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Experimental protocol of a randomized controlled clinical trial investigating the effects of personalized exercise rehabilitation on kidney transplant recipients' outcomes

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ABSTRACT

Background: This randomized controlled trial (RCT) will investigate the effects of a personalized exercise rehabilitation regimen on return to work and find work rate, vascular health, functional capacity, quality of life, kidney function, and body composition in kidney transplant (KT) recipients.
Methods/design: This RCT will recruit 120 men and/or women who have had a KT to participate in a 12 month exercise intervention or control (standard clinical care only) group. The 12 month exercise intervention will consist of one-on-one, progressive exercise rehabilitation sessions twice a week, for 60 min each session. The control group will continue standard clinical care as recommended by their post-transplant medical team without any intervention. The primary outcomes will be assessments of vascular structure and function, walking and strength measures to assess functional capacity, blood markers to assess kidney function, questionnaires to assess quality of life, DXA body scan to assess body composition, and a 1-week free living physical activity assessment. Additionally, employment status will be assessed. These assessments will be performed at baseline, 6 months, and 12 months.
Discussion: This investigation will increase the understanding of the role exercise rehabilitation has on managing the physiological and psychological health of the individual as well as on the individual's personal economic impact (via employment status). This study design has the potential to assist in constructing an effective exercise rehabilitation program that can be incorporated into part of standard post-transplant care.

1. Introduction and background

Approximately 25 million people in the U.S. suffer from chronic kidney disease. The prevalence of end stage kidney disease has increased 600% from 1980–2009 [1]. The number of patients undergoing kidney transplantation has also doubled between 1988 and 2009, with ~172,500 living with a transplanted kidney in 2009 [1]. While survival rates are much greater in kidney transplant (KT) than in dialysis patients when looking at survival rates at 5 years (85 vs 36%, respectively) [2] significant patient-identified issues remain. Following transplant, patients commonly report fatigue, difficulty with work and low emotional and physical function [3]. Low physical work capacity, mobility and low self-reported physical function are predictive of early mortality in end stage renal disease patients [3–5]. These issues not only are detrimental to the patient, but also become an economic burden [6].

Fatigue, low levels of physical work capacity, low self-efficacy, reduced ability to manage stressful emotions, and low levels of physical activity exacerbate the ability to return to work or to find employment [7,8]. When examining the United Network for Organ Sharing (UNOS) database from June 2004–December 2011, fewer than half (~45%) of patients with private insurance who worked at the time of transplantation were employed two years following transplant and only 14% among patients with public insurance (Medicaid and Medicare) (1/3 of the overall population) [6]. Only ~5% of patients who were unemployed prior to their transplant were employed after [6,9]. This inability to obtain employment or return to work can create difficult financial situations for these patients, as well as increase the reliance on financial assistance from public aid.

Exercise training is efficacious in KT patients [3,10], however most KT patients are not physically active or participating in exercise, despite physician recommendation [11]. The National Kidney Foundation recommends exercise for KT patients, but very little information is

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provided [12]. A recent meta-analysis by Heiwe and Jacobson suggested that future research in chronic kidney disease should concentrate on randomized control trials that evaluate various exercise regimes' effects on physical functioning, levels of physical activity during daily living, depression, adherence, compliance, adverse effects, and mortality [10]. Several studies have begun looking into exercise's effect on a variety of different measures of health. Painter et al. found an increase in high density lipoprotein fraction of cholesterol (HDL-C) with a 12 month exercise program in KT patients in comparison to standard of care patients [13]. Greenwood et al. found improvements in VO 2peak, sit-to-stand 60, isometric muscle force and pulse wave velocity in patients undergoing a 12 week resistance training group vs. standard care patients [14]. Heiwe and Jacobson also suggest that future research should specifically focus on resistance training interventions or mixed resistance and cardiovascular regimes with this population [10]. Other systematic reviews have come to similar conclusions [3,15]. We recently conducted a small pilot of this study with 17 patients (9 controls and 8 exercise intervention) which showed positive results in favor of the exercise group when looking at patient's glomerular filtration rates (GFR), quality of life, and employment rate [16]. This pilot provided a base for a full scale study to be conducted.

This study will address gaps in research by implementing an exercise rehabilitation program on a larger scale that is personalized to kidney transplant recipients and focuses predominantly on resistance training at low intensities designed to prevent a decline in function/independence. We will accomplish this by conducting a randomized controlled trial (RCT) that will examine the effect of a novel 12 month personalized exercise rehabilitation program compared to standard care following kidney transplantation. Data from this study should increase our understanding of the effect of exercise in this population on physical and vascular function, psychological markers, as well as on employment status which has not been observed in previous research.

