NCT03984994

Study Protocol and Statistical Analysis Plan

November 22, 2024

Study Design: We will use a randomized, parallel study design, wherein all subjects will undergo all 6 phases of the study and complete each of the research testing visits. After recruitment and screening, all subjects will undergo baseline research testing. Upon completion of baseline testing, subjects will be randomized 1:1, stratified by sex and race, to RT→AEX or AEX→RT. Subjects in the AEX→RT group will then begin 3-month AEX training and the RT→AEX will begin group will begin 3-month RT. Subjects will be in both groups will be tested before and after the RT aspect of the interventions to understand the effects of preceding AEX on responses to RT in terms of muscle morphology and phenotypes. The comparisons in this pilot study involve the changes brought about by RT either with or without preceding AEX.

Interventions:
Aerobic Exercise Training: Participants will exercise for 3 months, 3x/wk on treadmills at an intensity of 60-80% VO2max for 30-45 min. Participants will continue exercising during research testing. Exercise sessions will be monitored by trained exercise physiologists. Blood pressure and heart rate will be assessed before, during, and after each session. Exercise intensity will be monitored using heart rate monitors. Exercise intensity will be progressed as follows: a) subjects will begin exercising for 30 minutes at 60% of Vo2max, b) subjects will increase their increase exercise time as tolerated to 45 minutes at 60% of VO2max, c) subjects will increase their exercise intensity to 70% VO2max and 80% VO2max, respectively, as tolerated. Subjects will be encouraged to maintain their body weight and food may be given to supplement subjects' diets if weight loss is excessive at more than 2% per month.

Strength Training: Participants will participate in strength training for 3 months, 3x/wk. This will consist of approximately 2-3 sets of approximately 8-15 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 comparable strength training machines. Each session of ST will take approximately 30 minutes. Exercise sessions will be monitored by trained exercise physiologists. Blood pressure and heart rate will be assessed before and after each session.

Research Tests - Before and after the interventions, the following tests will take place:
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). Body circumference at several sites of the body will be taken with a measuring tape. Computed tomography scans of the abdomen and thigh and lower leg are done to quantify regional fat and muscle distribution.

Strength Testing: Subjects will perform 3 sets of knee extension Isometric Maximal Voluntary Contractions (IMVCs) on an isokinetic device (BIODEX System) with 1-2 mins of resting periods between sets. Knee extension will be performed in a seated position with the testing leg positioned at 60 degrees of knee flexion. For every trial subjects will properly stabilized to ensure minimal movement artifacts. Additionally, verbal encouragement, as well as visual feedback from the torque recordings will be provided during task to potentiate the volitional maximal contraction.

Muscle Biopsy: Participants will be asked to fast overnight (~8-12 hours) prior to the biopsy. A biopsy (approximately 300-1000mg) will be obtained from the vastus lateralis muscle after local anesthesia with 0.5-1% lidocaine. A scalpel is used to make a 1/4" incision and a Bergstrom cutting trocar and outer needle are inserted into the vastus lateralis muscle.

Statistical Analysis: Data will be verified by the PI and exploratory analyses will determine the distribution characteristics of the data. The general statistical methods for Aims 1 and 2 will be the same and our analyses will include data only on the effects of RT (i.e., the change brought about by RT in each arm/group), consistent with the aims of the study. Primary and secondary outcomes are evaluated before and after 3-month RT in each arm of the study (i.e., baseline to 3-month change in the RT→AEX arm, and 3-month to 6-month change in the AEX→RT arm). The analysis plan involved ANCOVA or repeated measures ANCOVA to assess the effects of the interventions; however, there was insufficient power for planned analyses and t-tests with a P-value of $P \leq 0.05$ were used to compare the changes brought about by RT in the two arms/groups.