CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

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PROJECT IRB #: 2008181
STUDY TITLE: RESTORING VASODILATOR ACTIONS OF INSULIN IN PATIENTS WITH TYPE 2 DIABETES: EFFECTS OF WALKING

INTRODUCTION
This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.

This is a research study. Research studies include only people who choose to take part. Before participating in a research study, you have the right to know about the study expectations and tests that will be used in this study. This will allow you to make a choice on whether or not to join. The information presented here is simply an effort to make you better informed so that you can make your choice of whether or not to join this research study.

This is a clinical trial and a description of this clinical trial is available on www.ClinicalTrials.gov (#NCT03203694), as required by U.S. law. This web site does not include information that can identify you. At most, the web site includes a summary of the results. You can search this web site at any time.

This study is being sponsored by the University of Missouri, Department of Nutrition and Exercise Physiology.

WHAT SHOULD I KNOW BEFORE I DECIDE WHETHER TO TAKE PART IN THIS STUDY?

- Research studies help us to learn new things and test new ideas about treating certain conditions/diseases.

- Taking part in a research study is voluntary. You decide if you want to take part, and you can stop taking part at any time. Your regular medical care at the University of Missouri Hospitals and Clinics will not be affected now or in the future if you decide you do not want to be in this study.

- We are doing this study to determine the effects of increased walking on leg vascular function in patients with type 2 diabetes (T2D).

- We invite you to take part in this study because you are between the ages of 35 and 65 years and have type 2 diabetes. Or are between the ages of 35 and 65 and do not have type 2 diabetes.

- About 60 people will take part in this study at the University of Missouri.

- The study involves two ~7 hour experimental visits that take place at the Clinical Research Center located at University of Missouri Hospital during which we will be performing various measures of arterial and metabolic health. We will explain these procedures in this form. These visits will take place 8-weeks apart during which you will be placed into either a walking group (walking 5 days per week) or a control group (not walking). The walking sessions will take place in McKee

Gymnasium located on the University of Missouri campus 3 days per week, with the participants completing the other two walking sessions per week at home on their own.

- The total amount of time you could be in this study is about 8-9 weeks.

- Taking part in this study may or may not make your health better. We hope that the information we learn from this study will help in the future treatment of people with Type 2 Diabetes. **There is no guarantee that taking part in this research will result in any improvement in your condition.**

- As with any research study, there are risks that we know about and there may be some we don't know about. We will explain these risks in this form.

- We will only include you in this study if you give us your permission first by signing this consent form. Please take your time to make your decision and discuss it with your family and friends.

WHAT IS INVOLVED IN THE STUDY?
You will initially be screened to see if you meet the criteria of the study.

If you take part in this study, you will be randomized to a control non-exercise group or walking group. Randomization will be accomplished by a computerized randomization software. The walking program will consist of 45 minutes of walking (at a moderate pace) 5 days per week for 8 weeks. Three days per week of the exercise intervention will be supervised and conducted at the MU Physical Activity and Wellness (MUPAW) center in the Department of Nutrition and Exercise Physiology. You will have the option to complete the other two days at home. Prior to initiating the walking program, you will undergo a standardized exercise stress test with assessment of ECG (heart activity).

Prior to participating in the study, you will provide written informed consent, complete a medical health history questionnaire, and receive randomization into experimental groups (walking v. control). You will also be given a FitBit pedometer to wear throughout the 8-week period in order to allow us to quantify steps taken. Subsequently, before and after the 8-week period, you will be scheduled to come to the University Hospital Clinical Research Center (CRC) for a single testing day (Experimental Visit). On testing days, you will arrive at 7am after an overnight fast, having not taken medications, and not exercised for 24-48 hrs.

Experimental Visit: This visit will last approximately 8 hours and will include the following measures/tests:

Basic measures: Body weight and height.

Urine sample: If you are a woman of childbearing potential, you will give a urine sample for a pregnancy test.

