Project Title: Targeting ADAM17 activity for correction of vascular insulin resistance in type 2 diabetes
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I. BACKGROUND AND OBJECTIVE

Eight out of 10 patients with type 2 diabetes (T2D) die from cardiovascular disease.[1] A primary connection between T2D and cardiovascular disease is insulin resistance;[2] a classic feature of T2D that is characterized by a blunted ability of peripheral tissues to regulate glucose homeostasis in response to insulin. Insulin, in addition to its role on cellular glucose uptake, also has vasodilatory effects that increase delivery of insulin and glucose to tissues such as skeletal muscle.[3-6] In healthy individuals, insulin-mediated increases in skeletal muscle blood flow account for as much as 35 percent of total insulin-stimulated skeletal muscle glucose uptake.[7] However, in T2D patients, abnormalities in vasomotor reactivity to insulin lead to a reduction in glucose uptake by skeletal muscle, contributing to impaired glucose homeostasis.[8,9] Data from our preliminary experiments in vitro and ex vivo demonstrate that increased ADAM17 activity sheds the insulin receptor in endothelial cells contributing to vascular insulin resistance in T2D.

The objective of this project is to determine the extent to which administration of the dietary supplement phosphatidylserine (PS), a competitive inhibitor of ADAM17 sheddase activity, effects vascular function and insulin-stimulated leg blood flow in subjects with T2D.

As part of a randomized (1:1, experimental/placebo), double-blinded parallel design, each of the 34 subjects will complete 4 weeks (+/-4 days) of supplementation with either 900mg of a PS supplement or placebo. Assessment visits (2) will occur pre-intervention and post-intervention and include: 24-hour ambulatory blood pressure measurement (ABPM), Vitals, DEXA scan for body composition, fasting blood work, carotid-femoral pulse wave velocity (cfPWV), brachial and femoral artery FMDs, Femoral blood flow imaging during passive leg movement (PLM), glycocalyx integrity assessment via Glycocheck, and an oral glucose tolerance test (OGTT) with blood flow measurements and beat-to-beat sphygmomanometry via Finometer.

II. RECRUITMENT PROCESS

Patients with T2D (n=34) will be recruited from the MU Cosmopolitan Diabetes Center, MU Department of Medicine clinics, and the Columbia community by our research team. MU Health Care's electronic medical record has informatics tools and databases used for developing research studies, including i2b2 (Informatics for Integrating Biology and the Bedside) and RedCap (Research Electronic Data Capture). As in prior studies, with IRB approval, we contact patients and inform them of the potential to participate in this research.

Recruitment methods:

1. A chart review of clinic patients from the Division of Endocrinology and the Department of Medicine who are between the ages of 45 and 64 and have been diagnosed with type 2 diabetes will be completed in Powerchart by study coordinator/staff based on the study inclusion/exclusion criteria. A letter, chart message, or phone call will be utilized to notifying them of their eligibility to participate in a research study. Study coordinator/staff will work in conjunction with healthcare providers that have a direct patient care relationship to recruit subjects from clinics.
2. Potential subjects may also be identified via use of i2b2 screening. Study coordinator/staff will work in conjunction with healthcare providers that have a direct patient care relationship to recruit these subjects. Subjects may be informed of their eligibility via chart messaging, letter, or phone call.
3. Subjects may also respond to the recruitment flyers or advertisements posted in MU Hospital clinics, MU Hospital television screens, MU Info, or any place generally accessible to the public

(i.e. grocery stores, community centers, etc). For all recruitment, subjects will be given a secure email address and/or a phone number to contact. Subjects may also be given a link to complete a screening questionnaire via Qualtrics.

4. Subjects will also be recruited through marketing services provided by BuildClinical. BuildClinical is a data-driven digital marketing company that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They will ensure that all IRB-approved guidelines and procedures are followed during recruitment. They use study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc. Participants who click on the advertisements will be redirected to a study-specific landing page. On the landing page, the person can complete an online pre-screen questionnaire. Pre-screening data is then routed to BuildClinical's Secure Socket Layer (SSL) software, which encrypts all information to keep it private and HIPAA compliant. Their backend servers are stored in secure data centers in the USA.

