Randomized case-control trial about the impact of targeted physical activity and diet modification on kidney transplant recipients' outcome

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BACKGROUND

It is well known that in the general population, metabolic syndrome is tightly linked to obesity and is a strong risk factor for cardio-vascular disease and mortality. After renal transplantation, obesity and metabolic syndrome are prominent risk factors for post-transplantation diabetes mellitus, chronic graft dysfunction, graft loss, and patient death in renal transplant recipients [1]. At the same time, obesity in the setting of end stage renal disease is associated with a condition called obese sarcopenia, which is characterized by protein energy wasting and thus a decreased ratio of lean body mass/fat body mass [2]. Both obesity and sarcopenia are associated with higher circulating concentrations of pro-inflammatory cytokines. These pro-inflammatory cytokines lead to systemic inflammation which contributes to cardio-vascular disease development and higher morbidity and mortality in patients with end-stage renal disease [3]. Behavioral changes to prevent or convert weight gain and improve the lean body mass rate may counteract the post-transplant development of obesity-related comorbidities and thereby improve renal graft function and survival in the long-term [4].

It is well known that lifestyle factors such as physical activity and diet are important modifiable factors for insulin resistance, and have been associated with the risk of kidney disease. In the second National Health and Nutrition Examination, the risk of chronic kidney disease was related to physical inactivity, both with and without adjustment for age, sex, race and body-mass index [5]. In hemodialysis patients, exercise has been reported to enhance insulin sensitivity, improve lipid profile, increase hemoglobin, improve insulin-like growth factor 1 (IGF-1) status, increase muscle strength, decrease blood pressure, increase physical functionality and improve quality of life. Little is understood about the state of muscle mass following transplantation. While the patient is in renal failure, catabolism of muscle occurs due to protein processing derangements.

Post-transplant, renal function is restored along with appropriate processing of protein and elimination of the catabolic state. Few studies have determined whether restoration of renal function allows the restoration of muscle mass, whether patients are sufficiently strong to accomplish activities of daily living, whether the use of immunosuppressants impedes the ability to increase muscle mass, and whether increasing muscle mass can lead to reduction of medication side effects as has been shown recently with chemotherapy patients. Further, little has been studied regarding protein content of post-transplant diets and its manipulation to increase muscle mass.

Furthermore, although recommendations to engage in physical exercise are routinely made by the Transplant Team, it has been extremely difficult to enroll post transplant recipients in regular exercise programs. Concern with performances, body images,

objective difficulty in performing physical exercise have all contributed to the low level of physical activity typical of this patient population.

The present study aims to analyze the effectiveness of a specific physical activity/nutrition training program (for a detailed description of the GH method see Appendix 1) in comparison to the standard of care for renal transplantations in kidney transplant recipients.

GH METHOD AND PHILOSOPHY

There are four major components of the GH Method (also known as the Greg Hachaj Method):

1) Become experts in our patients.

   The GH Method incorporates multiple disciplines including fitness, psychology and nutrition. The efficacy of the GH Method is built around the application of standard processes and curriculum that are then customized to the particular physiology and psychology of each individual patient. For the GH Method to work effectively, we must develop a comprehensive expertise in our patients that demands constant updating as the physiology, psychology and life circumstances of each patient evolves during the program.

   Typically, fitness programs are not customized to fit with a patients' physical and emotional life resulting in a much more limited health impact, shorter term participation, unsustainable changes, and an eventual return to the patients' status quo at the beginning of the program. However, the effective interplay of the distinct disciplines of fitness, psychology and nutrition is critical to the GH Method's success in achieving significant and sustainable health improvements in our patients measured in improved bodily function, mental health, and quality of life.

2) Build and expand their life tissue.

   The physical exercise component of the GH Method focuses on using the least amount of a patients' energy to achieve the maximum health improvements. We believe the most effective strategy for maximizing patient improvements with minimal energy is to focus on the building and expansion of patients' life tissue or muscle mass. This focus on the development of life tissue with minimal energy expenditure informs the strategy, intensity, techniques, and process of the physical exercise of the GH Method.

   Many exercise programs focus on improving many aspects of patients' physical health, while the GH Method focuses on strategies designed to maximize the development of life tissue. This systematic strategic focus on muscle mass development informs every aspect of the GH Method and is a critical driver of the significant measurable improvements experienced by patients.

3) Help them change their feelings and thinking patterns

The GH Method is designed to engage patients in an ongoing re-evaluation of their own health and behaviors, resulting in increased self-awareness of the cause-effect relationship of their lifestyle choices on their overall health and well being. While we use a range of strategies including cognitive behavior techniques, our more novel approach is to focus first on changing how patients physically feel and then engaging in cognitive therapy techniques to help them change their thinking and behaving patterns leveraging their already more positive feelings. We believe the most effective way to help patients modify behaviors is focus on helping them achieve a paradigm shift in their feelings from passive and negative regarding their health towards more positive and empowered feelings about their health before embarking on more detailed thinking and behaving pattern changes.

The inter-disciplinary approach of the GH Method requires us to patiently understand the mindset of our clients and then even more patiently work collaboratively with clients to change their mindset in order to achieve lasting lifestyle and behavioral changes. We believe the key to sustainable improvements in our patients' lives is working with them at this deeper psychological level rather than just focus on the behaviors we want to change. Far too often, physical fitness is handled independently of psychology and often that is delivered independently of nutrition guidance resulting in a disjointed patient experience that is difficult for patients to navigate. The GH Method integrates all of these resulting in deeper, more significant and more lasting measurable improvements in patient physical and mental health.

4) Coach them to make sustainable improvements in their lifestyle

Through the written assessment process supplemented by motivational interviewing and the use of cognitive therapy techniques, the GH Method identifies the most impactful behavior/lifestyle changes for a particular patient with particular emphasis on improving their optimum recuperation and therefore enhancing the development of their life tissue. After evaluating the impact of each potential behavior change (the GH Method uses 17 commonly accepted improvements including: reducing sodium intake, minimizing emotional eating, increasing protein to support muscle development, reducing cholesterol, eating more balanced meals), the GH Method then uses the Transtheoretical Model of Behavior Change to determine which external behavior changes should be introduced first. While we begin testing our hypothesis developed with the help of the MIPS profiling of how to be the most effective coach from the beginning, we do not ask patients to make significant behavior changes until after they have experienced a paradigm shift in their feelings about their own health and empowerment. Once we have initiated the phase of coaching external behavior changes, we stay focused on moving slowly so that the patient is only focused on one new behavior at a time, and they can connect that changed behavior with an

improved outcome in order to maximize sustainability and help the patient build momentum to increasingly more difficult external behavior changes.