Body composition: A DEXA scan will be performed to determine how much of your body is composed of fat, bone and muscle. This scan will expose you to a small amount of radiation. The amount of radiation received during the DEXA scan is less than that of an airline flight from California to New York and back.
Vascular function measures: A blood pressure cuff will be placed around the forearm or calf muscle. This cuff will be inflated (220 mmHg), as is done when your blood pressure is being measured, but instead of deflating the cuff immediately it will remain inflated for 5 minutes. We will measure the blood flow to your arm and leg by placing an ultrasound probe over the brachial artery (upper arm artery) and popliteal artery (lower leg artery) before, during and after inflating the cuff. The probe will provide a measure of the speed at which your blood is traveling through your artery and the extent to which your artery dilates (i.e., expands). A pressure sensor (tonomter, the size of a pencil) will be placed over the skin of the neck region to obtain the pressure wave form in the carotid artery. Additionally, in order to further characterize blood flow, we will be using an ultrasound to image the muscle of your leg and your abdomen during the administration of an ultrasound contrast agent that will be given through the IV. This agent, called Definity, is composed of tiny microbubbles smaller than the size of a red blood cell. These bubbles stay inside the blood vessels and go where the red blood cells go. This contrast agent allows us to evaluate blood flow in your leg muscle. Definity has been FDA approved for use in humans during ultrasound of the heart cavity and has been shown to be safe.

Insulin clamp: The insulin clamp test helps to determine how well your body disposes of blood sugar (glucose) in response to insulin. You will have a small catheter (tube) placed into a vein in both of your arms. The insulin clamp requires that insulin and glucose be slowly infused into the arm vein and then multiple small blood samples will be taken during a 3 hour period allowing us to accurately assess your insulin sensitivity. The total volume of blood drawn per insulin clamp will be less than 120mL (~25 teaspoons). During the entire test you will lay comfortably in a bed. During this time, we will perform repeated measures of leg blood flow and leg muscle blood flow using the ultrasound probe, measures of blood pressure, and measures of heart rate via ECG.

Muscle biopsy: During the insulin clamp, you will have a muscle biopsy performed on your quadriceps (thigh) muscle. Taking a small piece of muscle allows us to measure signaling proteins from the vasculature in the muscle that are thought to play a role in the development of the insulin resistance. The muscle biopsy procedure consists of initially shaving a three inch square of surface and then cleansing the area with an alcohol swab and iodine. The iodine may temporarily leave the skin with a yellowish tinge. A substance that becomes cold upon exposure to air (ethyl chloride) will then be sprayed on the biopsy site to numb the skin surface. A local anesthetic, much like that used at the dentist's office (lidocaine) will be injected just beneath the skin in an area the size of a nickel. This injection may feel like a bee sting, but will numb the skin. A small incision of approximately 3/8 inch will then be made in the numbed area. A sterile needle about the diameter of a pencil (1/4 inch) will then be inserted about ½-1 inch into the thigh muscle. A piece of muscle about half the size of an eraser at the end of a pencil (50-100 mg) will be obtained. The time to insert, cut, and remove the sample will be from 5-10 seconds and then pressure will be applied to the biopsy site for at least 5 minutes with a cold pack. The incision will be closed with a steri-strip and a band aid; a temporary pressure wrap will also be applied to the leg. The needle muscle biopsy technique is a research procedure designed to investigate phenomena in skeletal muscle. The procedure will occur with physician supervision.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for 8-9 weeks. You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects described below. You should discuss these with the investigator and/or your doctor. There may also be other side effects that we cannot predict. Risks and side effects related to the procedures in this study include:

Exercise testing and training:

The risks associated with high levels of physical activity are minimal but may include high blood pressure, irregular heartbeat, fainting, and in rare instances heart attacks. The rate of severe heart complications is less than 1 per 10,000 exercise tests. You will have a medical history taken and if you have a history of cardiovascular disease you will be excluded. The primary risks of exercise are likely to be fatigue or muscle soreness. If you experience muscle soreness, we will prescribe light stretching to reduce the soreness. We anticipate that soreness will occur primarily in the first few days but then subside as you become accustomed to the exercise. You will be fully informed of the potential discomfort and risks and will be able to withdraw from the study at any time. Graduate students trained in exercise physiology will be administering the testing and oversee all the training sessions. A physician will be present during stress testing.