III. CONSENTING PROCESS

Preliminary screening

Subjects who inquire about participation will answer screening questions. These questions are for preliminary screening only and are not used as study data since the data represent self-report. The questions include queries about health history/habits, age, sex, height, weight, tobacco use, medications/ supplements, over the counter medications use, illness, and chronic conditions. The study design is described in general terms to subjects, with mention of factors most likely to impact subject interest in participating. If the subject is determined to meet the inclusion/exclusion criteria, an appointment will be scheduled for a visit for consenting and review of medical history.

Screening visit

For all subjects, informed written consent will be obtained using HIPAA Research Description and Consent Forms approved by the MU IRB. The study physician will be available to answer any potential questions. During that process, the subject will be asked to describe, in their own words, what the assessment visits will be like. They will be provided with the study details. Review of the consent form will occur with study personnel in a quiet, unhurried setting. Comprehension will be assessed by asking the subject to explain the study in their own words. Participants will have adequate opportunity to review the informed consent and to ask any questions they may have about the research protocol, compensation, risks, and benefits of taking part in the study.

IV. INCLUSION/EXCLUSION CRITERIA

Inclusion criteria

1. Men and women with a BMI of 25-39 kg/m^2, who are 45-64 years of age at randomization.
2. T2D patients classified based on physician diagnosis.
3. No vulnerable populations (*e.g.*, prisoners, pregnant, children) will be enrolled.

Exclusion criteria

1. Cardiovascular disease including myocardial infraction, heart failure, coronary artery disease, stroke
2. History of chronic renal or hepatic disease
3. Active cancer
4. Autoimmune diseases
5. Immunosuppressant therapy
6. Hormone replacement therapy

7. Excessive alcohol consumption (>14 drinks/week for men, >7 drinks/week for women)
8. Current tobacco use
9. Pregnancy
10. Bodyweight change ≥5% within the last 6 months

V. NUMBER OF SUBJECTS

Sample size estimates are informed by our data presented in **Figure 1**. The trial is powered to detect a mean difference in percent change in insulin-stimulated leg blood flow between placebo and PS of 15%. This represents approximately half of the difference in mean response between healthy and T2D subjects. We also assumed a moderate within-subject serial correlation of 0.5. Sample size was estimated using the software package PASS and confirmed using code from Jones & Kenward. A total size of 30 subjects, 15 per group, will provide 80% power to detect a 15% difference when testing a two-tailed alpha of 0.05. The final sample size will be increased to 34, 17 per group, to accommodate as much as a 10% drop-out rate.

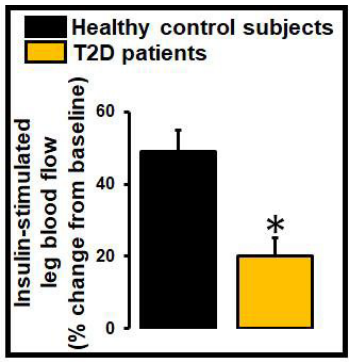

Figure 1. Evidence of impaired leg blood flow in response to a hyperinsulinemic-euglycemic clamp in T2D patients. Blood flow was measured at the common femoral artery via Doppler ultrasound at baseline and at 60 min of insulin infusion (n=10- 11/group; *p<0.05).

VI. STUDY PROCEDURES/DESIGN/TREATMENT PLAN

As illustrated in **Figure 2**, T2D patients will be randomized to either 4 weeks (+/-4 days) of a dietary supplement (900mg/day) with soy-derived PS or placebo condition, in a double-blind, parallel design. Study staff dispensing supplement and placebo pills will not be blinded, but all other members of the study team will remain blinded for the duration of the clinical trial. Each T2D patient will undergo two assessment periods, each involving 24-hour monitoring with an ABMP and an 8-hour in-person assessment. The proposed dose of PS is well-tolerated. No side effects have been reported. PS will be obtained from an accredited commercial source and its purity confirmed by third party analysis.

