Exercise and Weight Loss to Improve Mobility Function in Veterans With PAD

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Peripheral artery disease (PAD) affects an estimated 12 -15 million adults in the US and an estimated 20% of older Veterans. Those with PAD ambulate with slow gait and experience decreased leg strength, dysmobility, reduced quality of life, serious morbidity, and often premature death. It is estimated that over 60% of individuals with PAD are overweight or obese. While PAD itself worsens mobility, obesity adds a further functional burden to older adults with PAD. Individuals diagnosed with PAD, who are also obese typically claudicate 40% more quickly than non-obese individuals and take 20% longer to recover after claudication. Studies of older obese adults without PAD have demonstrated that the combination of exercise and weight loss is more effective at improving physical function and body composition than exercise alone. While these findings likely translate to older adults with PAD, this hypothesis has yet to be tested.

This study is designed to determine whether weight loss and exercise (WL+EX) versus exercise (EX) alone will improve mobility function (walking ability) to a greater extent than exercise alone, and determine the mechanisms underlying changes in mobility function. The investigators hypothesize that a combined intervention of weight loss and exercise (aerobic and restive) will result in greater improvements in mobility function through improved muscle perfusion and reduced muscle fat infiltration than exercise alone in obese Veterans with PAD. The aims of the study are as follows:

Aim 1: To compare the effects of WL+EX vs EX on mobility function in obese Veterans with PAD. The primary outcome will be claudication onset time during a standardized treadmill test.

Aim 2: To determine the intrinsic perfusion and muscle mechanism underlying changes in mobility function brought about by the interventions. The primary mechanistic outcome will be muscle perfusion.

Experimental Design:

Overview: This study is designed to determine whether WL+EX will improve mobility function to a greater extent than EX alone and determine the mechanisms underlying changes in mobility function. We will study men and postmenopausal women with PAD. Participants will be randomized to WL+EX or EX alone. All individuals will be studied at baseline and after 6 months of intervention.

Eligibility criteria include:
Inclusion Criteria:
-BMI >25 kg/m2
-ABI <.90
-Able to participate in a supervised exercise program at the Baltimore VA
-No current plan for surgical revascularization
-Claudication or leg symptoms when walking

Exclusion Criteria:
-Unstable angina or a recent heart attack
-Active cancer
-Diagnosis of dementia on medical record.
-Current foot or leg ulcers
-Already exercise 2x/week or more by self-report

Study Procedures:

The experimental design of this study involves 5 phases completed over 6-7 months (Table 1). Phase 1 involves screening and enrollment. Phase 2 involves baseline testing. Volunteers then will be randomly assigned to EX + WL or Ex (control) (phase 3). Phase 4 consists of 6 months of supervised exercise training. Phase 5 consist of post intervention final research testing.

Table 1: Research Design		
	Time Duration	Research Activity
Phase 1	1-3 weeks	Screening & Enrollment
Phase 2	1-3 weeks	Baseline Testing
Phase 3	1 day	Randomization
Phase 4	6 months	EX + WL or EX
Phase 5	1-3 weeks	Post Intervention testing

Subject Screening and Enrollment (Phase 1):
Based on our prior studies, a substantial proportion of potential participants will not qualify for the study (screen failures). Therefore, after written informed consent and HIPAA authorization is obtained, a history and physical exam will be performed to determine the presence of PAD and any contraindications to study participation. As part of this screening process individuals will complete 1) a six-minute walk test with ankle and brachial blood pressures taken before and after the test; and 2) a history and physical exam. If a subject has recently (within the past 3 months) had a history and physical examination as part of another research study already linked to this study, we will use the results of the history and physical exam from the prior study to reduce participant burden.

Baseline Testing (Phase 2):
There may be certain circumstances in which the Principal Investigator or clinical investigative team may choose not to perform some of the research procedures described below. If this occurs, it will be noted in the participant research notes. Participants may also be requested to repeat one or more of the research tests should it be necessary due to a technical error in its performance and/or measurement, an inadequate sample is obtained for analysis, or there was an unforeseen problem with data collection.

1. The tests described below will be supervised by staff clinicians with the assistance of CPR-trained study team members. Subjects will walk on a treadmill at approximately 2mph and grade is increased every 2 minutes until the subject cannot continue. Subjects will wear a mask with a mouthpiece that will collect expired air for measurement of ventilated gasses. Subjects are instructed to report the onset of claudication pain and then to walk if they can endure the pain (at which time the test will end). Heart rate and ECG are monitored continuously; arm and ankle blood pressure are monitored intermittently throughout the protocol using either auscultation or Doppler ultrasound. Exercise tests may be stopped if the subjects indicate they are unable to continue or they experience any of the following: chest pain, dizziness, faintness, fatigue, pallor,

cyanosis, cardiac arrhythmias, or decompensation, or severe hyper-or hypotension (American College of Sports Medicine 2006.Guidelines for Exercise Testing and Prescription 7th ed.).