Insertion of venous catheters: The potential risks of venous catheterization include infection, swelling and discomfort at the catheter insertion sites. Some bleeding may occur during the insertion of the catheters 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.

Muscle biopsy: You may experience muscle soreness, tightness, and discomfort during and after the muscle biopsy in the thigh muscle. There is also the possibility that the biopsy could become infected, however, this unlikely to occur. To avoid these issues the biopsy procedures are conducted with sterile techniques and with the use of local anesthesia. The study physicians will determine if medical attention is needed should an infection occur.

Insulin clamp: The potential risks during the clamp include mild nausea or light-headedness, and mild to moderately high or low blood glucose levels. However, blood glucose will be continually monitored throughout the test. Also, drinks and snacks will be available at the completion of testing should you have low blood sugar or feel nauseous.

Perflutren (Definity): A potential side effect from the perflutren ultrasound contrast agents is temporary back pain, joint pain, headache, shortness of breath, or flushing. These symptoms occur in about one in 200 subjects and are mild in intensity in 90% of those who experience this reaction. If this happens then let us know and infusion of the agent will be stopped. The back and joint pain will go away in a few minutes. A serious allergic reaction to ultrasound contrast agents is unlikely (1 in 10,000), but possible. Symptoms of an allergic reaction include: Rash, itching, swelling, severe dizziness, chest pain and trouble breathing. We are using this contrast agent to measure blood flow in your leg muscles using a dose approved by the FDA.

Heart rate measurements via ECG: 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.

Blood pressure cuff inflation and vascular function measures: The blood pressure cuff will squeeze your arm or leg tightly; however, any discomfort will be alleviated as soon as the pressure in the cuff is released.

Body composition: The amount of radiation received during the DEXA scan is less than that of an airline flight from California to New York and back. If you are a women of child-bearing age, you will be administered a home pregnancy test to ensure that you are not pregnant prior to the scan. You will be discontinued from the study if pregnant.

Drugs:
Ethyl chloride: Ethyl chloride will be sprayed on the skeletal muscle biopsy site to numb the skin surface. There are no side effects associated with this use of this drug.
Lidocaine: Lidocaine, a numbing agent, will be injected just beneath the skin in an area the size of a nickel prior to performing the muscle biopsy. There are no side effects from this localized administration. However, if systemic spill ever occurs, this drug may cause high blood pressure, constipation, nausea, vomiting, confusion, dizziness, headache, funny feeling or tingling in the toes, fingers, or hands.
Insulin**:** Insulin will be administered through the vein catheter to increase circulating levels of insulin during the clamp. The potential side effects of insulin infusion may include mild nausea or light-headedness as a result of too low levels of blood sugar. To ensure this does not occur, blood sugar will be checked throughout the clamp. In addition, dextrose (sugar) will be simultaneously administered to maintain constant levels of blood sugar. After completion of the insulin clamp, you will be given snacks if needed.
Dextrose: Dextrose is a sugar that will be administered through the vein catheter to maintain your levels of blood sugar constant throughout the clamp. Administration of fluid may increase the urge to urinate. A portable urinal and privacy will be made available if needed.
Perflutren (Definity): Contrast agent used in contrast enhanced ultrasound procedure. Definity will be infused IV utilizing a syringe pump at a rate of 2mL/min immediately prior to ultrasound imaging of the leg muscle.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct medical benefit to you. You may expect to benefit from taking part in this research to the extent that you are contributing to medical knowledge. Indeed, we hope the information learned from this study will lead to future strategies to combat cardiovascular disease. You may benefit from the proposed study by learning more about your cardiovascular and metabolic health. In addition, you may also benefit from the exercise intervention designed to improve vascular function.