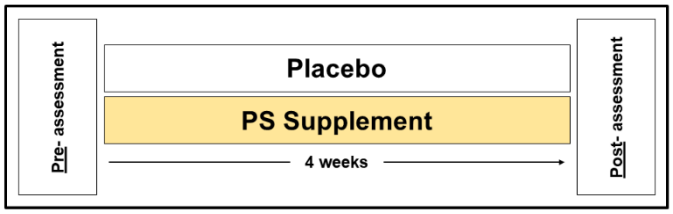

Figure 2. Randomized, double-blind, placebo-controlled, parallel design trial with pre and post intervention assessments.

Remote Screening

Subjects will be screened for the study remotely via telephone or Qualtrics survey. If the subject is determined to meet the eligibility criteria for the study, a visit for consenting and medical history will be scheduled.

Consenting Visit

The consenting visit will take up to one hour. After signing the consent form, medical information will be obtained by the study team, including: DOB, gender, ethnic/racial category, height, body weight (history of body weight gain or loss), waist circumference, vitals, and a medical history questionnaire. Subjects will be scheduled for an ambulatory blood pressure cuff fitting and pre-assessment visit.

Equipment fitting visits (duplicate):

In the week leading up to the pre and post assessment visits, the subjects will attend an appointment with the purpose of being fitted with an ABPM. The subjects will be instructed on the wear and use of

the ABPM and will take the equipment with them for home use over a 24-hour period. Participant will also complete training with the Glycocheck equipment at the time of their initial ABPM fitting.

Pre-Assessment

Pre-assessment will occur before subjects have been assigned to four weeks of supplementation or placebo. Procedures completed at this assessment will include vitals, DEXA scan for body composition, fasting blood work, cfPWV, brachial artery FMDs, Femoral blood flow imaging during PLM, glycocalyx integrity assessment via Glycocheck, and an OGTT with blood flow measurement.

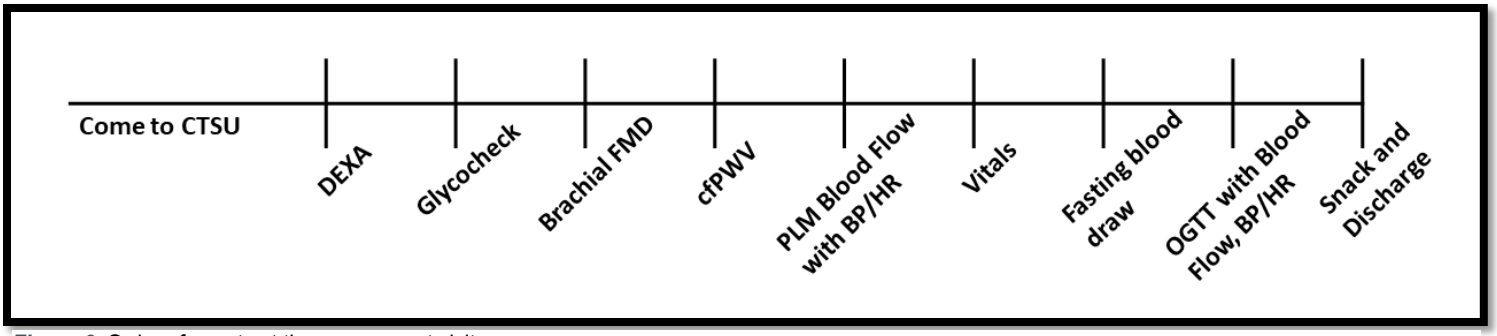

Figure 3. Order of events at the assessment visits.

Patients will be continuously monitored (heart rate and blood pressure) during the PLM and OGTT conditions (**Figure 3**). Subjects will be provided with four weeks of supplement/placebo and instructed on home-administration regimen. This visit should take approximately 8 hours.

Post-Assessment

Post- assessment will take place after the subjects have completed four weeks of supplementation or placebo intake. All study procedures will be repeated at this visit.

