intervention
Mean age
63.6 ± 15.1 years
Males
46%
White
55%
Mean BMI
38.7 ± 11.6 kg/m2
88% adherence rate
100% would recommend to others
No reported adverse effects
Feasible to collect:
Data on physical functioning, patient-reported symptoms, sleep & physical activity adherence rate
Muscle biopsy and blood samples
Conclusion: The COMEX intradialytic exercise intervention is safe and acceptable to patients. Outcome measures were feasible to obtain. Future studies should consider including exercise professionals to facilitate progression through a personalized exercise protocol.
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VA by Krithika Mohan, MD, DNB
@krithicism