Protocol Title: Assessment of Body Composition and Physical Function in Older Adults with Obesity

PI Name: Candida Rebello

Medical Investigator's Name: Frank Greenway

Protocol Version Date: March ~~6~~29, 2023

ABSTRACT

Objectives

Sarcopenia, which is the loss of muscle mass and strength or physical function, naturally occurs in aging. In sarcopenic obesity, growth of muscle mass and increments in strength do not parallel weight gain, and places older adults at increased risk of falls, fractures, physical disability, frailty, and mortality from too low muscle strength relative to body size.[1-4] Our goal is to assess body composition and physical function in older adults with obesity.

Design and Method

Aim 1. To assess body composition in older adults (aged 60-80 years) with obesity. We will measure body composition using biolelectrical impedance analysis.

Aim 2. To assess insulin resistance in older adults with obesity. We will measure homeostatic model assessment of insulin resistance (HOMA-IR) from fasting blood glucose and insulin concentrations.

Aim3. To assess physical function in older adults with obesity. We will measure physical function using the hand grip strength, six-minute walk, and Modified Physical Performance tests.

This is a pilot study to assess body composition in an older population and there is no hypothesis.

Study Design

We propose to conduct a cross-sectional study in 40 adults aged 60 to 80 years with obesity. We will measure body composition, insulin resistance, and physical function. Subjects who satisfy the eligibility criteria and sign the informed consent will be enrolled.

Subjects will complete an assessment of body composition by bioelectrical impedance analysis, hand grip strength, six-minute walk, and the Modified Physical Performance tests. Blood will be drawn for measurement of fasting serum glucose and insulin.

The results of the present study will guide the design and implementation of a clinical trial to determine the effect of a diet and exercise intervention on physical performance in older adults with sarcopenic obesity. Sarcopenic obesity poses an important health challenge given the demographic shift towards an older population. These results will be significant, in that they will potentially provide a cost-effective intervention that will substantially improve quality of life for the growing number of older individuals with obesity who have developed sarcopenia.

Background

Preserving muscle function with a weight loss diet in people with low muscle mass and determining whether muscle mass or strength is a valid marker of aging-related functional decline are some of the unanswered questions in aging. The proposed study will offer insights for refining an operational definition for sarcopenic obesity which currently lacks consensus and facilitate the development of an intervention study to treat sarcopenic obesity.

Sarcopenic obesity is highly prevalent and seriously debilitating. Epidemiologic studies show that the co-existence of sarcopenia (skeletal muscle disorder) and obesity increases the risk for cardiovascular disease, type 2 diabetes, and all-cause mortality.[5-8] In the United States (US), the prevalence of sarcopenic obesity in non-institutionalized older adults is 18.1% in women and 42.9% in men.[9] About a third of community-dwelling older adults fall each year and one in five falls causes broken bones or head injuries.[10-12] Fear of falling is a constant concern about falling, and 20-55% older adults report that they restrict their daily activities due to fear of falling.[13-20] Limiting activity leads to functional decline, decreased quality of life, and institutionalization.[17, 21-24] Yet, there are no evidence-based therapies that can sustainably treat impaired muscle function in patients with obesity.[25] It is critical to identify patient-centered strategies for altering the disease course in subjects with obesity and muscle dysfunction and improving patient outcomes in this vulnerable group.[25, 26]

Aging and musculoskeletal functional decline. Fat mass increases with age peaking at approximately 60 to 75 years of age, whereas muscle mass and strength display an accelerated loss.[27-31] In addition to muscle loss of 3% to 8% each decade after 30 years of age, changes in muscle fiber alter muscle quality.[32, 33] For instance, 70-year-olds have 25% less fibers in the medial vastus lateralis than 30-year-olds.[34] Adults over 70 years of age lose muscle strength at the extraordinary rate of 22% each year.[35] Selective loss of type II (high force fibers) and declines in protein anabolism are other factors that drive aging-related loss of muscle quality.[33] In the absence of clarity in defining sarcopenic obesity, research that advances our understanding of muscle mass and strength in an older population will facilitate the design of intervention studies to address sarcopenic obesity

STUDY AIMS

Aim 1. To assess body composition in older adults (aged 60-80 years) with obesity. We will measure muscle mass using Bioelectrical Impedance Analysis (BIA).

Aim 2. To assess insulin resistance in older adults with obesity. We will measure homeostatic model assessment of insulin resistance (HOMA-IR) from fasting blood glucose and insulin concentrations.

Aim3. To assess physical function in older adults with obesity. We will measure physical function using the hand grip strength, six-minute walk, and Modified Physical Performance tests.

STUDY DESIGN

This is an observational study and there are no hypotheses.