Often, the nutrition/lifestyle component of an exercise program is built on the assumption that patients foremost need knowledge of healthier living in order to help them improve their behaviors. The focus on knowledge is often communicated to the patient, sometimes in writing, and is intended to help patients make significant changes to their daily lifestyle. Said simply, many fitness programs simply put patients on a diet and focus on the desired outcome which is often weight loss. This type of dieting often leads to a classic pattern where patients that do have success struggle to maintain their success and the rate of recidivism is high. The GH Method emphasizes implementation over knowledge and we therefore focus our energy on identifying the easiest changes for that patient to implement that will have a significant impact, and then helping the patient methodically execute the agreed upon change. We focus patients on the process not the outcome, because they can have more control over the process, and we make them responsible for observing the results of the behavior changes in terms of their energy, mood, and health.

BECOME EXPERTS IN OUR PATIENTS

The process of becoming an expert in our patients begins through the written assessment process and continues to evolve throughout their participation with the GH Method as their psychology and physiology continue to change. We use five different written assessments, some given only at the beginning of the GH Method and some being given at multiple points in the process.

BUILD AND EXPAND THEIR LIFE TISSUE

At the core of the GH Method's approach to exercise is to build and expand life tissue or muscle tissue with a minimal amount of energy expenditure. The GH Method aims to increase individual muscle development by helping patients focus their energy on isolating the individual muscle that is being targeted through proper technique, improved self-awareness, active participation in the program, and a deepening understanding of their own physiology. The education of the patient is paramount, as they must be technically engaged and develop an increased awareness of physical sensations in order to fully participate in the precision required to build and expand life tissue. The GH Method requires such precision that it can only be delivered to one patient at a time with minimal distractions given the engagement and concentration required by both the coach and the patient. The patient is re-assessed consistently throughout the program as their physiology changes and, therefore, the exercise needs to change as well to maximize the development and expansion of their life tissue.

The GH Method is a systematic approach to increasing individual muscle development that is customized to each client based on the assessments completed as well as their energy and recuperation levels. Throughout the GH Method, we are constantly evaluating the patients' optimum recuperation level to determine the right intensity to achieve the exercise objective. We define optimum recuperation as the intensity level where the patients' body can effectively incorporate the workout. For example, if the

objective of the GH Method for a week is to increase the thickness of muscle tissue then the intensity level must be set so that the exercise effectively tears the appropriate layer of the muscle cell fibers while leaving enough energy in the body to repair and rebuild the impacted muscles resulting in increased thickness. Optimum recuperation levels are determined by a combination of a clients physiology, energy, strength, endurance, sleeping patterns, nutrition, and stress level.

The GH Method defines in detail the strategy and objectives for each day of exercise, including intensity levels, duration, muscle groups, order of exercises, repetitions, speed, breaks, techniques to enhance the effectiveness, along with an accompanying educational curriculum and psychological strategy correlated with the workout program. The detailed workouts are then customized to the individual patient based on the assessments of strength, recuperation, energy among others that are constantly updated throughout the program. The GH Method is organized into Levels and all patients begin in Level 0. For the purposes of this study, patients will experience at least 12 months of the GH Method which may incorporate the following levels:

Level 0. This level comprises approximately 8 separate weeks although many of the weeks may be repeated depending on the needs of a particular patient. The major physical objective of Level 0 is to effectively engage their muscle fiber (without much breakdown) to activate their innate strength, endurance and cardiovascular capacity. Before the end of Level 0, we measure patient strength, endurance, and cardiovascular capacity to ensure we can train patients to their optimum recuperation level. The major educational objective of this Level is to teach clients the technical form and self-awareness that is mandatory before they can proceed to the next Level. The major psychological objective of this Level is to establish a safe and caring environment for patients, to reframe how they think about exercise and their health, and for us to become experts in all aspects of the patient.

Level 1. This level comprises approximately 12 weeks although many of the weeks may be repeated depending on the needs of a particular patient. The major physical objective of Level 1 is to begin the process of increasing the development of individual muscles and therefore increasing patients' life tissue. More energy is directed towards the larger muscle groups which can increase in size the fastest resulting in improvements in patients energy levels, physical symptoms, and other measures. The major educational objective of this Level is to promote the patients autonomous relationship with their own body by increasing their own self-awareness of physical sensations during their exercise and recovery. The major psychological objective of this Level is to leverage the improved energy and autonomy to collaboratively initiate the process of making lifestyle/behaviorial changes. Before the end of Level 0, we measure patient strength, endurance, and cardiovascular capacity to ensure we can train patients to their optimum recuperation level.

Level 2. This level comprises approximately 20 weeks although many of the weeks may be repeated depending on the needs of a particular client. The major physical objective of Level 2 is to continue the process of increasing the development of individual muscles

and therefore increasing the patients' life tissue. The Level includes weeks focused on improving muscle strength, muscle endurance, muscle size, muscle thickness, heart endurance, lung capacity, and resistance strength. The main educational objective of this level is to promote patients awareness of the function of their bodies, including strength, energy, endurance, and recuperation so they feel more empowered and in-control of their physical health and aware of the improvements they are making. The main psychological objective of this Level is to help patients use the increased self-awareness of their own body (the educational goal of Level 1) to understand the impact of the dietary and lifestyle changes they are making. We aim to connect patients as closely as possible with feeling the impact of the individual changes they are making, as that is a key to both sustainability of the changes they have already made and empowerment to continue making more changes.

CHANGE FEELING AND THINKING PATTERNS

As we become experts in our clients through the use of assessments, motivational interviewing, and careful observation, we develop a deep understanding of how our patients see the world, their physical health, their mental health, their behavioral choices, and their future. We use each session to add to the body of knowledge we have about each person, including their verbal and non-verbal communication, how they react to management and autonomy, their ability to execute behavior changes, their motivations and their outlook on the future.

During Level 0, we are absorbing as much knowledge as possible about our patients. Often before the end of Level 0 patients feel some improvement in their daily function, whether its energy, attitude, or the reduction of pain. We help patients listen to their own bodies and become aware of the changes they are experiencing. When they confidently express on their own the changes they are feeling, we work closely to leverage those positive feelings into a paradigm shift in how patients may be viewing their physical and mental health. This is a critical step in how the GH Method achieves changes in feeling, thinking, and then behavior patterns.

