Title: Relative Sarcopenia and Cardiometabolic Risk in Young Adults with Obesity

NCT # 04195061

Version date: June 14, 2021

PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

[redacted]

PROTOCOL TITLE
Relative Sarcopenia and Cardiometabolic Risk in Young Adults with Obesity

FUNDING
[redacted]

VERSION DATE
6.14.21

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

[redacted]

EXERCISE SUB-STUDY
SPECIFIC AIM 1: *We hypothesize that compared to insulin-sensitive adults, insulin-resistant adults (1° exposure) will have an impaired skeletal muscle myokine profile in response to exercise, namely:*
Aim 1A: less reduction in serum myostatin levels from pre- to 3 hours post-exercise (1° endpoint)
Aim 1B: less increase in serum irisin levels from pre- to 3 hours post-exercise
Aim 1C: less increase in serum IL-6 levels from pre- to 3 hours post-exercise

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

[redacted]

It is known that regular exercise plays an important role in the prevention and treatment of DM, but the mechanisms responsible for exercise's beneficial effect on insulin sensitivity are incompletely understood. The myokines myostatin, irisin, and IL-6 may be important mediators of the relationship between exercise and insulin sensitivity because their synthesis and secretion from skeletal muscle are regulated by exercise, and lower myostatin, higher irisin, and higher IL-6 levels (acutely) are associated with higher insulin sensitivity in preclinical models. It is known that insulin sensitivity fails to improve with supervised exercise training in 20-42% adults with DM, but to what extent production and release of myokines from skeletal muscle in response to exercise is impaired in adults with insulin resistance is not known.

Since adults who are insulin resistant (vs insulin sensitive) may not improve their insulin sensitivity in response to exercise, our overarching hypothesis for the exercise sub-study is that adults who are insulin resistant (vs insulin sensitive) will have impaired myokine profiles in response to exercise. *If this is true, then therapeutic manipulation of myokine pathways could be a potential therapeutic target for the prevention and treatment of DM.*

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site

restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

[redacted]

Eligibility:

Subjects will undergo a pre-study telephone screen to determine eligibility for the study.

Inclusion criteria:

- Ages 18-70 and previously enrolled in protocol 2004P000013 or protocol 2012P002276, which had overweight or obesity as inclusion criteria. They may also have participated in protocol 2009P002820 and had a baseline BMI of 25 kg/m^2 or more

Exclusion criteria:

- For women: pregnancy, nursing
- Routine MRI exclusion criteria including the presence of pacemaker or cerebral aneurysm clips
- Use of testosterone, growth hormone, or glucocorticoid medications
- History of HIV/AIDS, metastatic cancer or bariatric surgery
- For the Oral Glucose Tolerance Test (OGTT), the use of insulin therapy (Subjects taking insulin may complete all other study procedures)

Exercise sub-study

We expect to enroll 30 (15 women and 15 men) total men and women in the exercise sub-study for an evaluable population of 30 subjects. The sub-study is powered for 30 subjects. Eligibility criteria for the sub-study are the same as for the main study, with the additional eligibility criteria to be determined at a pre-study telephone screen. Participants who completed the main study prior to the addition of the exercise sub-study in December 2019 may be invited back to complete the exercise sub-study and repeat the main study if they remain eligible for both.

Additional exercise sub-study inclusion criteria:

-Ability to walk up 3 flights of stairs and 3 city blocks (to ensure ability to complete exercise testing)

Additional exercise sub-study exclusion criteria:

- Unstable heart or lung disease
- Exercise >150 minutes/week (to exclude those who are very fit)
- Participation in college sports (to exclude those who are very fit)

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

[redacted]

The study visit will be broken up into 2 days, and the following assessments will occur within a 30-day period of each other:

- Medical history (may be over the phone) and physical exam (optional), including height, weight, waist/hip circumference
- Blood draw to determine levels of hormones and other chemicals
- Urine pregnancy test for women (may be mailed to the subject's home and completed remotely)

[redacted]

- Oral glucose tolerance test (OGTT)

[redacted]

Exercise Sub-Study Visit (n=30, 15 women and 15 men)

The sub-study visit will take 4 hours to complete, and the following assessments will occur:

