Home-Based Exercise to Treat Decreased Physical Function

in Patients With Varying Levels of Kidney Function

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PI: Elizabeth Lorenz, MD, Baylor College of Medicine

Background Information

Frailty and/or decreased physical function are significant risk factors for adverse outcomes in kidney transplant candidates, including worsening health-related quality of life, falls, hospitalizations and death. Furthermore, frailty is associated with numerous adverse outcomes after kidney transplant. For example, pre-transplant frailty is associated with delayed graft function, increased length of stay, re-hospitalizations, and mortality following kidney transplant. Given the scarcity of donor organs for transplantation, better objective methods of identifying kidney transplant candidates who are at high risk of adverse outcomes are needed, and modifiable risk factors such as frailty should be addressed prior to kidney transplantation.

Although frailty has been shown to be modifiable in non-transplant populations, anti-frailty interventions are understudied in kidney transplant patients. We recently demonstrated that 8-weeks of supervised, center-based exercise is associated with improved frailty parameters and SPPB scores in patients with advanced chronic kidney disease, including kidney transplant candidates. Specifically, we conducted a pilot study involving 21 participants who attended center-based Pulmonary Rehabilitation (PR) for up to 1 hour twice per week for 8 weeks. Center-based PR involves a regimen of standardized aerobic conditioning, strength training, and flexibility training according to American Thoracic Society guidelines. We found that the intervention was safe, feasible, and associated with improved frailty parameters and SPPB scores.

Although center-based rehabilitation programs have proven benefit in terms of morbidity and mortality, they are underutilized and limited by lack of participation. A promising alternative to center-based programs is home-based programs. In these programs, patients do not need to leave their homes to exercise. Center personnel can provide indirect supervision, coaching, troubleshooting, and motivational interviewing via phone. One of the most widely available, standardized home-based programs currently available in the United States is home-based CR. Recent studies have demonstrated that home-based CR can be as beneficial as center-based CR and associated with better adherence and participation rates (Thomas RJ et al. Circulation 2019). The exercise component of CR is very similar to that of PR. Both programs are accredited by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) and involve aerobic conditioning, strength training, and flexibility training. Thus, home-based CR may be a safe and viable option for patients with chronic kidney disease unable to attend a center-based program. The aim of our current study is to determine whether home-based CR will improve frailty parameters and SPPB scores in patients with varying levels of kidney function. If our hypothesis is supported by the findings of this study, a home-based exercise program could be implemented prior to kidney transplantation with the ultimate goal of improving HRQOL and transplant outcomes in kidney transplant candidates.

Purpose and Objectives

The purpose of our current study is to determine whether home-based cardiac rehabilitation is an effective intervention that will improve frailty parameters and Short Physical Performance Battery scores in patients with varying levels of kidney function. We will also determine if home-based exercise improves health-related quality of life, physical activity, and adverse outcomes, including hospitalizations and death. If our hypothesis is supported by the findings of this study, a home-based exercise program could be implemented prior to kidney transplantation with the ultimate goal of improving health-related quality of life and transplant outcomes in kidney transplant candidates in the future.

Protocol Risks/Subjects

Risk Category

Category 1: Research not involving greater than minimum risk.

Subjects

Gender:

Both

Age:

Adult (18-64 yrs), Geriatric (65+ yrs)

Ethnicity:

All Ethnicities

Primary Language:

English

Groups to be recruited will include:

Patients

Which if any of the following vulnerable populations will be recruited as subjects?

Vulnerable populations require special protections. How will you obtain informed consent, protect subject confidentiality, and prevent undue coercion?

Pregnant woman/fetus

Will pregnant women and/or fetuses (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

Neonates

Will neonates of uncertain viability or nonviable neonates (as described in 45 CFR 46 Subpart B) be enrolled in the research?

No

Children

Will children be enrolled in the research?

No

Design/Procedure

Design

Select one category that most adequately describes your research:

c) Pilot

Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.

This study is a prospective interventional study, which involves use of existing and prospectively collected data. This pilot study will be conducted at Baylor College of Medicine examining the feasibility, safety, acceptability, and preliminary efficacy of home-based exercise on frailty parameters and Short Physical Performance Battery score in patients with varying levels of kidney function. We plan to accrue up to 20 adult patients with chronic kidney disease. The effects of exercise on health-related quality of life, physical activity, and adverse outcomes including hospitalizations and death, will also be explored.

