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Prehabilitation Prior to Kidney Transplantation: Results from a Pilot Study

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Abstract

Prehabilitation is the process of enhancing pre-operative functional capacity to improve tolerance for the upcoming stressor; it was associated with improved post-operative outcomes in a handful of studies, but never evaluated in transplantation. Kidney transplant (KT) candidates may be uniquely suited for prehabilitation because they experience a profound loss of functional capacity while waiting years on dialysis. To better understand the feasibility and effectiveness of prehabilitation in KT, we conducted a pilot study of center-based prehabilitation for candidates; this intervention consisted of weekly physical therapy sessions at an outpatient center with at home exercises. We enrolled 24 participants; 18 participated in prehabilitation (75% of enrolled; 17% of eligible). 61% were male, 72% were African American, and mean age=52 (SD=12.9); 71% of participants had lower extremity impairment and 31% were frail. By 2 months of prehabilitation, participants improved their physical activity by 64% (p=0.004) based on accelerometry. Participants reported high satisfaction. Among 5 prehabilitation participants who

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AUTHOR'S CONTRIBUTIONS

Mara A. McAdams-DeMarco: participated in concept design, data analysis/interpretation, securing funding, drafting article, critical revision of article, and approval of the article. Hao Ying participated in the concept design, data analysis/interpretation, critical revision of article, and approval of the article. Sarah Van Pilsum Rasmussen participated in the concept design, data analysis/interpretation of the qualitative data, critical revision of article, and approval of the article. Jennifer A. Schrack contributed to accelerometry design and analysis and critical revision of the article. Christine E. Haugen participated in the concept design, data analysis/interpretation, critical revision of article, and approval of the article.

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CONFLICT OF INTEREST

The authors of this manuscript declare no conflict of interest.

received KT during the study, length of stay was shorter than for age, sex, and race-matched control (5 vs. 10 days; RR=0.69; 95%CI:0.50–0.94;P=0.02). These pilot study findings suggest that prehabilitation is feasible in pre-transplant patients and may potentially be a strategy to improve post-KT outcomes.

Keywords

kidney transplantation; prehabilitation

INTRODUCTION

Prehabilitation is the process of enhancing patient functional capacity prior to surgery to improve tolerance for the upcoming physiologic stressor (1); it commonly includes an exercise component with strength, aerobics, and stretching components (2), and sometimes includes nutritional (3–5) or psychological components (6). Prehabilitation may be useful for patients undergoing surgery (7,8) because it shifts the focus to optimization prior to the physiological stressor rather than rehabilitation afterwards. Improving pre-operative functional status is important because poor functional status, and particularly lower extremity function, is associated with adverse peri- and post-operative outcomes (2,9–11).

Exercise based prehabilitation has been studied in a limited number of surgical populations including elective abdominal surgery (12), total knee replacement/arthroplasty (13–15), abdominal aortic aneurysm surgery (16), coronary artery bypass surgery (17), and colorectoral cancer surgery (18–20). In these surgical populations, prehabilitation resulted in patients increasing physical activity and improving functional capacity before a major surgical stressor, contributing to a reduction of postoperative recovery time and a quicker return to functional ability (12–20). For example, among 95 patients undergoing colorectal cancer surgery, 6 weeks of prehabilitation (cardiovascular and weight training with recommended walking) was associated with a 33% improvement in post-operative physical function (19). Additionally, prehabilitation among patients undergoing coronary artery bypass graft surgery (n=249; >10 weeks of exercise training) and arthroplasty (n=71; 4–8 weeks of resistant, flexibility, and strength training, respectively) reduced post-operative length of stay (14,17).

It has been theorized that prehabilitation prior to KT might be effective (21), because candidates often have to wait months to years for a deceased donor or spend months identifying an appropriate live donor; furthermore, pre- and post-KT physical inactivity is high among patients with ESRD (22–26). While awaiting KT, candidates experience a profound loss of functional capacity due to the combination of aging, chronic conditions, and higher risk of frailty in addition to the stress of undergoing dialysis (27). In fact, by the time of admission for KT, there is a high burden of patients with compromised physiology leading to the inability to withstand the stressor of a major surgical intervention. Pre-KT frailty is present in approximately 20% recipients (10) and associated with poor outcomes after KT (28–32) including a longer length of stay (28). Furthermore, pre-KT lower extremity impairment, a physical function measure that captures a candidate's ability to

perform lower extremity physical tasks, is present in 48% of KT recipients at admission (9) and increases length of stay (10,11). Intervening through exercise training post-KT may not be optimal, given the steep decline in physical activity in the first year post-KT and poor compliance with prescribed rehabilitation therapy, as demonstrated through the relatively high dropout rates in the two trials of post-KT exercise (33,34). In contrast, KT candidates may be more motivated to exercise knowing that they will be undergoing a major surgery in the coming months; in fact, patients and their providers strongly support prehabilitation in ESRD patients, particularly for vulnerable candidates such as those who are frail (35).