Special consideration in case of unforeseeable hardships

(i.e. public health emergencies or weather-related events)

In the event that subjects are not able to complete study visits, the following remedial steps will be taken:

1. Supplement or placebo may be mailed to the subject through the investigational pharmacy.
2. In the case that subjects are unable to complete their assessments at the originally scheduled dates, their visits may be scheduled +/-~7 days from the originally scheduled date provided that the subject maintains the assigned intervention for the duration of the study.
3. In the event of the Clinical Translational Science Unit (CTSU) not being available or if it is considered by the study physician that performing studies there can be an increased risk of exposure to infectious agents or related hazards, the following alternative sites will be made available for screening, safety and study visits:
    a. University hospital clinic rooms

These locations are not carpeted, and we do not anticipate an increased risk for the subjects given that medical supervision and nursing staff assistance will be unchanged.

Study procedures

Ambulatory blood pressure monitoring (ABPM)

Blood pressure monitoring will be conducted with a Welch Allyn ABPM 7100 Ambulatory Blood Pressure Monitor or equivalent device and adult blood pressure cuff. Subjects will be fitted with the

ABMP and instructed to wear the device for a 24-hour period. Subjects will be asked to fill out an activity form during the corresponding 24-hour period. This procedure is not standard of care.

Carotid-femoral pulse wave velocity (cfPWV)

A special non-invasive device will be used to assess arterial stiffness. A blood pressure cuff will be wrapped around the upper leg of the participant. The cuff will periodically inflate to squeeze tightly for less than 2-minutes. A pressure sensor, the size of a pencil will be placed over the skin of the neck region to obtain the pressure wave form in the neck vessel (i.e., carotid artery). This procedure takes about 15 minutes and requires an upper arm blood pressure to be taken beforehand Risks: The blood pressure cuff will squeeze the leg tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released. This procedure is not standard of care.

Dual-energy X-ray absorptiometry (DEXA) scan

This will be performed to assess body composition. This procedure is not standard of care.

Brachial artery flow mediated dilation (FMD)

Arterial measurements will be performed by imaging the brachial artery longitudinally using high-resolution duplex ultrasonography. Arterial vasodilatory responses to hyperemia (*i.e.*, FMD) will be examined by inflating a cuff, distal to brachial artery, up to 250 mmHg for 5 minutes. Before, during and after rapid release of the cuff, brachial artery blood flow velocity and diameter will be continuously measured. This procedure is not standard of care.

A blood pressure cuff will be inflated on the forearm for up to 5 minutes. During this time, the participant's arm may get numb due to decreased blood flow. An ultrasound image/video of the upper arm will be taken before, during, and after the inflation of the blood pressure cuff. This is a measurement of endothelial function. There are no risks associated with this procedure. When assessing FMD, the blood pressure cuff will squeeze your arm tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released. This procedure will be performed in duplicate. This procedure is not standard of care.

Passive Leg Movement (PLM)

Blood flow measurements will be performed by imaging the femoral artery using high-resolution duplex ultrasonography. Briefly, participants will be seated in an upright posture in a chair with sufficient ground clearance for unimpeded leg movement. After baseline ultrasound measurements, research staff will move the participant's leg through a 90° range of motion at a cadence of 1 Hz for, wherein the leg will pass through a cycle of 180°-90°-180° each second. Importantly, care will be taken to ensure the movement is completely passive and the participant does not assist with any form of muscle contraction. PLM tests will be performed, in duplicate, separated with 5-10 minutes rest, to obtain outcome measures of PLM-induced blood flow. This measure is highly reflective of vascular function in the resistance arteries and most of the blood flow response to PLM is nitric oxide dependent (up to 80%).

Oral glucose tolerance test with leg blood flow (OGTT)

After an overnight fast, a catheter will be inserted into an antecubital vein for sampling of venous blood. Additional blood will be collected every 15 mins over the next 60 mins after consuming the glucose beverage (75 grams of dextrose). OGTT will be coupled with measures of leg blood flow. Subjects will be instrumented for measures of heart rate (using standard lead II electrocardiography), arterial blood pressure (non-invasively using finger photoplethysmography), and leg blood flow (using duplex Doppler ultrasound. After a minimum of 20 minutes supine rest, baseline cardiovascular measurements will be collected, blood samples obtained, and OGTT will start. This procedure is not standard of care.