Inclusion Criteria:

1. Age 18 years or older 2. Ability to consent to research 3. Chronic kidney disease (stages 1-5) 4. A Short Physical Performance Battery score ≤10 and/or considered frail or pre-frail according to the Fried Frailty Phenotype

Exclusion Criteria:

1. Younger than 18 years 2. Patients being evaluated for combined organ transplantation 3. Significant comorbidities that limit rehabilitation potential including pulmonary disease requiring continuous oxygen supplementation, active angina, critical aortic sclerosis, decompensated heart failure, or known ventricular arrhythmia. 4. An Short Physical Performance Battery score >10 or not considered frail or pre-frail by the Fried Frailty Phenotype 5. Non-English speaker without availability of adequate interpreter services (safety concern) 6. Failure to pass submaximal exercise test in patients not approved for kidney transplantation at our center

Procedure

Screening and Recruitment:

Potential participants will be identified from dialysis units, nephrology clinics, primary care clinics, or kidney transplant clinics at Baylor College of Medicine clinic. If the study team is unable to reach the patient after three attempts involving phone calls and/or portal messages, an Institutional Review Board-approved contact letter may be sent up to two times. Patients who express interest in the study will go through the informed consent process with a member of the study team, and patients wishing to participate in the study will complete written consent. If patients have not had frailty and Short Physical Performance Battery testing within the two weeks prior to consent, the study team member will perform frailty and Short Physical Performance Battery testing at baseline in a supervised setting. Patients who are not frail or pre-frail and have a Short Physical Performance Battery score > 10 will be ineligible for study participation. Patients with stage 1-5 chronic kidney disease who are not currently approved for kidney transplant at our center will undergo a submaximal exercise test to rule out any significant, undiagnosed cardiopulmonary disease if they meet one or more of the following criteria: 1) diabetes, 2) age > 59, 3) prior coronary artery disease defined as history of myocardial infarction, coronary artery stenting, or coronary artery bypass grafting, or 4) current smoking. During the initial study visit, consenting patients will be provided with a pedal exerciser, resistance bands, and exercise pamphlets (Mayo Clinic Patient Education Pulmonary Rehabilitation: Exercise Program, Exercise Program Guidelines, Exercises for the Legs). Participants will be given the option of having the pedal exerciser mailed to their home.

Exercise Intervention:

Participants will be asked to complete an 8-week home-based exercise program with a focus on the core components of physical activity counseling and exercise training according to guidelines from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation (Balady GJ Circulation 2007). During the program, participants will receive weekly semi-scripted phone calls from an exercise physiologist from the Mayo Clinic Cardiac Rehabilitation program. During the baseline phone call, the exercise physiologist will assess the patients current level of physical activity; discuss warm-up, cool-

down, and flexibility exercises; review the Borg Rating of Perceived Exertion (RPE); set goals with the patient; and answer any questions they might have. The exercise physiologist will then document in the electronic medical record any warning symptoms the participant experienced during physical activity or exercise; recent hospitalizations, important medical appointments, urgent care, or emergency department visits; goals set during phone call; an individualized exercise prescription. Study personnel will then send the individualized exercise prescription to the participant via mail, portal, or email. Recommended aerobic exercises will include arm and/or leg ergometry using a pedal exerciser. Recommended resistance training will include resistance bands. Patients will be encouraged to obtain at least 30 minutes of moderate-intensity physical activity at least five days per week. Gradual increases in the volume of physical activity will be recommended over time. Participants on dialysis will be advised not to exercise after in-center hemodialysis on dialysis days (if applicable). Participants will be asked to log information regarding their exercise sessions on paper, including type, duration, and Borg RPE scale.

During the subsequent weekly phone calls, the exercise physiologist will inquire about any interim symptoms or events, answer any questions regarding the exercise program, review goals set during the previous phone call and what the patient has done to work toward those goals, and set new goals if applicable. During each weekly phone call, the exercise physiologist will review and record information from the patients exercise log and enter it into the patients electronic medical record. Information entered by exercise physiologists into the electronic medical record will also be entered into REDCap by study personnel.

Participants will be instructed to stop exercising and sit down and rest if they develop any of the following signs: chest tightness, pressure, or pain; severe shortness of breath; light-headedness or dizziness; stomach pain; upset stomach, throwing up or a headache; pulse rate that is not normal for them; extreme fatigue; profuse sweating. They will be advised to seek emergency care (call 911) immediately for chest tightness, pressure, or pain in the chest or severe shortness of breath that does not go away within 3 to 5 minutes. Home-based exercise will be stopped if the study team feels it is no longer safe for the participant to continue exercise. If a participant experiences any of the above symptoms during or after exercising, the principal investigators will be notified. If the principal investigators determine it is no longer safe for the participant to continue the exercise program following discomfort, injury, or a medical emergency during an exercise session, the participant will be withdrawn from the study. Reasons for participant withdrawal will be recorded.