The goals of this preliminary pilot study were to: 1) assess the feasibility of a weekly center-based prehabilitation program among KT candidates and 2) test whether KT candidates who receive prehabilitation have a shorter post-KT length of stay as compared to age-, sex-, and race-matched controls.

MATERIALS AND METHODS

Patient Eligibility and Enrollment

This pilot study was a single-arm intervention trial with matched standard of care historical controls. We recruited KT candidates who were active on the KT waitlist at Johns Hopkins as a pilot study nested within our longstanding prospective cohort study of frailty among KT candidates. Between 5/2016 and 9/2017, we screened all active KT candidates who had been enrolled in our cohort study. Inclusion criteria for this study included: 1) patients with end-stage renal disease (ESRD) who were estimated to be within 3–6 months of kidney transplantation and on the deceased donor kidney transplant waitlist at Johns Hopkins; 2) at least 18 years or older at enrollment; 3) English speaking; 4) enrolled in our ongoing cohort study of adults with ESRD who were being evaluated for KT; 5) willing to participate in a prehabilitation program and able to give informed consent. We excluded any KT candidates who lived outside of Maryland and those with the following medical conditions: active angina pectoris, chronic lung disease and daily use of oxygen, cerebral vascular disease, musculoskeletal conditions that would limit participation in prehabilitation, lower- or upper-extremity amputation, orthopedic disorders exacerbated by physical activity, or decreased mental capacity. Control selection is described below.

This study was approved by the institutional review board of the Johns Hopkins Bloomberg School of Public Health and registered with ClinicalTrials.gov (NCT02895243; September 9, 2016).

Participant Characteristics

At evaluation, participants were assessed for frailty using the Fried physical frailty phenotype (frailty defined as ≥3 of the 5 components) (36) and the Short Physical Performance Battery (impairment defined as score<11) (37) as we have previously reported (9). Additionally, candidate factors (age, sex, race, household annual income, marital status, education, body mass index [BMI], time on dialysis, causes of ESRD, and type of renal replacement therapy) were abstracted from medical charts. A Charlson comorbidity index

(CCI) adapted for patients with ESRD was calculated based on both abstracted and self-reported comorbidities at the time of evaluation (22).

Center-based Prehabilitation Intervention

Prehabilitation began with a one-hour baseline assessment by a physical therapist (PT) to identify an appropriate plan for prehabilitation for each participant based on their individual goals, ability, and progression at a Johns Hopkins outpatient Physical Medicine and Rehabilitation center. The KT candidates then participated in weekly physical therapy sessions at these centers. The prehabilitation sessions were structured around the goals of improving global physical functioning and performing cardiovascular exercises as well as targeting any specific concerns that a patient expressed (ie fall risk, lower back, etc). Prehabilitation sessions were individualized based on the goals of the participant with feedback from the PT providers. Each session was 40 minutes long and conducted by a PT assistant, with 20 minutes of supervised exercises of their choice. The exercises included in the prehabilitation sessions included: 1) diaphragmatic breathing exercises, 2) stretching and strengthening muscle tone with and without elastic stretch band exercises, 3) Swiss ball exercises to build balance, core stability, and pillar strength as well as improve range of motion, 4) trampoline exercises to develop and promote motor skills, balance, and coordination, 5) low impact cardiovascular exercises, 6) strength training exercises using weights, and 7) cardiovascular and aerobic exercises using a treadmills, exercise bikes, and elliptical trainers. Each month, participants had a subsequent 1-hour in-depth assessment with a physical therapist. Vital signs were routinely monitored during all sessions. Additionally, participants were asked to participate in daily at-home exercise between prehabilitation sessions. Informed consent was obtained for the prehabilitation intervention from all participants.