Participants will have their blood glucose levels checked via finger stick/glucometer prior to initiating the oral glucose tolerance test procedure. If the participant's fasting blood glucose exceeds 200mg/dL, the oral glucose tolerance test will not be performed. Baseline blood draw will still be performed.

Glycocheck

The Glycocheck video microscope instrument will be placed under the subject's tongue for a brief period (5 minutes approximately) to measure capillaries, blood vessel density, red blood cell concentration, flow rate, and red blood cell penetration of the glycocalyx lining. Glycocheck is an FDA Class 1 Medical Device. This procedure is not standard of care.

Participant Monitoring (heart rate, blood pressure)

Electrocardiogram (ECG) patches will be placed on the participant's chest to measure the heart's electric activity. A finger blood pressure cuff will be placed on the participant's finger to monitor pressure. These procedures are not standard of care.

Phosphatidylserine Supplement (PS)

Subjects will be instructed to take 900mg of a Phosphatidylserine supplement or placebo daily for 4 weeks (+/-4 days). Subjects will be provided with a pill organizer and the study team will periodically contact the subjects during the dosing window to facilitate dosing compliance. The proposed dose of PS is well-tolerated. No side effects have been reported. PS will be obtained from an accredited commercial source and its purity confirmed by third party analysis. PS supplementation is not standard of care.

Study medications

Glucose Beverage

Glucose (D-glucose/dextrose) mixture used in the administration of oral glucose tolerance tests (OGTT). Subjects will consume 75g of dextrose at minute 0 of the OGTT.

Sources of research material

Sources will include the subject's medical history, physical exam, DEXA (total and regional fat mass and fat-free mass), blood tests, brachial artery FMD, leg blood flow, insulin clamp results, muscle biopsy, and Glycocheck. Demographic data (plus other related data: emergency contact person, pregnancy status), blood pressure, and anthropometrics will be measured (height, weight, waist circumference). Each subject will donate up to 240 mL of blood (consenting through end of assessment #2) which will occur over a period of 12 weeks.

Blinding and subject safety

All of the laboratory staff will be blinded as they perform biochemical assays. Vascular measurements will also be performed in a blinded fashion. Once the subject is randomized, the subjects themselves, investigators, and all CTSU staff working with the subjects will be blinded to the condition (PS or placebo). No adverse effects of PS supplementation are anticipated, but should subjects exhibit changes in their health status across any system related or unrelated to the dietary supplement, Dr. Guido Lastra, the safety officer, will be consulted for advice.

Results of Study Evaluations

Results of the 24-hour blood pressure evaluation will be reviewed by Dr. Camila Manrique, MD If the average blood pressure reading from the 24-hour ambulatory blood pressure monitoring evaluation is >180/110, results of the evaluation will be shared with the study participant within 5 days of result availability. Participants will be advised to follow up with their primary care provider regarding hypertensive management. If the average blood pressure reading from the 24-hour ambulatory blood

pressure monitoring evaluation does not exceed 180/110, results will not be share with participants until the completion of all study activities.

VII. POTENTIAL RISKS/ADVERSE EVENTS

Potential risks

The following are potential risks to human subjects:

Insertion of venous catheters

The potential risks of venous catheterization include infection, swelling and discomfort at the catheter insertion sites. Some bleeding may occur as well after the catheters have been removed. There is also the possibility of fainting, dizziness, and possible pain and bruising as a result of catheter insertion. These risks will be greatly minimized by using sterile procedures and having an experienced registered nurse placing the venous catheters. Risk of bleeding is reduced by applying pressure at the site of puncture. Bruising is treated with ice. Fainting is prevented by drawing blood in the semi-recumbent position.

Ambulatory blood pressure monitoring (ABPM)This procedure poses no risks but may cause some discomfort due to cuff inflation. This procedure is not standard of care.

Carotid-femoral pulse wave velocity (cfPWV)

There are no risks associated with this procedure. When assessing PWV, the blood pressure cuff will squeeze the leg; however, any discomfort will be alleviated as soon as the pressure in the cuff is released. This procedure is not standard of care.