Often, patients start out with a focus on negatives (concerns, fears, obstacles, limitations) which inform their cognitive thinking patterns and capacity for behavior change. As patients become aware of changes in their body and life, we work to shift their paradigm from the negative to the positive (empowerment, sense of control, ability to improve symptoms, autonomy, hope for the future). While each patient is different, a common early patient experience is improved energy, so that is a key point of focus and provides the most common pivot point in patients' feelings moving from negative towards positive. We use many motivational interviewing techniques to help maximize the impact of this shift.

Cognitive behavior theory postulates that thinking patterns inform feeling and behavior patterns so changing the way we think can greatly impact how we feel and behave. While we use cognitive behavior techniques, our more novel approach is to focus first on changing how patients physically feel and then leveraging that momentum towards encouraging changes in thinking and then behaving. We believe the most effective way

to modify behaviors is to work in a collaborative process with our patients and help them first achieve a paradigm shift from negative to positive before embarking on more detailed thinking and behaving pattern changes. We incorporate cognitive therapy techniques with the workouts so that we can leverage the most teachable moments, set a slow and steady pace, and continue to learn more about the most effective techniques of cognitive therapy and motivational interviewing to create changes in each individual patient.

The GH Method also utilizes Neuro Linguistic Programming (NLP) to better understand and then impact the outlook of patients and by maximizing the effectiveness of our communication with those patients. We study the conscious and unconscious process of how our patients code and store their feelings, insights, obstacles and successes so that we can impact that coding and therefore influence their thinking. The key components of NLP are:

a) Neuro. The key for this component is to understand how patients translate the experience of their key senses into thought processes, both conscious and unconscious. We are trying to learn how their senses, their mind, their feelings combine to function as one system.
b) Linguistic. The key for this component is to understand how patients use language to make sense of their experiences and how they choose to communicate that experience to themselves and others. Language patterns have an enormous impact on how a patient feels, thinks and ultimately behaves, so learning their language patterns positions us to have a more significant impact on our patients.
c) Programming. This is the coding of experience. How patients mobilize their own experiences and vocabulary to attempt and execute changes in their own lives. Individuals typically demonstrate some consistency in patterns of success and patterns of failure, so we study how patients most effectively program themselves for success so that we can help them emulate or establish consistent and sustainable patterns of success.

COACH THEM TO MAKE SUSTAINABLE IMPROVEMENTS IN THEIR LIFESTYLE

We combine the written assessments with the knowledge we have accumulated about our clients behaving patterns, routines, capacity for behavior change and attitude towards change to establish the priorities for that client for behavior/lifestyle changes. The GH Method includes a formulaic approach to identifying the order and speed of changes for each patient based on the clients need for independence in terms of agenda-setting (discovered in the MIPS), their evaluation of general health (PROMIS v.1.1 Global Health questionnaire), their evaluation of mental health and pain intensity (PROMIS 29 Profile v2.0) their readiness to change according to the Transtheoretical Model of Change (discovered in the Lifestyle Inventory), their actual habits and routines (discovered in the Food Journal) and our ongoing motivational interviewing and assessment process.

The formulaic approach determines which of 17 possible behavior changes we will focus on first, and then we use the MIPS profiling, our identification of where they are in terms of their stage of change, our understanding of their Neuro Linguistic Programming, and the rapport we have established to coach patients to most effectively execute behavior change plans. The integration of the coaching program from physical exercise to lifestyle changes is critical to the GH Method's effectiveness.

The GH Method targets only one behavior change at a time and does not move onto the second until patients have achieved some level of success with the behavior change and become aware of the impact that change has on their health. This methodical and slow approach helps sustainability as patients feel the connection between the cause (the behavior change) and the effect (an improvement in their health). After identifying the starting point for guiding the client through behavior changes, we use motivational interviewing to help the patient collaboratively accept the starting point or reject it and select another starting point where they are more ready to implement a change. We then focus on helping patients develop a strategy and a plan for implementing the change, set their own goals for the change, and then we help create accountability for the implementation.

Hypotheses:

1. Counseling twice weekly on diet and nutrition will improve food choices to more healthy choices of fresh fruits and vegetables and low fat protein sources. To test this hypothesis, patients will undergo a food frequency questionnaire at baseline to document choices prior to intervention. A food frequency questionnaire will be performed at the end of the intervention to determine the effect of counseling on protein source, number of calories, and frequency of fresh fruits and vegetables. Counseling will consist of the diabetes prevention program counseling which is a well-established, well-verified intervention, commonly accepted as an effective means of providing a standardized nutritional education.

2. The combination of exercise and dietary intervention positively affects body composition. With this hypothesis we will test whether muscle strength (Biodex measurements) and muscle mass (DEXA scan) changes after 12 months of an exercise intervention. We hypothesize that the transplant itself will not affect activity levels, strength levels or muscle mass. Baseline measurement will be performed before the intervention, at 6 months post intervention, and the final measurement would be taken at 12 months with muscle mass measured by DEXA and strength measured again by Biodex.

3. Patients receiving strength training will have significantly higher activity levels when compared with no intervention or physical therapy. The rationale for this hypothesis is that patients without strength training will fail to increase muscle mass and strength and this inability will translate to persistently lower activity levels than those patients with strength training. Once again levels will be documented with an accelerometer and PROMIS questionnaires, 6 months and 12months to document the effect of intervention. In addition, if patients in the control group and GH group decide to

have the optional muscle biopsy, it will help evaluate how targeted exercise may change muscle development measuring expression of mature microRNAs using total RNA extraction.

4. Patients with strength training will activate type II macrophages which are anti-inflammatory and pro-regenerative, tipping the balance away from inflammation towards regeneration when compared to the other treatment groups. Since strength training is likely to initiate signals of muscle regeneration, and since type II macrophages play a key role in this effect, it is possible that increasing the signaling to the muscle for regeneration may also increase the proportion of active type II macrophages which are anti-inflammatory. To test this hypothesis, we will test the proportion of peripheral blood M1/M2 macrophages at baseline,6 months and 12 months after the initiation of the intervention. Recognizing that immunosuppression may significantly confound this proportion and overall suppress it, we will also test circulating levels of pro-inflammatory cytokines such as C-reactive protein(CRP), IL-6, IL-1, TNF-alpha, homocysteine, adiponectin, leptin, and resistin as well as pro-regenerative cytokines such as TGF-beta and IL-10.

5. We expect patients with strength training will experience less renal dysfunction, decreased hemoglobin A1C, increased peripheral vascular function, decreased fasting blood sugar when compared to the other treatment groups. The rationale for this hypothesis is the finding that muscle mass provides active regulation of glucose and other metabolites. Therefore increasing this may provide improved metabolic function. These laboratory panels are part of the standard transplant follow-up labs and add no cost to the project.