Inclusion Criteria. For an eligible subject, all of the following criteria must be answered "yes": 1) age from 60 to 80 years 2) body mass index (BMI) >30 kg/m^2; 3) ability to provide written informed consent.

Exclusion Criteria: For an eligible subject, all of the following criteria must be answered "no": 1) self-reported history of diabetes, or cancer within the past five years or significant cardiovascular or hepatic or renal disease or dysfunction; and 2) clinically significant gastrointestinal malabsorption syndromes such as chronic diarrhea, or celiac disease; and 3) Use of pacemakers, implanted cardiac defibrillators, and Class III electrical medical devices.

Number of Subjects

We will enroll 40 males and females**.**

Recruitment

Subjects will be recruited through the use of printed material, targeted solicitation through the Pennington Biomedical Research Center (PBRC) email listserv and social media. Participants will complete an online screening and will be contacted by a PBRC recruiter for a brief telephone interview to assess eligibility criteria, prior to being scheduled for a clinic visit. Subject eligibility criteria will be evaluated at a single screening visit. The screening visit will occur in the outpatient clinic, in the morning following confirmation of an overnight (at least ten hours) fast. Subjects who provide informed consent will proceed with the tests and measurements of the screening visit. Subjects who satisfy the eligibility criteria will be enrolled in the study.

Study Timelines

This is an observational study. We expect to complete the study within four months. Each eligible subject's participation in the study will be approximately one day. Primary analyses are expected to be completed within a month of the study completion.

Study Endpoints

Eligible subjects will complete tests of body composition and physical function. Our primary aim is to assess body composition. The secondary outcomes will be to assess insulin resistance and physical function.

CLINIC VISITS

Subjects will complete one screening visit which will be followed by the study measurements if the eligibility criteria are met.

Screening and Study Visit (2½ hours)

Subjects will report to Pennington Biomedical in the morning following an overnight fast (except for water) that began no later than 10 hours prior to the study appointment. The screening visit includes explanation of the study purpose, procedures, and signing of the informed consent. If the participant agrees to participate by signing a consent form, the following procedures will be performed:

- Completion of personal and family medical history questionnaire
- Measurement of height and metabolic weight.
- Measurement of vital signs (blood pressure and pulse).

- Blood collection for completion of serum glucose and insulin measurements.
- Bioelectrical Impedance Analysis.
- Hand grip strength.
- Six-minute walk test.
- Modified Physical Performance test.

The schedule of assessments is provided in Table 1.

Table 1. Schedule of Assesments

Procedure	Screening and Study Visit
Informed Consent	x
Height and Weight	x
Blood Pressure and Pulse	x
Medical History Questionnaire	x
Blood Draw	x
Blood Sample for Archives	x
Bioelectrical Impedance Analysis	x
Hand grip Strength	x
Six-minute Walk Test	x
Modified Physical Performance Test	x

STUDY PROCEDURES

Bioelectrical Impedance Analysis (BIA) Measurements (about 10 minutes):

Body composition will be measured by BIA.

Modified Physical Performance Test (PPT)

The modified PPT is a performance-based global measure of physical performance that evaluates the ability to perform usual daily activities, including both basic activities of daily living (ADL) and instrumental activities of daily living (IADL). The PPT involves a combination of 9 items that have been developed and tested in both frail and well, community-dwelling and institutionalized older and elderly adults and has been used to describe and monitor physical performance, degree of disability, loss of independence and early mortality.[36, 37] This Modified PPT[38] includes 6 tasks that are timed: 1) climb a flight of 10 stairs, 2) stand up 5 times from a standard chair, 3) walk 50 ft., 4) put on and remove a coat, 5) pick up a penny placed 12 inches in front of the foot on the dominant side, and 6) lift a standard book to a shelf ~12 in above shoulder height. The other three tasks include an evaluation of the ability to climb up and down 4 flights of 10 stairs; evaluation of the performance of a 360° turn; and a test of standing balance with feet side-by-side, semi-tandem and full-tandem. The score for each item ranges between 0 and 4, with 36 representing a perfect total score for the test.

Six-minute Walk Test

The six-minute walk test is a self-paced test of walking capacity. Subjects are asked to walk as far as possible in six minutes along a flat corridor. The distance in meters is recorded.

Hand Grip Strength

Hand grip strength is measured using the Jamar Hydraulic Hand Dynamometer (JLW Instruments, Chicago, IL) according to the NIH Toolbox® guidelines for assessment of hand grip strength.

Biochemical Assessments

All measurements will be performed according to standard PBRC procedures for drawing blood and the relevant measurement.