Study measures:

Participants will complete the following Short Physical Performance Battery testing and other study measures at baseline and after completion of the exercise program:

1. Fried Frailty Phenotype: The Fried Frailty Phenotype consists of a gait speed test, a grip strength test, and self-reported measures of physical activity, weight loss, and exhaustion. a. Gait speed test: The time required for the participant to walk a distance of 15 feet at a self-

selected walking speed will be measured using a stopwatch. To determine whether the participant is frail by the Fried Frailty Phenotype, the average of 2 trials will be calculated and adjusted for sex and height. b. Hand grip strength test: Hand grip strength will be measured using a Jamar Digital Hand Held Dynamometer. Participants will complete the grip strength test 3 times with their dominant hand (or the arm without their dialysis fistula or graft). The 3 trials will be averaged and adjusted by sex and body mass index using a normative table. c. Minnesota Leisure-time Physical Activity Questionnaire: Participants will answer questions from this questionnaire regarding how often they engage in different activities. d. Self-reported weight loss: Patients will be asked whether they unintentionally lost 10 or more pounds within the last year. e. Center for Epidemiologic Studies Depression Scale (CES-D): Participants will answer 2 questions from the CES-D about their level of exhaustion. 2. Short physical performance battery (SPPB): The Short Physical Performance Battery consists of a gait speed test over 4 meters (13.1 feet), timed repeated chair stands, and three balance tests. a. Gait speed test: The participants gait speed velocity over 4 meters will be calculated by converting the results of the participants gait speed test (please see Fried Frailty phenotype above) to meters per second. b. Timed repeated chair stands: Participants will be asked if they feel safe to stand from a chair without the use of their arms and without assistance. If the participant feels safe to stand from a chair without the use of their arms and without assistance, they will be asked to complete 5 repeated chair stands. The participants SPPB score will be determined by the time required to complete 5 repeated chair stands. c. Balance testing: The participants balance will be tested in side-by-side, semi-tandem, and tandem stands. In the side-by-side stand, participants will stand with their feet as close together as possible. In the semi-tandem stands, participants will stand with one heel touching the big toe of the opposite foot. In the tandem stands, participants will stand with the heel of one foot in front of the toes of the other foot (as if on a balance beam). Participants will be asked to hold each position for up to 10 seconds.

3. Kidney Disease Quality of Life Short Form (KDQOL-SF), Version 1.3: Participants will complete this 37-item questionnaire, which consists of questions regarding the patients kidney disease, their quality of life, and demographic characteristics. 4. Actigraph: Participants will be asked to wear an actigraph on their upper extremity for 7 days in a row and mail the device back to us in a prepaid envelope. The actigraph monitoring will be performed both at baseline and after completion of the exercise intervention. 5. Weight: Participants' weight will be measured on a scale.

Demographic and health information: At baseline, participants will be asked to self-report their marital status, employment status, insurance, education, income, smoking history, time on dialysis, dialysis type and location, and dialysis days. If patients do not provide this information, it will be collected from the medical record when possible. Medical information, including body mass index, cause of renal disease, previous kidney transplant, and comorbidities, will be abstracted from the participants' medical record.

Participants will be offered the option of completing questionnaires via Baylor College of Medicine iPAD, on paper, or over the phone. Participants will be able to skip any question that makes them uncomfortable or that they do not want to answer.

If a participant feels unsafe or if the study team member performing the frailty/Short Physical Performance Battery tests feels the participant is unsafe at any point during the frailty/Short Physical Performance Battery tests, the participant will not be asked to complete that measure.

End of Intervention Qualitative Survey:

Following completion of the home-based exercise program, participants will be asked to complete a qualitative/satisfaction survey. Approximately one month after completion of the exercise program, participants will be asked to complete some additional questions via phone or mail to ascertain if they are still exercising.

A Data Transfer Agreement will be obtained between Mayo Clinic and Baylor College of Medicine so that a limited data set involving subjects from Mayo Clinic can be accessed from Baylor College of Medicine. Mayo Clinic will share the data with Baylor using encrypted email and/or Microsoft Simple Share. The limited dataset that will be shared will include demographics, dates of participation in the exercise intervention, information about the exercise intervention (i.e. duration of study phone calls, participant exercise log), study outcome data (including data from frailty assessments, body composition assessments, accelerometers, and questionnaires), and medical/laboratory information abstracted from the medical record.

Sample Size/Data Analysis

Sample Size

How many subjects (or specimens, or charts) will be used in this study?

Local: 20 Worldwide: 20

Please indicate why you chose the sample size proposed:

This is a pilot study so it doesn't require sample size calculations. However, we chose our recruitment target based on a prior study examining the impact of exercise on frailty parameters which was able to show significant differences with a similar number of study participants.