6. Patients with strength training will have an overall improved sense of well-being and energy level compared to those with physical therapy or no treatment. With twice weekly counseling for activity and nutrition, patients will be asked about their general health, mental health and pain intensity using the PROMIS questionnaires.

METHODS

Setting: The study will include 225 patients, to achieve a goal of 180 patients in the GH study group and 45 patients in the control group. Every patient will be followed for 3 years after the start of the intervention. Patients will start the intervention at least 2 months post-transplant; however they can be enrolled prior to transplant.

Main Study Inclusion criteria:

-Successful kidney transplantation (KTx) with primary graft function
- Age between 18 and 65 years
- Adequate cognitive ability to complete the questionnaires, give consent for the study and follow the physical and diet instructions

Main Study Exclusion criteria:

- transplant of any other organ besides kidney alone or a combination of a kidney/pancreas

-non-ambulatory or significant orthopedic problems
- cardiac/pulmonary disease that contraindicate the physical training
- any contraindication to exercise testing per the American Heart Association
-unable to comply with the training program

Muscle Biopsy Inclusion:
- Age between 18 and 65 years
-Patients who have a brachial–cephalic arteriovenous fistula (AVF) in the elbow or brachial–basilic AVF in the arm
-Exercise Arm- the biopsy will only be performed once, after the 12 month exercise intervention is completed (which will be longer than 1 year post transplant surgery)
-Control Arm- this procedure will be performed once, around one year post transplant surgery (may occur at any time during the study)

Muscle Biopsy Exclusion:
-Patients that do not meet the inclusion criteria

Identifying potential subjects for recruitment:
A waiver for an alteration of consent and waiver of documentation of consent is being requested for review of medical records to identify potential patients for study recruitment and also for a telephone screening process for patients that response to a recruitment flyer. The principal investigator already has access to these records as part of daily care for all patients seen in clinic. This presents no more than minimal risk since this data will be kept confidential.

Moreover, as part of the telephone screening process for patients interested in this study there will be oral consent obtained to start the screening process in order to determine if the patients are eligible to be in the study. If the patients are eligible, they will be schedule for a visit where they will be consented to be in the study.

Randomization: All patients who meet the enrollment criteria will be randomized 4:1 to the GH group or the control group.

- GH group: patients will be treated for 12 months with the GH method (Appendix 1) for one hour twice a week
- Control group: patient will be treated according to the standard of care for post-transplant recipients; control patients will be offered the opportunity to undergo the GH regimen for the 1 year after their final visit as a control patient. If the control patients chose to undergo the GH regimen, the extended follow up will be completed after 1 year from their final GH visit (totaling 4 years from the start of intervention).

Long-term follow-up
After the 12 month intervention period all patients will be followed for 2 additional years. Patients will be contacted by phone to assess current activity level, employment status, graft function and current weight. Patient's medical records will also be reviewed to confirm BMI and graft function. This will be done every 6 months.

A separate waiver of documentation of consent, for long-term follow up, is being requested for patients that have previously enrolled and completed the study (January 3, 2012 to July 28, 2014).

Parameters to analyze in all patients:

The PROMIS v.1.1 - Global Health short form will be administered to all patients at the time of enrollment, 6 months and at the end of the study (12 months). The PROMIS v.1.1 - Global Health short form will assesses health in general (i.e. overall health). The PROMIS Global Health short form is a 10-item instrument representing multiple domains (physical function, fatigue, pain, emotional distress, social health) as well as perceptions of general health that cut across domains. Global items allow respondents to weigh together different aspects of health to arrive at a "bottom-line" indicator of their health. Similar global health items have been found predictive of future health care utilization and mortality.

PROMIS 29 Profile v2.0 will be administered to all patients at the time of enrollment, 6 months and at the end of the study (12 months). The PROMIS 29 Prolife v2.0 is a short form containing four items from seven PROMIS domains (Depression, Anxiety, Physical Function, Pain Interference, Fatigue, Sleep Disturbance, and Ability to Participate in Social Roles and Activities) along with a single item on Pain Intensity.

Multiple studies have been conducted by the PROMIS Network validating these instruments. Studies are shown at: http://www.nihpromis.org/science/validitystudies.aspx

Body composition and strength
BMI will be calculated at the time of enrollment, at 6 months, and at the end of the study (12 months).The most exact method to determine body fat and lean body mass is DEXA, a method that has been validated in patients with renal failure before and after transplantation [6,7]. Waist circumference as well as blood pressure will be measured for general health markers. Muscle strength will be measured using a Biodex machine. Exercise capacity will be measure with a 6 minute walk test and an accelerometer. Fitness level will be measure with a maximal aerobic capacity test (VO2 max). These 7 tests will be done at baseline, 6, and 12 months.

Waist Circumference:
Waist circumference will be measured at the narrowest part of the torso (above the umbilicus and below xiphoid process) in the standing position using a tape measure. This will be completed at baseline, 6 months and 12 months post-intervention.
Blood Pressure:
Blood pressure will be measured in the supine position (lying on back) in a dimly lit room after resting for fifteen minutes. This will be completed at baseline, 6 months and 12 months post-intervention.

DEXA Scan: We will determine percent body fat via a whole body scan by dual energy x-ray absorptiometry (GE, IDXA, Madison, Wi), which will be operated and calibrated using the manufacturer's stated guidelines. The duration of the scan will be less than 10 min and the subject will be exposed to a radiation dose of ≤0.3 mrem based upon the manufacturer's specifications and calculations from Standford Dosiometry, LLC RADAR Medical Procedure Radiation Dose Calculator. This amount of research protocol radiation exposure is minimal given the estimated effective equivalent dose is below the 100 mrem per year, a limit set by the Nuclear Regulatory Commission for "general public" exposure.

Biodex: Bilateral isometric knee extensor and flexor peak torque will be measured using a Biodex System 3 dynamometer (Shirley, NY). Participants will be positioned in the dynamometer according to the manufacturer's recommendation. Briefly, the axis of rotation of the machine will align with the lateral epicondyle of the femur. The calf pad against which the participant exerts force will be positioned halfway between the lateral malleolus of the fibula and lateral epicondyle of the femur, and securely attached using straps. Straps will be placed over the thighs, pelvis, and torso regions to minimize movement during the test. We will use an anatomical reference position of 90° knee flexion, and isometric torque will be assessed at joint angles of 45°, 60°, and 75°. Peak torque will be obtained by having the participant perform 3 maximal contractions with the knee extensors for 5 seconds, which will be immediately followed by a 5 second maximal contraction with the knee flexors; 1 set will be performed. There will be no rest period between contractions within a set, and the rest period between each angle set will be 3 minutes. The highest recorded peak torque will be used as a measure of knee extensor and flexor isometric strength, and expressed as strength per body weight.