Heart Rate Monitor

Subjects wear a heart rate monitor during tests of physical performance (hand-grip strength, PPT, and six-minute walk)**,**

STATISTICAL CONSIDERATIONS

We will calculate the homeostatic model assessment of insulin resistance (HOMA-IR) and determine the mean and variability of the results for fat mass, lean mass, skeletal muscle index, [39] the hand grip strength, physical performance scores, serum glucose and insulin, and HOMA-IR. All analyses will be conducted for the entire sample and separated by sex.

POTENTIAL RISKS AND BENEFITS FOR PARTICIPANTS

The study involves the following procedures which may pose a potential risk:

- **Blood Draws.** There is the possibility of discomfort, pain, and bruising at the vein on the arm where the needle is inserted. There may also be a small risk of bleeding and a very small risk of infection at the site of the blood draw. Sterile technique and trained personnel minimize these risks.
- **Anthropometric Measurements and Vital Signs.** The PBRC outpatient clinic staff are trained to perform these procedures in accordance with PBRC standards of practice.
- **Bioelectrical Impedance Analysis.** There are no known associated risks involved with this measurement.
- **Hand grip strength, six-minute walk, and physical performance tests:** There is minimal risk of injury during the testing protocols. However, there is a possibility of discomfort, muscle fatigue and soreness, shortness of breath, elevated heart rate, and dizziness. There is also a risk of falling or losing your balance associated with these tests. All tests are conducted in the presence of personnel with extensive experience in conducting these tests who will follow at a close distance and be of immediate assistance, if required.

In addition to the potential risks listed above, participants may experience a previously unknown risk or side effect.

Potential Benefits

This is a study to assess muscle mass and physical performance and there are no benefits.

Adverse Event and Serious Adverse Event Collection and Reporting

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the study procedures. We define AE as any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the study procedures.

We will define a serious adverse event (SAE) as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or in a congenital anomaly.

Safety will be assessed by recording all adverse events. The study team will inquire regarding adverse events while minimizing the chance for bias when detecting AEs/SAEs. The study team will employ open-ended and non-leading verbal questioning of the subject as the preferred method to inquire about AE occurrence. For example, an appropriate question would be: “How are you feeling?”, It is the responsibility of the investigator to attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Assessment of Intensity. An assessment of intensity for each AE and SAE reported during the study will be provided by the investigator and the investigator will assign it to one of the following categories:
Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE and both AEs and SAEs can be assessed as severe. Severe Adverse Event is a category utilized for rating the intensity of an event.

Assessment of Causality. The investigator is obligated to assess the relationship between study procedures and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

Events meeting the definition of an AE:

- Any abnormal laboratory test results (clinical chemistry) or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study procedures even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

Events that do not meet the definition of an AE:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Reporting of AEs. The reporting of AEs will follow the standards of practice as outlined by the Pennington Biomedical Research Center (PBRC) IRB in the 'Unanticipated problems Involving risks to subjects or others' policy. Once the investigator determines that an event meets the definition of an AE that must be reported, the investigator will not wait to receive additional information before notifying the responsible parties of the event and completing the appropriate forms. An assessment of causality at the time of the initial report will be provided. Email transmission of the AE data collection tool will be the preferred method to transmit this information followed by notification by telephone and/or fax. A copy of the AE report will also be sent to the institution officials. New or updated information will be recorded in the originally completed data collection tool. We are assessing muscle mass and physical performance using standardized tests and the risks are minimal.

The investigators will abide by PBRC policy for ensuring prompt reporting to the IRB, of any Unanticipated Problem involving risks to study participants or others (45 CFR 46.103(b)(5)). Accordingly, events meeting the definition of unanticipated problems will be reported within 48 hours, when possible, to avoid potential harm to subjects. PBRC Unanticipated Problems reporting procedures require completion and submission to the IRB of forms which include detailed information on the event and the actions that will be taken to prevent reoccurrence. Reports of Unanticipated Problems, as defined above, will be forwarded to OHRP using ohrp@osophs.dhhs.gov, within two weeks of the event.

DATA AND SAFETY MONITORING

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. For each AE, the seriousness, intensity, and relationship to study product will be assessed, documented, and supported by an entry in the subject's medical records. During the study, each subject will be carefully monitored for any adverse events. After the initial AE/SAE report is completed and sent, the investigator is required to follow each subject at subsequent contacts.

PROTECTION AGAINST STUDY RISKS

Informed Consent Process.

The subjects will be interviewed in the privacy of an exam room and their records will be protected by a secure medical records area and a password-protected electronic database monitored by the Pennington Research Computing group. Subjects will be asked to sign a written consent after reading it, having it reviewed with them by the study staff and having all their questions answered. The consent conversation will be conducted in the privacy of an exam room and the subject will be allowed to take the consent home to discuss their decision with their family or counselor, if desired. Written informed consent will be obtained in the outpatient research clinic by the coordinators and one of the physicians will be available to answer questions if needed. A waiting period will be allowed, if desired by the participant. The coordinators and investigators will be available for questions throughout the study.