DEXA and anthropometrics

Radiation exposure during DEXA is equivalent to about 2% of the average radiation dose from all sources (natural background radiation, consumer appliances, radon gas, medical tests, etc.) that a person in the United States receives each year. For premenopausal female subjects, a urine pregnancy test is administered before the DEXA. Body weight is measured to the nearest 0.1 kg and height to the nearest 0.1 cm. This procedure is not standard of care.

Brachial artery FMDs

This is a measurement of endothelial function. There are no risks associated with this procedure. When assessing FMD, the blood pressure cuff will squeeze the arm tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released. This procedure is not standard of care.

Passive leg movement (PLM)

This procedure poses no risks. Guided movement at the knee joint may cause minor discomfort. This procedure is not standard of care.

Oral glucose tolerance test (OGTT)

This procedure could cause possible nausea from glucose beverage. This procedure can also cause elevated blood glucose levels in subjects with T2D. This procedure is not standard of care.

Participant Monitoring (heart rate, blood pressure)

This procedure poses no risks. Some people may have a skin irritation from the patches that connect the wires on your chest to the computer. Skin and hair are pulled slightly when the patches are removed after the test. Research personnel will attach and remove the patches as carefully as

possible. Some minor discomfort may occur with finger blood pressure cuff inflation. This procedure is not standard of care.

Glycocheck

This procedure poses no risks. This procedure is not standard of care.

Phosphatidylserine Supplement (PS)

The proposed dose of the PS supplement (900mg/day) is well-tolerated and posed no risks. No side effects have been reported. Administration of this supplement is not standard of care.

Randomization and Blinding

Subjects will either take a placebo or a supplement as part of this study. There is a 1:1 (experimental/placebo control) randomization. The study team and participants will be blinded to the study assignment. There is no risk associated with randomization or blinding in this study.

Protection against risks

Risks to loss of confidentiality are reduced by assigning all subjects a data identifier code. Hard copies of data are stored in a locked office, and only the PI and study coordinator have access to the locked files. Individual names or initials are not used in any discussions or publications of the data. We have assembled a research team which includes scientists, physicians, and clinician-scientists with significant experience in human research and metabolic diseases to help anticipate and reduce the risks to subjects.

Plan for reporting study deviations

Any **minor** problem/deviation will be summarized and reported to the IRB at the time of annual review, including any event that does not: 1) increase the risk to the subject, 2) decrease the benefit to the subject, or 3) significantly affect integrity of the research data.

Any **major** problem/deviation will be summarized and reported to the IRB within five working days of awareness, including any event that: 1) increases the risk to the subject, or 2) significantly affects integrity of the research data.

Stopping rules

We will stop an individual study in the event of an unanticipated serious adverse event. If four or more subjects experience adverse events requiring termination of the study, the study will be stopped and the events will be discussed with the IRB to determine whether it is appropriate to continue and/or determine appropriate modifications to the protocol to avoid further adverse events. All adverse events will be submitted for review according to current protocols. The supplementation will be discontinued at the discretion of the study safety officer.

Breach of confidentiality

Subject confidentiality will be rigorously maintained. The data collected as part of this study will be for research only. It will be de-identified after collection. Confidentiality of data will be assured by coding of unique subject identities and that coding will be known only to the research team, including the use of secure files, locked in an office, and a unique subject coding system. The original study data will be kept in locked in an office (hard copy) or entered into a secure computer database password protected under a secure server space allocated for use by only the study team (electronic). Furthermore, data analysis will be appropriately blinded and any individual data presented in manuscripts will also be presented in an anonymous nature. No identifying information will be disclosed. Confirming with University of Missouri policy, all research records will be retained for a period of seven years following completion of the study.

All protocols and techniques to be used will be approved by the Institutional Review Board (IRB) prior to initiation of any studies. Each subject will give written informed consent after all questions have been answered by a study team member. Adverse event reports and annual summaries will not include subject-identifiable material. No information will be given to anyone without permission from the subject. Electronic communication with study team members will involve only coded, unidentifiable information. Any unanticipated breach of confidentiality will be summarized and reported to the IRB within five working days of awareness.