2. Methods

2.1. Study design, overview, and hypotheses

The proposed study, data collection, and intervention will be performed in the Integrative Physiology Laboratory at the University of Illinois at Chicago. Blood samples will be collected in the Transplant Clinic at the University of Illinois at Chicago. The study will use a two-arm RCT design to examine the effects of personalized exercise rehabilitation versus standard clinical care in KT recipients. This protocol is currently registered on clinicaltrials.gov (NCT02409901). The primary outcome will include physical and vascular function, body composition, perceived quality of life, kidney function and blood lipid markers, and adherence. A secondary outcome will be patient employment status. 120 kidney transplant recipients will be randomized 2:1 into either an exercise rehabilitation program or a control group, which involves standard clinical care only. The sample size was determined as we anticipate a total of 1100–1200 kidney transplant patients will be available to participate over the two-year recruitment period. We further estimate that 60% of these patients will be eligible to participate based on the inclusion/exclusion criteria; and among them 25–30%% will agree to participate (percentages derived from our pilot data). The effect sizes of primary and secondary endpoints are estimated from our pilot data. Our power analysis is based a two-sided alpha of 0.05, an intraclass correlation (ICC) of 0.5 (common estimate for longitudinal data), and three repeated measures. We performed our power analysis using the repeated measures approach for multivariate analysis accounting for up to 8 covariates (age, gender, marital status, race/ethnicity, education, income, functional status, time since transplant, previous employment status). We anticipate that randomization will be able to balance most of the confounding factors between the two treatment arms, thus the actual power should be larger. A sample of 152 will allow us to detect effect sizes between 0.47 and 5.55 with 80%–99% power for the study outcomes. We further estimate a 15% attrition due to subject withdraw/drop out and unusable data. Thus, we will include a total sample size of 150 for the proposed study. Randomization will be done after obtaining informed consent and baseline testing, utilizing a computerized randomization program as a way to prevent potential selection bias (randomization.com). This program will be set to randomize in a 2:1 fashion (exercise:control). Subjects will be aware of the study's primary and secondary outcome measures and the purpose of the study prior to consent. The exercise rehabilitation arm includes low intensity, personalized resistance trainings two times per week for a 12 month period in addition to standard clinical care (including regular check-ups and blood work as recommended by their post-transplant physician). The control group will continue standard care as advised by their post-transplant medical team with no additional intervention. We will collect data on employment status, and all physiological and psychological data at baseline (before intervention), during (6 months), and immediately after the intervention (12 months). Adherence will be monitored throughout the entirety of the study by recording study visits as well as having the exercise trainers keep record of the patient's attendance in the exercise arm. A 2×3 (condition $\times$ time) mixed factor, analysis of variance with intent-to-treat principles will be utilized for testing the effect of the intervention on the outcome variables. Our primary hypotheses are that a 12 month exercise rehabilitation program will prevent a decline in subclinical atherosclerosis, increase functional capacity, and increase lean muscle mass. Outcome measures for subclinical atherosclerosis include aortic pulse wave velocity (PWV), carotid intima–media thickness (IMT), endothelial function and carotid arterial stiffness. The outcome measures for functional capacity include the 6 minute walk test (6 MW), unilateral isometric strength test, and free-living accelerometry. Fat and lean muscle mass will be assessed via Dual-energy X-ray absorptiometry (DXA). Additionally, fasting blood lipid profile, inflammatory markers, and markers of kidney function including glomerular filtration rate (GFR) and creatinine levels will be measured. Our secondary hypothesis is that a 12 month exercise rehabilitation program will increase the employment rate in kidney transplant recipients.

Ethical approval will be obtained from the Office of the Vice Chancellor of Research at the University of Illinois Chicago.

2.2. Participants

We plan to enroll a sample of 120 kidney transplant recipients from the University of Illinois at Chicago and Northwestern University in Chicago Illinois. Recruitment will be carried out by approaching qualified patients face to face during regular clinical visits. Patients will have medical records screened to determine qualification prior to being approached and asked to participate. Participants will be fully informed of the voluntary nature of the study as well as all procedures prior to consenting. A written informed consent will be given to all participants prior to testing. Participants will be given the opportunity to ask any questions prior to consenting.

The criteria for inclusion are successful kidney transplant recipient (not currently rejecting the most recently transplanted kidney), age of 18–65 years, must be 2–18 months post-transplant, and must have adequate cognitive ability to complete questionnaires, give consent for the study and follow the physical instructions. Exclusion criteria include transplant of any other organ besides kidney, non-ambulatory or significant orthopedic problems, bariatric surgery/any other weight reduction surgery, cardiac/pulmonary disease that contraindicates the physical training, any contraindication to exercise testing per the American Heart Association, and/or if the patient is unable to comply with the training program.

2.3. Measures

Participants in both arms will come in for testing three times over 12 months. All measurements will be conducted at baseline, and at 6 and 12 months following exercise training (or standard care for the control