The 6 minute walk test involves walking as far as possible (down the hallway) over a six-minute period with distance recorded by researchers on one trial. During this test the subjects will wear a mask on their face that measures how much oxygen their body uses during this task (Cosmed K4b2, Rome, Italy). VO2 will be assessed during this test to evaluate the amount of oxygen the subject's body utilizes during acts of regular daily activity, such as walking, which will be completed on a treadmill (as described below). Distance will also be collected as a way to measure the subject's functional capacity and to track progression. This test will be completed at baseline, 6 months and 12 months post-intervention.

Maximal aerobic capacity test (VO2 max): For subjects over 55 yrs or that are classified as moderate to high risk according to ACSM's risk stratification scale, this will occur in the presence of a physician. We will use a modified Balke Treadmill protocol: the treadmill will be set at a constant speed (3.3 mph) while the incline is increased by 2% every two minutes. This protocol is selected to ensure that the elderly subjects will be able to perform a maximal aerobic test. For younger (18-35 yr) subjects, the test will begin at a 10% grade and increase 2% every 2 minutes. If maximal effort is not reached

by minute 10 and a 20% grade, speed will be increased by 0.3 mph until maximal effort is achieved.

Accelerometer: subjects will be given an accelerometer with instructions for use and be asked to wear it around their waist for 1 week while awake to measure their level of physical activity. This will be completed at baseline, 6 months and 12 months post-intervention.

Muscle Biopsy
Optional muscle biopsies for GH group and control group, will be performed to measure expression of mature microRNAs using total RNA extraction, which will help evaluate how targeted exercise may change muscle development. The muscle biopsy will be performed by Dr. Ivo Tzvetanov, Dr. Benedetti, Dr Di Bella, and/or Dr Spaggari, all of which areexperienced surgeons with prior experience performing muscle biopsies. The muscle biopsy will be performed at the University of Illinois at Chicago Outpatient Clinic, with an address at 1855 W Taylor St, Chicago, IL 60612.

Prior to kidney transplantation many patients undergo hemodialysis treatments to sustain life. Hemodialysis is a process of purifying the blood of a person whose kidneys are not working normally. Arteriovenous fistula provides an access route for hemodialysis to be possible, by providing a direct connection of an artery to a vein. As part of standard of care at UIC, the AV fistula is ligated (a surgical procedure of closing off a blood vessel) at around one year post-transplant. As a way to retrieve bicep muscle biopsy samples we will retrieving samples during the closing AV fistulas (ligation) in kidney transplant patients with stable renal function. Patients will be consented with a supplemental consent for the bicep muscle biopsy.

In the upper extremities, the typical sites for muscle biopsy are deltoid or biceps. We want to focus on the bicep muscle only and we will include only patients with brachial–cephalic AVF in the elbow or brachial–basilic AVF in the arm will be selected in order to have easily access to the biceps muscle.

The skin incision for closing brachial–cephalic or brachial–basilic AV fistula in the upper extremity is made over the area of the arteriovenous anastomosis: in the elbow for brachial–cephalic AVF or in the arm for brachial–basilic AVF.

After shaving and disinfection of the external part of the surgical site, local subcutaneous anaesthesia is achieved using 4 mL of lidocaine (2%) with special attention to ensure that no lidocaine is injected in the muscle. Thus, injection of lidocaine is done superficially and obliquely.

In case of voluminous fistula, a regional anesthesia via peripheral nerve block is preferred. In these cases, the anesthetic (a mix of lidocaine and ropivacaine) is injected by anesthesiologist near the brachial plexus to block sensations of pain from a specific area of the body. Nerve blocks usually last longer than local anesthesia.

A small cutaneous incision (about 4-5 cm) is made in the antecubital fossa, over the area of the arteriovenous anastomosis, following the medial border of the biceps muscle. The muscle is retracted slightly laterally in order to allow access to the thin aponeurotic sheath which contains the neuro-vascular bundle. Biceps brachii muscle is visualized and cut. Muscle fibres are carefully dissected in their longitudinal axis away from the tendon insertion, to obtain a sample of 300 mg. This is about the size of 2-3 grains of rice. Both ends are immediately clipped and hemostasis is controlled. The bundle is fixed on a cork support at its apparent resting length.

The skin incision is closed with 3.0 Nylon suture and pressure is applied to the incision site.

This procedure will be done once at 12 months for patients randomized to the exercise arm (after the exercise intervention is completed) and once at any time during the 12 month study duration for the control arm as long as the patient is at least one year post transplant.

Status of systemic inflammation
At baseline, after the patients have fasted overnight, blood samples will be drawn for analyses of pro-inflammatory cytokines such as C-reactive protein (CRP), IL-6, IL-1, TNF-alpha, homocysteine, adiponectin, leptin, and resistin as well as pro-regenerative cytokines such as TGF-beta and IL-10. Peripheral blood M1/M2 macrophages will also be measured. These tests will be performed at baseline, 6 months and 12 months post-intervention. Blood sampling will require approximately 20ml of blood at each blood draw. The total amount of blood drawn will be about 60 ml.

Metabolism and renal function changes
All patients will be monitored for fasting plasma Glucose, HbA1c, Lipid profile (Serum Cholesterol, Triglycerides, HDL Cholesterol, LDL Cholesterol), and serum creatinine during the study per standard of care for kidney transplant patients.

Vascular Function and Vascular Stiffness
Brachial FMD will be used to assess macrovascular endothelial function. This method involves the measurement of vascular reactivity of the brachial artery using non-invasive ultrasound technique. While the subject rests in the supine position, an 11 MHz probe will be used to determine brachial artery diameter above the antecubital fossa in the non-dominant arm. In addition, continuous wave Doppler will be used to determine brachial artery blood flow velocity. Brachial artery diameter and blood flow velocity will be measured under the following conditions: 1) At rest, 2) During reactive hyperemia produced by a five minute interruption of flow with a blood pressure cuff inflated >50mmHg above systolic pressure, 3) For three minutes after reactive hyperemia (30-second intervals for the first minute and 1-minute intervals thereafter).