Minimizing risks

Study procedures will be conducted by trained staff in accordance with PBRC outpatient clinic standards of practice and with the subjects' informed consent. Continuous monitoring by the PI and/or the medical investigator of the study will minimize all potential risks and discomforts. Research participants will be immediately withdrawn from the study upon evidence of any significant adverse event if the investigative team deems that the safety of the participant is in jeopardy.

DATA COLLECTION AND QUALITY ASSUARANCE

Privacy

The subjects will be interviewed in the privacy of an exam room and their records will be protected by a secure medical records area and a password-protected electronic database monitored by the Pennington Research Computing group. Subjects will be asked to sign a written consent after reading it, having it reviewed with them by the study staff and having all their questions answered. The consent conversation will be conducted in the privacy of an exam room and the subject will be allowed to take the consent home to discuss their decision with their family or counselor, if desired. Study procedures will be conducted by trained staff in accordance with PBRC outpatient clinic standards of practice and with the subjects informed consent. Confidential subject information including medical records and test results will be available only to persons authorized by the Pennington. Information collected from subjects will be the minimum amount of data necessary to accomplish the research purposes.

Data and Specimen Management

Study participants will be assigned unique subject identification (ID) numbers. Study subject ID numbers will be used on all data collection instruments, to include questionnaires, data collection forms, and computer records. The forms used for data collection will be the standard forms used in PBRC studies. A master list linking the participants' names and ID numbers will be kept in a password-protected computer file with access restricted to the PI and co-PI. Data collection forms will be kept secure, or password-protected if computerized, and under the control of the PI, co-PI/medical investigator. Only personnel assigned to the research study by the PI will have access to the data. Hard-copy data records will be stored for a minimum of 3 years.

The PBRC has a fully integrated, campus-wide, automated data management system. All data are entered into a central database using existing methodology that has been fully validated and undergoes continuous quality assurance by the PBRC Research Computing Core. All data are backed up daily, and the Research Computing Core at the PBRC oversees all data management. The research team has extensive experience using the procedures and methods required to conduct this study. Standard operating procedures in place throughout the units at Pennington Biomedical will be utilized for repeatable, valid data collection and quality.

In accordance with the standards of practice followed by the Clinical Chemistry core, blood samples will be stored frozen at PBRC until analysis can be completed.

Protection of Confidentiality

The only people who will know that these patients are research participants are members of the research team. No information about them, or provided by them during the research, will be disclosed to others without their written permission, except if it is necessary to protect their rights or welfare (for example, in case of injury or emergency care), or if it is required by law. When the results of the research are published or discussed in conferences, no information will be included that would reveal the identity of these patients. All data will be kept in locked files, and subjects will be identified by codes when the data gathered in this procedure are presented or published.

WITHDRAWAL OF SUBJECTS

It is our desire to analyze the results of all participants who were enrolled in the study. In accordance with the declaration of Helsinki/Tokyo/Venice/Hong Kong, participants have the right to withdraw from the program at any time for any reason. The investigator also has the right to withdraw participants from the program treatments in the event of inter-current illness, adverse experience, treatment failure, protocol violation, or other reasons. Should a participant decide to withdraw from the study, all efforts will be made to complete observations as thoroughly as possible.

PAYMENT FOR PARTICIPATION

At the completion of all study visits and procedures, participants will be paid $75 for the time spent in the clinic. This compensation is in line with all the other studies conducted at the Pennington Biomedical Research Center. There is no compensation for the screening visit.

EMERGENCY CARE AND COMPENSATION FOR RESEARCH-RELATED INJURY

No form of compensation for medical treatment is available from the Pennington Biomedical Research Center. In the event of injury or medical illness resulting from the research procedures the research volunteer (from any group) will be referred to their physician/surgeon or a treatment facility. The Pennington Biomedical Research Center is a research facility and provides medical treatment only as part of research protocols. Should a volunteer require medical treatments, community physicians and hospitals must provide them to him/her.

SHARING OF RESULTS WITH SUBJECTS

At the end of the study, a manuscript will be prepared for submission to a peer-reviewed journal. A summary of the results will be posted on ClinicalTrials.gov which subjects may access.

RESOURCES AVAILABLE

The outpatient research units are well equipped and staffed to carry out the requirements of this study and appropriate standards of practice are in place to ensure appropriate research procedures.

ECONOMIC BURDEN TO SUBJECTS

There are no costs for which the subjects will be responsible.

CONSENT PROCESS

Written informed consent will be obtained in the outpatient research clinic by the coordinators and one of the physicians will be available to answer questions if needed. A waiting period will be allowed, if desired by the participant. The coordinators and investigators will be available for questions throughout the study.

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