Recruitment and Intervention Feasibility

Recruitment feasibility was assessed by recruitment into the pilot study and participation in the prehabilitation intervention. We reported the most common reasons for not consenting to participate in the prehabilitation intervention. Additionally, intervention feasibility was assessed by the total number of prehabilitation sessions and the percentage of participants who attended at least 4 sessions.

Safety

We included a medical monitor to assess any potential adverse events or serious adverse events to evaluate whether the event was attributable to prehabilitation. Any adverse events or serious adverse event occurring during the prehabilitation session were recorded; any event occurring between sessions was recorded at the next visit or during a phone call follow-up.

Physical Activity

At the initial PT evaluation, participants were fitted with an Actigraph GT9x activity monitor and asked to wear it on their wrists for 24 hours a day for the week prior to prehabilitation, and again for one week after each monthly prehabilitation evaluation. The

Actigraph GT9x is an FDA approved tri-axial device which measures activity at a frequency of 80 Hz (80 observations per second) and averages the data into 1-minute epochs. The accelerometers capture all movement above a resting/sedentary state. The intensity of the activity is reflected by the number of counts per unit time (e.g., the higher the counts the more intense the activity).

Participants were asked to wear the activity monitors at all times except when planning to bathe or swim longer than 30 minutes and to also record in a diary any time that they took off the monitor. Activity monitors were returned at the next prehabilitation session. Actigraph data were downloaded using commercially available software (Actilife, Version 16.13.2) to estimate the mean activity counts/minute (the mean of the sum of the readings for all 3 axes divided by the total minutes of wear per day); we required at least 3 days of wear per week. We calculated the % change in mean activity counts/minute between pre-intervention, 1 month, and 2 months post-intervention. We excluded any days in which the participant did not wear the activity monitor at all or reported no wear on their diary. Minute-level activity counts were averaged across to calculate the average counts per minute for every minute of the day (12:00am – 11:59pm).

Participant Feedback

After 1 month of prehabilitation, participants were asked to report: 1) How satisfied they were with prehabilitation (1= very dissatisfied to 5=very satisfied); 2) Whether they thought that prehabilitation is helping them (1= definitely not to 5=definitely yes); and 3) Whether it was easy or difficult to fit prehabilitation into your life (1= very difficult to 5=very easy). We calculated the mean response for participants who responded to these questions. Additionally, participants were then asked in open text to explain their answers. Open ended explanations and responses to the question, “Is there anything else you’d like us to know about your experience with prehabilitation?” were abstracted from the survey responses and entered into NVivo 11 (QRO International). Open-ended responses ranged in length from a single word response to 72 words. Codes were derived inductively from the open ended responses by a single coder (SVR) using the constant comparative method (38,39). The resulting nine codes were applied to the responses by two independent coders (SVR and MMD). Differences in coding were reconciled by consensus.

Control Selection

The standard of care historical controls were selected from our ongoing cohort study of adults with ESRD who were being evaluated for KT but were transplanted prior to the start of our prehabilitation pilot and thus, not eligible. These controls would have met all other inclusion and exclusion criteria of the study.

Post-KT Length of Stay

Prehabilitation participants who received KT were matched (1:5) based on age, sex, and race to KT recipients who were enrolled in our cohort study but did not receive prehabilitation. We estimated the median and interquartile range of KT length of stay in the prehabilitation participants and matched controls. Then we used linear regression to test whether the KT

recipients who received prehabilitation differed between those who received prehabilitation and their matched controls.

Statistical Analysis

For all analyses, a p-value of <0.05 was considered statistically significant. All data were analyzed using Stata 14 (College Station, Texas).

RESULTS

Feasibility

Of the 190 active KT candidates enrolled in our prospective cohort study, 111 met inclusion and exclusion criteria and were able to be contacted about participating in our pilot study; 5 were ineligible when contacted because they were being removed from the waitlist or already scheduled for KT when we approached them about the prehabilitation pilot study. Of the remaining 106 participants, 84 declined to participate and 24 were enrolled (23%). However, those who declined to participate were similar to those who agreed to participate based on age (P=0.71), sex (P=0.75), and race (P=0.95). The top three reasons for refusing to participate were: 1) geographical limitations (clinic is too far or not conveniently located; unable to commute); 2) too much commitment (weekly appointments difficult to fit into schedule because of work, school, medical or dialysis appointments; too much of a time commitment); and 3) transportation issues (dependent on relative or someone for transportation).