- Urine pregnancy test for women (if not already completed that day as part of main study visit)
- Vital signs
- Blood draw to determine levels of hormones and other chemicals
- Cardiopulmonary exercise test (CPET) to assess exercise capacity and overall fitness
- Blood draws at 0, 1, 2, and 3 hours after CPET

Exercise Sub-Study Endpoints

Aim 1A: change in serum myostatin levels from pre- to 3-hours post-exercise
Aim 1B: change in serum irisin levels from pre- to 3-hours post-exercise
Aim 1C: change in serum IL-6 levels from pre- to 3-hours post-exercise

[redacted]

[redacted]

CPET: Fasting CPET studies will be performed in the Cardiovascular Performance Program (CPP) exercise lab [redacted]. Subjects will undergo CPET on an upright cycle ergometer with continual measurement of metabolic gas exchange via a commercially available metabolic cart (Ultima CardiO_2, Medgraphics, St. Paul, MN), as well as heart rate (HR) and blood pressure (BP). Exercise will proceed according to a maximal effort clinical protocol. Exercise testing will end when the subject indicates they have reached exhaustion or if any contraindication to exercise is present, i.e. abnormal BP (>220/120), ventricular arrhythmia, decreased oxygen saturation (>15% from baseline), development of chest discomfort, lightheadedness, or excessive shortness of breath or at the discretion of subject and/or physician for safety. A trained exercise physiologist is present in the room with the subject at all times, and a physician is immediately available on the floor. The highest VO2 will be recorded as VO2max when the following criteria are met: (1) plateau of VO_2 despite increasing work load, (2) final respiratory exchange ratio (RER) >1.1, and (3) HR >85% of age-predicted maximum HR. Total exercise time, work, VO2max, VO2AT [the VO2 at anaerobic threshold (AT)], RER, baseline HR, HR_{AT} (HR at AT), and peak HR will be recorded.

Endocrine testing:

- CBC, CMP, TSH, HbA1c

[redacted]

-75-g oral glucose tolerance test (OGTT)

[redacted]

[redacted]

- Pre- and post-exercise myostatin, irisin, and IL-6

In the event that a portion of the study visit cannot be completed at the time of the scheduled visit, the subject will be asked to return for another day to complete all study procedures for that visit.

Information on Planning for Potential Study Disruptions due to COVID-19

[redacted]

- The medical history may be done over the phone.
- The urine pregnancy test may be mailed to a subject's home and completed there. The result will be photographed and sent to study staff.

[redacted]

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

[redacted] We will share DM [redacted] testing results with study participants and their physicians (with participants' permission). If a significant abnormality is identified on CPET, we will inform that participant and their physician (with participant's permission).

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

A number of procedures will be instituted to protect against potential risk involved in this protocol. We will follow PHRC blood drawing guidelines. [redacted]

[redacted]

A physician will be available at all times during the study by pager to answer any questions a patient might have. The physician will arrange to immediately see every patient with a concern. All efforts will be made to protect the confidentiality rights of the study subjects who will be referred to by code numbers only. Confidentiality of the patients will always be of paramount importance to study investigators. No data on patients will be shared with persons other than those directly involved in the study, except at the documented request of the patient. Samples that are sent to laboratories outside of [redacted] Quest Diagnostics will be labeled with a non-identifying numeric code.

All adverse events will be reported to the IRB in a timely manner according to the guidelines provided by Partner's Human Subjects Research Committee.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Safety Assessments

- Urine pregnancy test for all premenopausal women [redacted]

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

[redacted]

Blood drawing may result in bruising or infection at the venipuncture site.

[redacted]

[redacted]

Regarding CPET, the electrocardiogram may produce some mild discomfort when the adhesive recording pads are applied or removed. CPET is a safe procedure, with the risk of death for patients between 2 and 5 per 100,000 exercise tests performed. The risk is likely much lower in those without known heart or lung disease. Throughout the test, participants will be closely monitored. If a participant develops chest pain, an abnormal fall or rise in blood pressure, shortness of breath and fall in oxygen saturation, loss of coordination, lightheadedness, or dizziness, the test will be stopped for safety concerns.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

[redacted]

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

[redacted]