Assessment of vascular stiffness using peripheral tonometery and ultrasound imaging
Upon entering the lab, participants will be required to rest quietly in the supine position in a dimly lit room for 10 minutes. Arterial size and stiffness will then be measured via ultrasonography using several different methodologies: 1) Pulse wave velocity: this test

allows for a non-invasive way to measure arterial stiffness. Three disposable electrodes will be placed on the subject's torso. A pen-shaped transducer is placed over the carotid artery (side of the neck), over the femoral artery (top of the leg), over the anterior tibialis artery (inner ankle), and over the radial artery (wrist). The distance between each of these sites will be measured using a tape-measure. 2) Arterial Distensibility and function by ultrasound imaging: this test allows for non-invasive imaging of the carotid, brachial, and femoral arteries. Central blood pressure will be determined using the aforementioned pulse-wave analysis method (SphygmoCor SCOR, PWV Medical, Sydney, Australia). In brief, the pressure waveforms that are obtained at the radial artery site are subjected to a generalized transfer function to derive the corresponding central arterial waveforms

Cardio-ankle vascular index (CAVI) and Ankle Brachial Index (ABI)
CAVI and ABI will be assessed by pulse wave velocity analysis at the brachial and ankle arteries (VaSera VS 1500AU, Fukuda Denshi, Japan). The CAVI measurement requires the placement of ECG electrodes on both wrists, and a microphone for phonocardiography on the sternum in the second intercostal space, and 4 blood pressure cuffs. CAVI between the heart and ankle arteries is assessed using measurements of time between heart sound II and plethysmograms taken at the brachial and ankle arteries. This will be done to measure the stiffness of arteries and is independent of blood pressure. This test will be performed at baseline, 6 months and 12 months post-intervention.

Wrist Artery Stiffness
A very sensitive pen-shaped microphone will be placed on the subject's wrist (radial artery). This microphone measures how stiff the radial artery is. This test will be performed at baseline, 6 months and 12 months post-intervention.

Central Artery Stiffness
The same pen-shaped microphone used before will be placed on the subject's neck and then the artery at the top of their thigh. We will use these measurements to measure how stiff their central arterial system (the arteries in the midsection of the body) is. This test will be performed at baseline, 6 months and 12 months post-intervention.

Carotid Artery Stiffness and Compliance
We will look at the artery in the subject's neck using an ultrasound machine. This machine is similar to what doctors use to look at babies within the womb. We will place a small amount of gel on their neck to help us get a clearer picture. This gel is hypoallergenic and washes off very easily. We will place the probe on their skin, over the artery on the inside of their right neck. This probe will allow us to look at the carotid artery and see how it moves with each heart beat. This test will be performed at baseline, 6 months and 12 months post-intervention.

Cardiac Ultrasound
We will measure the subject's heart function with ultrasonography using ultrasound gel and a probe. It is the same probe used to visualize babies in the womb. We will measure

how quickly the subject's heart contracts and relaxes. This test will be performed at baseline, 6 months and 12 months post-intervention.

Other measurements: Resting heart rate will be measured in the supine position. Resting blood pressure will be measured in the brachial artery using a digital sphygmomanometer in the supine position according to the guidelines of the American Heart Association. Blood pressure will be measured twice, one minute apart, and the average of the two values will use as resting blood pressure. Body mass index will be calculated as weight (kg) divided by height (m) squared. Employment status will be confirmed. These measures will be completed at baseline, 6 months and 12 months post-intervention.

GH subjects only:

Personality Assessment

Millon Index of Personality Styles (MIPS) is a 180 question true/false questionnaire that can typically be completed in approximately 30 minutes and was developed to evaluate normally functioning adults who may be experiencing problems in various aspects of their lives. The MIPS addresses three key dimensions of normal personalities: motivating styles, thinking styles, and behaving styles. Based on the patients motivating style we learn how to balance coaching with autonomy, and how patients engage emotionally with their surrounding environment. The outcome of thinking styles helps us understand the patients' cognitive processes and prepares us for effectively influencing their cognitive thinking patterns. The outcome of behaving styles helps us understand the patients' way of interrelating with others so we can be the most effective coach when it's time to help them change their behaviors. This will only be administered to the GH patients at the time of enrollment.

Lifestyle Inventory

The GH Lifestyle Inventory was developed by GH as a lifestyle inventory questionnaire combining factual assessment questions regarding their lifestyle, as well as questions evaluating their emotional relationship with their health, and finally a series of questions evaluating their readiness to change informed by the Transtheoretical Model of Behavior Change. The tool typically takes 8 – 10 minutes for completion, involves 26 questions many of which are multiple choice but some free form fields. The GH Lifestyle Inventory is primarily used to: allow patients to self-report lifestyle habits, understand their emotional relationship with their health and with their lifestyle. And develop hypothesis for where the patient is in terms of behavior change stages according to the Transtheoretical Model of Behavior Change (pre-contemplative, contemplative, preparation, action, maintenance). This will only be administered to the GH patients at the time of enrollment.

Food Journal

The Food Journal was developed by GH as to allow client self-reporting of actual eating and sleeping habits. This is typically administered for two consecutive weeks at various times in their participation with the GH Method, but never earlier than four consecutive weeks of participation. The food journal is used to: validate or disprove the patients self-

reporting done via the Lifestyle Inventory, understand their eating and sleeping patterns in greater detail by eliminating their opinions and emotional relationship and just focusing on actual intake, and provide a tool for ongoing monitoring and an opportunity for increasing patient's self-reflection on their food and sleeping habits. This will only be administered to the GH patients. Importantly, this is not a measurement tool that we would give at a specific time during the study; it is being used during the study by the research personnel and GH Method personnel to help manage self-reported behavior changes with the patients.

Counseling
Patients in the both arms will be counseled regarding weight loss per standard of care which consists of a pre-transplant and a post-transplant nutrition evaluation and education.

Video recording (optional)
Video recordings will be an option on the consent form for patients that are randomized into the GH exercise group. The option to be video recorded by the GH team at the beginning and end of the patient's 12 months of training. The recordings will be used to compare the progress of the patient from the beginning and end of GH training.

GH Study Visits:
At least one week prior to the first GH session with a patient, the written assessments will be completed and returned to GH personnel for scoring and processing. The first four GH sessions (over 2 weeks) for any patient will be 75 minutes. Following the first 4 sessions, ongoing patients will be slotted into recurring 60 minute time slots for the remaining 50 weeks. All of these visits will occur in the UIC Disability Health and Social Policy Building (DHSP) located at 1640 W. Roosevelt Road in Suites 158, 190, and 195. The procedure visits at baseline, 6 and 12 months will take 2-3 hours.

At least twice per week, GH personnel will attempt to follow-up with patients via text message, email or a phone call to evaluate their physical recuperation and overall health and energy or to track their performance with a behavior change goal.