Of the 24, 18 participated in prehabilitation (75% of those enrolled; 17% of these eligible). Participants who were consented but did not participate in prehabilitation were similar to those who did participate (Table 1); the reasons provided for not attending a prehabilitation session included transportation issues, schedule conflicts, health/medical issues, and too much of a time commitment. In addition to the baseline assessment by a physical therapist, the 18 participants attended a total of 227 prehabilitation sessions with a maximum of 76 sessions. Eight participants (44%) attended fewer than 4 prehabilitation sessions, 4 (22%) attended between 4–12 prehabilitation sessions and 6 (33%) attended 12 or more prehabilitation sessions.

Study Population

Of the 18 KT candidates who participated in prehabilitation, 46% were female, 72% were African American, and the mean age was 52 (SD=13); 22% were older (age≥65) (Table 1). Additionally, 59% were obese, 71% had lower extremity impairment, 31% were frail, 5% reported poor HRQOL, 26% reported depressive symptoms, and 18% reported an ADL disability. The most common comorbidity was diabetes (53%). 18% of all KT candidates reported a visual impairment, a physical impairment and a walking impairment. The mean time on the waitlist prior to starting prehabilitation was 3.1 years.

Adverse Events

There were no safety concerns or deaths among the 18 prehabilitation participants.

Prehabilitation and Physical Activity

In total, there were 200 days of wear (mean of 1,219 minutes/day of wear) for the activity monitors among 15 participants (3 participants lost or did not return their monitors). The mean physical activity count/minute before prehabilitation was 1,717 and was 1,741 by the first month and 2,814 by the second month. This represents no improvement (1% change; p=0.90) in physical activity after 1 month of prehabilitation, but a 64% improvement by the second month (p=0.004). By the second month of prehabilitation, the physical activity level had improved throughout the day (Figure 1).

Participant Feedback

When asked about satisfaction with the prehabilitation program, 100% of participants reported being very satisfied (mean=5.0). Additionally, participants almost completely agreed (mean=4.9) that prehabilitation is helping them. Finally, participants reported that it was somewhat easy to fit prehabilitation into their lives (mean=4.1). The main limitation noted in the open text was that it was hard for participants to find time for prehabilitation due to their dialysis schedule and the time/distance to get to the rehabilitation center.

Four common themes emerged (Table 2). The first theme was: *increased physical function and energy*: “Helped me get ‘all the kinks out of my body’ which helped me to move more than before” (Male, 40s). The second theme was: *sustained endurance*: “Giving me better endurance” (Male, 60s). The third theme was: *better weight control*: “I needed to find an exercise program to help me lose the weight so I can get a transplant… the program has helped me get motivated to exercise” (Male, 40s). The fourth and final theme was: *improved attitude*: “Program helps me feel a little better in life,” (Male, 50s). These themes suggest that participants felt that prehabilitation helped them become more physical and mentally prepared for transplantation.

Prehabilitation and Length of Stay

5 candidates received KT and 1 was removed from the waitlist. Compared to age, sex, and race matched controls, the length of stay was shorter for KT recipients who participated in prehabilitation (5 days vs. 10 days). KT recipients with prehabilitation had a reduced length of stay (RR=0.69; 95% CI: 0.50–0.94; P=0.02).

DISCUSSION

In this pilot study of prehabilitation, we were able to recruit a diverse group of KT candidates, including those who were frail (31%) and those with lower extremity impairment (71%). There were no adverse events reported during 227 prehabilitation sessions. There was a high level of satisfaction with the prehabilitation intervention and participants overall reported that it was helping them prepare for KT. Participants noted common themes surrounding prehabilitation including an increased physical function and energy, a sustained endurance, a means of weight control, and an improved attitude. By 2 months of prehabilitation, there was a 64% increase in objectively measured physical activity. Finally, our preliminary findings suggest that prehabilitation was associated with a 31% decreased length of stay compared to age, sex, and race matched controls.

Previous randomized controlled trials testing exercise interventions in ESRD and KT have been shown to improve graft function, quality of life, self-reported physical function, aerobic fitness, exercise capacity, and muscle strength, as well reduce body fat and cardiovascular risk (23,33,40,41). Our findings of improved physical activity based on objective measures are consistent with two reports that post-KT exercise interventions increased self-reported physical activity (33) and improved peak V02 (33,34). However, these hospital-based and home-based intervention studies that targeted the early post-KT period experienced high dropout (42% and 23%), suggesting that exercise interventions post-KT may be challenging. We saw different challenges when targeting the pre-KT period: while feasible, our intervention was limited in that it was challenging to enroll participants who lived further from the center. Nevertheless, we found that prehabilitation prior to KT may increase objective measures of pre-operative physical activity leading to a reduced risk of adverse post-KT outcomes including longer length of stay.