2. Strength Testing: A) Muscular strength (e.g., leg extension, leg press, and/or leg flexion) will be measured by 1-repetition maximum (1RM) testing on Keiser K-300 air powered machines, a Biodex strength testing system, or using hand-held strength testing devices. Participants will complete a brief, low-intensity warm-up prior to the test. Participants will be asked to perform exercises against a gradually increasing resistance after each successful exercise repetition until the maximal load is obtained. They may perform multiple trials (typically ~3-7) with a brief rest period between trials. B) Plantar and dorsiflexion will be measured using a hand-held dynamometer or a Biodex strength testing system. Participants will be properly stabilized to ensure minimal movement artifacts. Additionally, verbal encouragement will be provided during task to encourage maximal volitional contraction.

3. Functional Tests and Questionnaires: The physical performance tests include the Modified Physical Performance Test [standing balance, chair rise, book lift, put on and remove jacket, pick up a penny, turn 360 degrees, 50-foot walk, stair ascent/descent, self-selected gait speed (8-foot walk)], grip strength, and the 6-minute walk. We will also administer questionnaires (attached) including the Walking Impairment Questionnaire (WIQ).

4. Body Composition: Total and regional fat mass, lean tissue mass, % body fat, bone mineral content, and bone density will be determined by dual-energy x-ray absorptiometry (DXA). Computed tomography scans of the abdomen and leg are done to quantify regional fat and muscle distribution. We will also measure body circumferences with a tape measure.

Randomization (Phase 3): Participant are randomly assigned to either EX + WL or EX as described below.

Interventions (Phase 4):
Individuals will be randomly assigned to six months of supervised exercise in one of the interventions below

1. Active Exercise Training: All participants who are in the exercise program will exercise for approximately 6 months, 3 times per week at VA exercise facilities. These exercise sessions will be supervised by exercise physiologists or trained staff. The aerobic exercise training program will include a warmup followed by 30-45 minutes of cumulative walking on a treadmill, around a track, or around their home if home exercise program is utilized. Individuals will initially begin walking for 10-15 minutes per exercise session (depending on tolerance) and will progress weekly until 30-45 minutes of cumulative walking has been achieved. For individuals who experience claudication pain, they will be asked to walk until the claudication pain reaches a 3 on a 0-4 scale (0= no pain, 1 = onset of pain, 2 = moderate pain, 3 = intense pain, and 4 = maximal pain) after which they will rest. They will then be asked to walk again. This pattern of intermittent walking will be continued until the prescribed number of minutes of walking is met. Subjects will also be asked to walk at home on days they do not perform supervised exercise. Participants may also participate in strength training (ST) during the same session. This will consist of training of the knee extensors, knee flexors, plantar flexors and dorsiflexors. Subjects will perform approximately 1-3 sets of 4-15 repetitions for each exercise as tolerated. Training may be performed on Keiser K-300 air powered machines utilizing pneumatic resistance (Leg Extension Machine, Leg Curl Machine, Leg Press Machine) or with resistance bands or tubes. Each session of ST will take approximately 15-30 minutes. Blood pressure and heart rate will be

assessed before and after each session. If the participant has type 2 diabetes and is on medications that may result in hypoglycemia, we will monitor blood glucose levels before and after exercise or educate patient to do so if they are exercising at home.

2. Active Exercise + Weight Loss: Participants with BMI>25kg/m2 may be assigned to a weight loss group. This group will also receive active exercise as described above for 6 months. These participants will be counseled to lose body weight to assess the additive effect of weight loss on study outcomes. These participants will be encouraged to attend weekly weight loss classes where they will receive instructions on how to implement a heart-healthy weight loss diet (250-350 kcal reduction per day). If they are unable to participate in person, this may be done over the phone. During these sessions, participants will learn how to adjust their eating habits, record and weigh what they eat, read food labels to eat low calorie high nutritional value foods low in saturated fat and cholesterol and sugar, develop proper eating behavior at the dinner table, and by following the recommendations for the America Heart Association and including approximately 1g of high-quality protein per kilogram of body weight per day. Participants may be asked to use The ASA24 system (https://asa24.nci.nih.gov/) to collect 24-hour food recalls during baseline testing and the intervention to self-monitor progress and document adherence. National Cancer Institute (NCI) investigators created the free, web-based Automated Self-Administered 24-hour Recall (ASA24) system to administered 24-hour recalls. The ASA24 system consists of a Respondent Website, used to collect data from participants, and a Researcher Website for managing study logistics and access nutrient and food group data files. The coordinator or study dietician will log into the VA computer and access the website and subject specific food logs. These subjects may be asked to continue the intervention until at least 5-10% weight loss is achieved.

Post Intervention testing (Phase 5): After six-months of the intervention, testing will be repeated as described in Phase 2.

Statistical Analysis Plan:

We will use exploratory data analyses to review our data looking for extreme values which will be checked for transcription or other errors. Because our outcome measures will be measured multiple times, our intent is to use repeated measures ANOVA to compare outcome measures among treatment (EX + WL) and the active control (EX). However, as this is a pilot study designed to demonstrate proof of concept and to generate data with which to make accurate power calculations, we may initially analyze within-group changes using paired t-tests and among-group differences with independent samples t-tests.

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