Patients will be asked to complete a physical regimen based on the following:

Summary of GH Study Visits:
- Patients may be asked to repeat previous weeks and/or skip a particular week depending on their energy, progress, and overall health.
- Depending on a patient's individual physical need, mobility, the program may be slightly modified (number of repetitions, number of exercises, etc...) to be safe and appropriate for that individual.
- Each week comprises two different exercise days, each incorporating approximately 5-10 minute light warm-up plus stretching and then the exercises.
- Unless specified as a cardio or endurance week, all weeks consist of basic strength training/resistance workouts.

- The attached exercise list includes all possible strength training exercises, and clients complete the appropriate exercises for that week during their two, one-hour appointments each week. Depending on a patients particular physical health (e.g. shoulder problems) certain exercises may be eliminated or modified in terms of the safe range of motion and intensity.
- These sessions can be directly supervised by the GH instructors or performed by trained personnel implementing written instructions given by the instructors.

Week	Overview	Intensity/Weight	Breaks
Week 1	1st Set: 30 Seconds with Only Safety Instruction 2nd Set: 90 Seconds with More Focus on Form	Light	2 or more minutes
Week 2	1st Set: Holding at top and bottom of range (20 seconds each hold) 2nd Set: 20 rep's and possible to add plus 5 depending on energy	Light	2 or more minutes
Week 3	1st Set: Warm-Up of 15 repetitions 2nd Set: Resistance focused 60 seconds, possible plus 5	Light/Moderate	2 or more minutes
Week 4	3 Sets for every exercise. Each set is 12 repetitions with some holding for five seconds.	Moderate	30 seconds between sets. 2 minutes between exercises.
Week 5	1 Warm Up Set of 15 repetitions. 1 Heavier Set of 11 Repetitions.	Moderate/Heavy	3 minute breaks
Week 6	Cardio Exercises (e.g. run in place). 5 different exercises are done as one round and two rounds total.	Light/Moderate	2 minutes between exercises and 4 minutes between rounds.
Week 7	1st Set: Warm up of 12 repetitions. 2nd Set: 6 repetitions	Moderate/Heavy	3 minutes
Week 8	1 Set: 90 seconds	Light	3 minutes
Week 9	1 Warm Up Set of 15 Repetitions. 3 Sets of 6-8 repetitions (depending on exercise)	Moderate/Heavy	3 minutes
Week 10	3 Sets of Declining Heaviness with 6 reps, 8 reps, and 10 reps	Moderate	3 minutes
Week 11	2 Sets Per Exercise without break between: 18 reps and 16 reps	Moderate/Light	2 minutes
Week 12	1 Set of 25 - 30 repetitions	Moderate/Light	2 minutes
Week 13	Cardio Exercises (e.g. run in place). 7 different exercises are done as one round and three rounds total.	Moderate	2 - 3minutes

Week 14	1 Set of 12 - 16 Repetitions	Moderate	2 minutes
Week 15	3 Sets of declining heaviness with 8, 10 and 12 repetitions	Moderate	3 minutes
Week 16	3 Exercises in Each Set and 7 sets	Moderate	3 minutes
Week 17	1 Set 90 Seconds	Moderate/Light	3 minutes
Week 18	Cardio Exercises (e.g. run in place). 3 different exercises per set. 3 Sets equal one Round. Three Rounds total	Light	2 minutes
Week 19	1 Warm-Up Set of 12 repetitions 1 Set of 7 Repetitions	Moderate/Heavy	3 Minutes
Week 20	1 Set of 25 - 30 Repetitions	Moderate	3 Minutes
Week 21	1st Set: Warm up of 12 repetitions. 2nd Set: 6 repetitions	Moderate/Heavy	3 minutes
Week 22	1 Set: 35 - 40 repetitions	Moderate/Light	3 minutes
Week 23	1 Warm Up Set: 15 repetitions 1 Heavier Set 8 - 10 repetitions	Moderate/Heavy	3 minutes
Week 24	1 Set of 90 Seconds focused on resistance	Moderate	3 minutes
Week 25	Cardio Exercises. 10 exercises in a set. 2 Sets.	Moderate	3 minutes
Week 26	3 Exercises in 1 Set. 9 Sets.	Moderate	3 minutes
Week 27	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 28	1 Warm Up Set 8 reps 1 Heavy Set 8 reps. Medium speed.	Heavy	3 minutes
Week 29	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes
Week 30	1 set 90 seconds. Medium speed.	Lighter	2 minutes
Week 31	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 32	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes
Week 33	1 set 90 seconds. Medium speed.	Lighter	2 minutes
Week 34	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 35	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes

Week 36	1 set 90 seconds. Medium speed.	Lighter	2 minutes
Week 37	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 38	2 Sets Per Exercise without break between: 18 reps and 16 reps	Moderate/Light	2 minutes
Week 39	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes
Week 40	1 set 90 seconds focused on resistance. Medium speed.	Lighter	2 minutes
Week 41	Cardio Exercises. 10 exercises in a set. 2 Sets.	Moderate	3 minutes
Week 42	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 43	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes
Week 44	1 set 90 seconds focused on resistance. Medium speed.	Lighter	2 minutes
Week 45	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 46	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes
Week 47	1 set 90 seconds focused on resistance. Medium speed.	Lighter	2 minutes
Week 48	1 Warm Up Set: 8 – 12 reps. 1 Heavy Set: 8 – 12 reps. Slower Speed.	Moderate/Heavy	2 minutes
Week 49	3 Sets on each exercise of 6, 8, 12 repetitions. Lower weights each set. Medium speed.	Moderate	3 minutes
Week 50	1 set 90 seconds focused on resistance. Medium speed.	Lighter	2 minutes
Week 51	1 Warm Up Set 8 reps 1 Heavy Set 8 reps	Heavy	3 minutes
Week 52	Cardio Exercises. 10 exercises in a set. 2 Sets.	Moderate	3 minutes

GH Method: List of Strength/Resistance Exercises

MEN	**WOMEN**
Exercise	**Exercise**

Chest: Smith Bench Press/Incline	Glutes: Abductor
Glutes: Abductor	Biceps: Cable Easy Curl / Free Bar
Biceps: Cable Easy Curl/Free Bar	Quads: Leg Extension
Quads: Leg Extension	Chest: Smith Press
Calves: Calf Machine	Abs: Decline
Biceps: Preacher	Quads: Leg Press
Quads: Leg Press	Back: Pull Down Behind
Quads: Leg Extension	Hamstring: Machine
Abs: Decline	Shoulders: Dumbbell Press / Smith Press
Back: Pull Down Behind	Triceps: Push Down / Kick Back / Rope Pull down
Hamstring: Curl Machine	Back: Low Roll
Shoulders: Dumbbell Press / Smith Press	Abs: Sit-Ups
Back: Low Roll	Shoulders: Side Raise with Dumbbells
Hamstring: Good Morning with Dumbbell/ 1 Leg Hamstring Curl	Triceps: Close Grip
Shoulders: Side Rise with Dumbbells	Hamstring: Good Morning with Dumbbells/1 Leg Hamstring
Triceps: Push Down / Kick Back	Triceps: Push Down / Kick Back
Abs: Sit Ups	Abs: Sit Ups
Triceps: Close Grip	Triceps: Close Grip