Our findings on improved objective physical activity by 2-months of prehabilitation are also consistent with previous studies of prehabilitation in other surgical specialties that found improvements in physical function after the intervention (18–20). For example, one randomized trial of 95 patients undergoing scheduled colorectal cancer surgery, found that prehabilitation was associated with a 33% improvement in physical function based on the six-minute walk test (19). Additionally, in two randomized trials of 77 and 112 patients undergoing scheduled colorectal cancer surgery 53% improved functional walking capacity and 37% improved functional capacity during prehabilitation (18–20). Our findings on improved physical activity are important given the findings from prior observational studies that suggest that there is a high burden of physical inactivity among ESRD both pre- and post-KT; this inactivity is associated with poor graft and patient outcomes, including reduced cardio respiratory fitness, impaired metabolic and nutritional status, reduced quality of life, and increased mortality (22,23).

Finally, our findings of reduced length of stay are consistent with a 10 week or longer exercise training and education intervention in 249 coronary artery bypass surgery patients (hospital LOS reduced by 1 day, P=0.002) (17) and a 6 week pre-operative exercise training and education prehabilitation in 131 patients undergoing total knee arthroplasty, although this was not statistically significant (14). In our preliminary data from this pilot study, there was a suggested reduction in LOS that was substantially lower (5 days versus 10 days among matched controls), possibly because a longer intervention in a population that was highly deconditioned prior to surgery and due to the longer length of stay that occurs at the transplant center, as we have previously published (11,28). However, it is critical that these findings be confirmed in a larger study with more KT recipients receiving prehabilitation.

The strengths of this pilot study were a unique study population and multiple domains of investigation, including safety, feasibility, objectively measured physical activity level using accelerometry, participant feedback, and length of stay. We were able to identify logistical challenges in recruiting and conducting prehabilitation at a physical medicine and rehabilitation center that seem unique to KT. Prehabilitation prior to KT is more challenging than other surgical settings, because the date of the transplant is often unknown; in fact, 72% of the candidates who were estimated to be between 3–6 months of KT received

transplantation by the end of the pilot. Furthermore, not all KT candidates were able to attend weekly in-center prehabilitation sessions as they often had to balance with hemodialysis schedules; we found that KT candidates who were working were the most likely to decline participation. Unfortunately, we do not yet have the follow-up time, nor were we powered, to study long-term outcomes like death or graft loss, as well as other important clinical outcomes that result from increased physical activity (42–44).

Success of this pilot study and all randomized controlled trials hinges on attaining high retention and protocol adherence (45). Poor retention has been shown to increase study duration and costs, threaten internal and external validity, and/or result in premature termination of research in severest cases (46,47). However, effective strategies such as allowing for flexible scheduling of appointments, discussing potential barriers to attending appointments, expressing sincere appreciation for participants' efforts, ensuring confidentiality of information, providing extra monetary incentives for participation, scaling down demands of study requirements, conducting adherence assessments, and formulating working hypotheses to explain nonadherence have been shown to improve retention rates, identify, and later address potential threats to non-adherence in both the design and analytic phase (46). We were able to use these strategies to help improve retention in our pilot study; for example, we provided transportation to any participant who need a dependable way to attend the prehabilitation sessions.

In conclusion, our preliminary pilot study of prehabilitation suggests that this intervention is feasible and safe among KT candidates. We found preliminary evidence that by 2 months of prehabilitation there was significant improvement in physical activity. Additionally, our preliminary findings suggest that KT recipients who participated in KT may have a shorter length of stay than age, sex, and race matched controls; these findings should be confirmed in a larger study. Although we have some preliminary evidence of the feasibility, safety, and efficacy of prehabilitation among KT candidates this intervention should be confirmed in a larger randomized controlled trial; if successful, this work could be expanded to include intradialytic prehabilitation to help improve physical functioning among candidates undergoing hemodialysis and particularly those who live far from a rehabilitation center. Future research should build off this pilot to identify subgroups who would most benefit from KT and identify the necessary components and timing of a successful pre-KT prehabilitation program.