WHAT OTHER OPTIONS ARE THERE?
An alternative is to not participate in this research study. At any point, you can change your mind about being in the study.

WHAT ABOUT CONFIDENTIALITY?
Information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a

separate, secure location. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law. It is possible that your medical and/or research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the Food and Drug Administration (FDA), federal or state government agencies, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the University of Missouri will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

We will keep the information we collect from you for this study to use in future research/to share with other investigators to use in future studies without asking for your consent again. Information that could identify you will be removed from your research data so no one will know that it belongs to you.

WHAT ARE THE COSTS?
You will not be charged for any of the tests or procedures done for the research study. You will be responsible for your travel to and from the laboratory/testing facilities.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?
You will be compensated $800 for completion of the duration of the study. If you are a control subject not participating in the 8-week intervention, you will be compensated $200 for your participation in the single Experimental visit. If you or the investigator discontinue the study, you will be compensated $15 for every hour spent in the laboratory/testing facility.

The method of payment will be check.

WHAT IF I AM INJURED?
It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate. If you decide to participate, you can change your mind and drop out of the study at any time without affecting your present or future care in the University of Missouri Health Care System. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. In addition, the investigator of this study may decide to end

your participation in this study at any time after he/she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Health Sciences Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at (573) 882-3181.

PARTICIPANT DATABASE OPTION

WHAT INFORMATION IS COLLECTED IN THE DATABASE?

You are being asked to grant permission to review your screening file and enter some of your personal and medical information in a computer database (spreadsheet). The following information will be collected: Demographics, study-relevant diagnoses (i.e., diabetes, heart disease, etc.); relevant treatment history (medications, surgeries, lifestyle or other interventions, etc.); and basic contact information together or separate from your study information as requested. The information will be placed in a "database," which will be kept on file indefinitely. This file will be maintained within the secured server of the Department of Nutrition and Exercise Physiology. Access will only be granted to investigators within the department who are approved to conduct associated human health research studies.

It is anticipated that information from the database will be used to conduct research projects and eventually help improve the quality of information upon which future treatment decisions are based. These include reviewing the information for patterns or extracting pieces of information to look at more closely in order to understand the course of disease or the effect of particular treatments. Investigators within the Department of Nutrition and Exercise Physiology may contact you in the future (if you select this option below) to participate in additional research studies for which you may qualify. You are free to decline participation in such projects even after your information is entered into the database. You may also opt out of future contact at any time by notifying us in writing.

PERMISSIONS FOR USE OF YOUR INFORMATION

Please indicate your choice about research being performed on your database information by answering the questions below.

Do you give your permission for your information to be entered in the database and to be used for anonymous research, where no identifying information will be released?

Yes _____ No _____ Initials _____

Do you give your permission to be contacted in the future and asked for your consent to participate in any research project which would require identifying information to be released to the investigators?

Yes _____ No _____ Initials _____

Do you give your permission to be contacted about possible participation in future research projects that may grow out of research on the database information?

Yes _____ No _____ Initials _____

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact Dr. Jaume Padilla at padillaja@missouri.edu or (812) 345-3566

A copy of this consent form will be given to you to keep.

I authorize the investigators to keep this information and any information from my participation in their studies in a database so that they may contact me regarding future studies.

YES _____ **NO** _____

SIGNATURE

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

_____ _____

Subject/Patient Date

_____ _____

Witness Date

SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

_____ _____

Study Representative**** Date

****Study Representative is a person authorized to obtain consent. Per the policies of the University of Missouri Health Care, for any 'significant risk/treatment' study, the Study Representative must be a physician who is either the Principal or Co-Investigator. If the study is deemed either 'significant risk/non-treatment' or 'minimal risk,' the Study Representative may be a non-physician study investigator.