5)Statistical analyses:

The efficacy of the methods will be determined by:

1. a significant difference in term of pre and post treatment perception of well being between the groups

2.a significant difference in the lean/fat body mass ratio between the groups

3. a significant difference in BMI between the groups

4. a significant difference between the inflammatory parameters between the groups

5. a significant difference between the metabolic parameters between the groups

The data will be entered into an Excel spreadsheet and stored on the UIMCC hospital server. The patient data, including age, sex, race, underlying kidney disease, length of hospital stay, rejection episode, comorbidities, and medications will be coded and patient names will not be included in the datasheet.
The de-identified collected data will be entered into a SAS database. Initial descriptive analysis will include calculating means, standard deviations, ranges and frequencies. T-tests for continuous variables and Chi Square or Fischer exact tests of association for

categorical variables will be used to compare results of the study between the two groups for the efficacy parameters listed above. A P value<0.05 will be considered significant.

6) Benefits/risks

The main risk of this research is loss of confidentiality of medical information. Consent will be obtained for all patients. Master patient code list will be kept in a separate file accessible only by the primary investigator. A member of the transplant team will be available to answer any questions or discuss any concerns that patients may have.

The patient may experience mild anxiety or discomfort in providing information about their health and well-being. The patient may also have a potential to feel anxiety when being video recorded (if applicable).

Risks associated with the exercise program

The likely risks and discomforts expected in this study are those that largely involve being engaged in an exercise program after a prolonged period of inactivity. Such risks include: strains, sprains, and muscle soreness. Serious physical injury is considered unlikely given the screening for inclusion and physician approval. We will attempt to reduce risks of injury and harm by promoting gradual increases in exercise across time throughout the 3 month period and having exercise be instructed and supervised by trained professional fitness personnel.

Risks associated with the blood draw:

The risks associated with a blood draw include: mild pain, bleeding or bruising at the site of the draw. In general, any bruising should completely disappear within several days. There are minimal risks of fainting or hypotension (low blood pressure) during or after the blood draw.

Risks associated with the Maximal Aerobic Capacity Test (VO2 Test) and the 6 minute walk test include:

The risks associated with the treadmill max test and 6 minute walk test include: fatigue, being out of breath, muscle soreness, heart rhythm irregularities, dizziness, loss of consciousness and death. However, serious adverse events (side effects) are very rare and by careful screening and monitoring during the test, the risk of such events are minimized. Further risks include slips, trips, ankle sprains and falls. These risks will be minimized by having a research assistant within arm's reach for stability. All personnel assisting in testing are trained in CPR and emergency lab procedure (including calling 911 and the principal researcher) as outlined by the Department of Kinesiology and Nutrition's procedures and policies.

Risks associated with Vascular Function and Vascular Stiffness measures:

There are no known risks associated with the ultrasound tests used to measure artery stiffness and heart function.. Because we will need to place 3 electrodes on the skin to measure heart rate during these procedures, we may need to shave the area on males where these will be placed which may cause some discomfort and/or redness. Some

adhesive may remain once electrodes are removed which may cause redness. This should wear off within 1-8 hours. For the assessment of endothelial function (FMD), the act of inflating a blood pressure cuff around the arm for five minutes before deflation may cause some discomfort, temporary numbness, or tingling. These discomforts, however generally last for a minimal amount of time post deflation.

Risks associated with the Biodex include
Risks associated with the measure of muscular strength (Biodex) testing include strains, sprains, and muscle soreness, as with an exercise program.

Measures of Physical Activity:
There are no risks associated with the accelerometer. Some other risks include shortness of breath, fatigue and rarely heart attack or stroke, and very rarely dealth.

Radiation Exposure from the DEXA scan:The duration of the scan will be less than 10 min. The participant will be exposed to a radiation dose of less than or equal to 0.3 mrem based upon manufacturer's specifications and pre-determined calculations. This amount of radiation exposure is minimal given the estimated effective equivalent dose is below 100 mrem per year, a limit set by the Nuclear Regulatory Commission for "general public" exposure.

Risks of Muscle Biopsy and lidocaine use
Risks of a muscle tissue biopsy include bleeding, bruising, and infection at the procedure site. A subfascial hematoma (a pocket of blood that forms beneath the fatty layer of the skin next to the muscle) may occur. Medical conditions or use of medications or supplements that causes excessive bleeding creates a higher risk of bleeding from the procedure site. Risk associated with any surgical procedure include infection. Due to the immunosuppressant drugs these patients are on as part of standard care, this risk may be increased, however the procedure will be done in a sterile environment with a minimal incision to protect against infection. Less common risks include muscle contracture (shortening of the muscle) and nerve damage leading to loss of feeling at or around the procedure site. Arm may be tender or sore for 2 to 3 days post biopsy. Common side effects of lidocaine include injection site pain, feeling lightheaded, shaking, low blood pressure, drowsiness, confusion, weakness, blurry or double vision, and dizziness. Serious reactions such as seizures, abnormal heart beats, slow heart beat, heart block, severe allergic reactions, respiratory arrest, and coma have occurred.

Benefits
This study is not being done to improve the subject's health. We anticipate that the results of this study will contribute to our understanding of exercise training effects on persons who have had a kidney transplant. It is hopeful that the knowledge gained from this research will benefit others who undergo kidney transplant in the future.

The patients in the supervised physical therapy and GH arms will have the benefit of increased supervision of their physical activity and nutrition compared to what is normally provided per standard of care. In order to assure safety, a medical doctor within the department of surgery who is not affiliated with this research will be appointed to review patient outcomes and monitor the research.

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	Baseline	6 months	12 months
Screening & consent	X	X	X
BMI	X	X	X
DEXA	X	X	X
Biodex	X	X	X
6 minute walk test	X	X	X
7 day accelerometer	X	X	X
Vascular function and stiffness	X	X	X
Blood draw	X	X	X
Questionnaires	X	X	X
Muscle Biopsy			X