Data Analysis

Provide a description of your plan for data analysis. State the types of comparisons you plan (e.g. comparison of means, comparison of proportions, regressions, analysis of variance). Which is the PRIMARY comparison/analysis? How will the analyses proposed relate to the primary purposes of your study?

Categorical variables will be summarized as counts and percentages with continuous variables summarized via medians and interquartile ranges. Pre- and post- comparisons will be made using paired, one-sample Wilcoxon signed rank tests for continuous variables and chi-square tests for categorical variables. Differences between groups will be assessed using two-sample Wilcoxon tests for continuous variables and Fisher's exact tests for categorical variables. P-values less than 0.05 will be considered statistically significant. We will make no adjustments in the p-value for multiple hypothesis testing.

Potential Risks/Discomforts

Describe and assess any potential risks/discomforts; (physical, psychological, social, legal, or other) and assess the likelihood and seriousness of such risks:

We expect the occurrence of adverse events to be rare. All AEs will be reported immediately to the principal investigators and properly documented. Serious Adverse Events (SAEs), Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs), and any major protocol violations will be reported to the IRB within 5 working days of the event. AEs and any minor protocol violations will be reported at the time of the continuing review. An explanation of the event and how the event was handled will be submitted with each report. The number of complaints and the number of study participants who withdrew from the study will be reported at each continuing review along with explanations for each complaint and for each withdrawal.

There is a minimal risk of injury or discomfort during the exercise sessions, and participants may be unwilling to answer certain questions within the questionnaires. The potential risks of the study are estimated to be equivalent to daily activities.

Potential Benefits

Describe potential benefit(s) to be gained by the individual subject as a result of participating in the planned work.

There are no immediate benefits to the participants from this study. The potential benefits of this study include improved physical function for the participant.

Describe potential benefit(s) to society of the planned work.

The investigators hope is to identify whether our hypothesis of a home-based exercise program will be feasible, safe, acceptable to patients, and improve frailty parameters and Short Physical Performance Battery scores in patients with varying levels of kidney functions. And if the findings of the study support hypothesis, a home-based exercise program could be

implemented prior to kidney transplantation with the ultimate goal of improving health-related quality of life and transplant outcomes in kidney transplant candidates in future.

Do anticipated benefits outweigh potential risks? Discuss the risk-to-benefit ratio.

The expected benefits of developing a feasible and effective exercise intervention in patients with decreased physical function outweigh the possible risks.

Consent Procedures

Waiver of Consent

Will any portion of this research require a waiver of consent and authorization?

NA

Waiver of requirement for written documentation of Consent

Will this research require a waiver of the requirement for written documentation of informed consent?

NA

Consent Procedures

Who will recruit subjects for this study?

PI
PI's staff

Describe how research population will be identified, recruitment procedures, any waiting period between informing the prospective participant and obtaining consent, steps taken to minimize the possibility of coercion or undue influence and consent procedures in detail.

Potential participants will be identified from dialysis units, nephrology clinics, primary care clinics, or kidney transplant clinics at Baylor College of Medicine. If the study team is unable to reach the patient after three attempts involving phone calls and/or portal messages, an Institutional Review Board-approved contact letter may be sent up to two times. Patients who express interest in the study will go through the informed consent process with a member of the study team, and patients wishing to participate in the study will complete written consent. If patients have not had frailty and Short Physical Performance Battery testing within the two weeks prior to consent, the study team member will perform frailty and Short Physical

Performance Battery testing at baseline in a supervised setting. Patients who are not frail or pre-frail and have a Short Physical Performance Battery score > 10 will be ineligible for study participation. Patients with stage 1-5 chronic kidney disease who are not currently approved for kidney transplant at our center will undergo a submaximal exercise test to rule out any significant, undiagnosed cardiopulmonary disease if they meet one or more of the following criteria: 1) diabetes, 2) age > 59, 3) prior coronary artery disease defined as history of myocardial infarction, coronary artery stenting, or coronary artery bypass grafting, or 4) current smoking. During the initial study visit, consenting patients will be provided with a pedal exerciser, resistance bands, and exercise pamphlets (Mayo Clinic Patient Education Pulmonary Rehabilitation: Exercise Program, Exercise Program Guidelines, Exercises for the Legs). Participants will be given the option of having the pedal exerciser mailed to their home.

Are foreign language consent forms required for this protocol?

No

Privacy and Intrusiveness

Will the research involve observation or intrusion in situations where the subjects would normally have an expectation of privacy?

No

Children

Will children be enrolled in the research?

No

Neonates

Will non-viable neonates or neonates of uncertain viability be involved in research?

No

Consent Capacity - Adults who lack capacity

Will Adult subjects who lack the capacity to give informed consent be enrolled in the research?

No

Prisoners

Will Prisoners be enrolled in the research?

No