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Abbreviations:

(KT) kidney transplant

(LOS)	length of stay
(SD)	standard deviation

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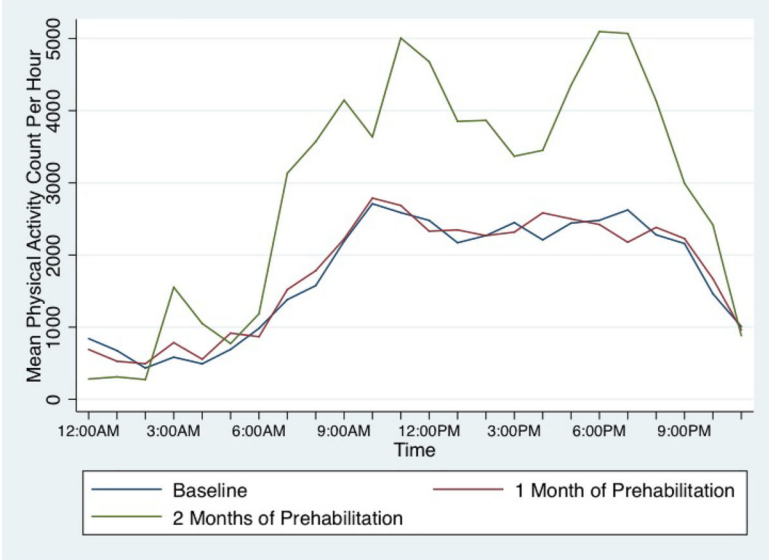

Figure 1.

Mean Physical Activity Count Per Hour of KT Candidates By Month of Prehabilitation Intervention (n=15). There was a non-significant 6% change (p=0.99) in the mean daily activity count by 1 month of prehabilitation and a 61% improvement (p=0.001) in the mean daily activity count by 2 months of prehabilitation.

Table 1.

Characteristics of the Prehabilitation Participants and Controls

	Prehabilitation Participants			
	Consented (n=24)	**Attended Prehabilitation (n=18)**	**Received KT (n=5)**	**Controls (n=25)**
Age, years				
18–34	8.3	11.1	20.0	4.0
35–49	37.5	38.9	40.0	56.0
50–64	33.3	27.8	20.0	24.0
≥65	20.8	22.2	20.0	16.0
Female, %	45.8	38.9	60.0	60.0
African American, %	62.5	72.2	80.0	80.0
>High school education, %	65.2	64.7	80.0	60.9
BMI (kg/m^2), mean (SD)	28.1 (5.8)	28.7 (6.4)	26.2 (8.8)	28.3 (5.1)
Frail, %	28.6	31.3	20.0	17.4
SPPB Impairment, %	65.2	70.6	60.0	61.9
Cause of ESRD, %				
Glomerular	29.2	33.3	20.0	16.0
Diabetes	20.8	16.7	20.0	16.0
Hypertension	33.3	33.3	40.0	48.0
Other	16.7	16.7	20.0	20.0
CCI, median (IQR)	2.0 [0.0, 3.5]	2.0 [1.0, 4.0]	2.0 [2.0, 2.0]	1.0 [0.0, 3.0]
Time on dialysis, (years)	1.8 (2.1)	2.3 (2.3)	4.1 (3.0)	1.8 (1.6)

Note: BMI, body mass index at KT; CCI, Charlson comorbidity index; ESRD, end-stage renal disease, IQR, interquartile range

Table 2.

Common Themes on Kidney Transplant Prehabilitation from Participant Feedback

Theme	Representative Quotes
Increased physical function and energy	"Can move around better" (Male, 50s) "Getting stronger" (Male, 40s) "Helped me get 'all the kinks out of my body' which helped me to move more than before" (Male, 40s) "It is helping [me] by regaining strength in my lower body and learning new exercises to maintain strength" (Male, 30s) "Helping to improve my mobility and daily physical functioning." (Female, 40s)
Sustained endurance	"Giving me better endurance" (Male, 60s) "I sleep better, feel stronger, and have more endurance" (Male, 40s)
Better weight control	"It has helped me to lose the weight I need [to]." (Male, 40s) "Able to maintain…weight" (Male, 30s) "I needed to find an exercise program to help me lose the weight so I can get a transplant…the program has helped me get motivated to exercise." (Male, 40s)
Improved attitude	"Program helps me feel a little better in life" (Male, 50s) "It helps me work and gave me a better outlook on what I'm doing and has been helpful" (Male, 40s)