VIII. ANTICIPATED BENEFITS

There may be no benefit to the subjects in this study. These data will aid in the understanding of how competitive inhibition of ADAM17 sheddase activity with PS administration effects vascular function and leg blood flow in subjects with T2D. From the assessments, all subjects will gain health information about themselves (*i.e.*, blood work results and body composition information).

IX. COMPENSATION

We have completed multiple clinical studies involving human subjects with adherence rates of greater than 95% and subject retention rates of greater than 85%. We utilize a validated retention strategy published by Jeffrey et al (Am J Clin Nutr. 2003;78(4):684-689) that has been successful. With respect to subject honoraria, subjects will be paid $200 following the completion of pre-assessment and $400 after the completion of post-assessment. Checks will be sent through the mail and usually take 1-2 weeks to arrive.

Visit	Compensation
Consenting	$ 0
Pre- Assessment	$ 200
Post- Assessment	$ 400

X. COST

The subjects will not be charged for any procedures that are part of this research study. The costs of the study will be covered by a federal grant from the NIH.

XI. DATA SAFETY AND MONITORING PLAN

Plan for data management

A password-protected database will be used to manage all study data. To ensure confidentiality only subject ID numbers will be entered into the database. Signed informed consent forms are kept in a locked office. Participants will not be individually identified in any publication. Participants' right to privacy will be protected.

Plan for safety monitoring

The data and safety monitoring plan (DSMP) for this trial focuses on close monitoring by the study physician and the safety officer.

Frequency of monitoring, including any plans for interim analysis and stopping rules. Monitoring will include enrollment, attrition, efficacy end-points, and adverse events. In addition to monitoring by the PIs, study physician, study coordinator, and safety officer, the DSMC conducts its reviews on a semiannual basis. The frequency of the structured data review for this study can be summarized in the following table:

Data type	Frequency of review
Subject accrual (adherence to protocol regarding demographics, inclusion/exclusion)	At the end of each recruitment
Adverse event rates (injuries)	semi-annually
Compliance to supplementation	semi-annually
Stopping rules report regarding statistical power implications of dropouts and missing data	semi-annually
IRB review	annually
DSMC review	semi-annually

Managing and reporting adverse events (AE), serious adverse events (SAE) and unanticipated problems (UP)

Unanticipated events will be reported to MU IRB, and both serious and non-serious adverse events will be reported to the MU School of Medicine DSMC. For reporting to the DSMC, adverse events will be categorized and classified according to Common Terminology Criteria for Adverse Events Scale (CTCAE v3.0). Safety reports will be sent to the safety officer. Serious adverse events will be reported to the funding agency in addition to MU IRB and the MU DSMC. The PIs will be responsible for assembling the data and producing these reports, as well as assuring that all parties obtain copies of these reports.

Qualifications and responsibilities of the safety officer

The safety officer for this trial will be Guido Lastra, MD, an Associate Professor in the Division of Endocrinology. In addition to practicing medicine, he is a clinician scientist. As Safety Officer, Dr. Lastra will be unblinded as to supplement assignment. He will review all reports sent by the study coordinator to determine whether there is any corrective action, trigger of an ad hoc review, or stopping rule violation that should be communicated to the MU IRB and the DSMC. In addition, the safety officer may comment on whether the study PIs need to report any specific out-of-range laboratory data.

MU Data and Safety Monitoring Committee (DSMC):

The DSMC provides education for investigators, research teams, and faculty regarding data and safety monitoring; reviews proposed Data & Safety Monitoring Plans; establishes Data & Safety Monitoring Boards; conducts independent, interim reviews of study safety and progress; and makes recommendations concerning the continuation of studies, including recommendations regarding the modification, suspension, or termination of a study. The data safety monitoring board minutes will summarize the topics discussed and list the recommendations. Minutes will be signed by the board chair. For the current study the DSMC has 3 voting members representing: Endocrinology, Diabetes and Metabolism, Cardiovascular Diseases and Echocardiology, and Biostatistics. Additional members may be consulted ad hoc as needed and would be reflected in the minutes.

XII. REFERENCES

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