CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

INVESTIGATOR'S NAME: JAUME PADILLA PHD

PROJECT IRB #: 2008181

STUDY TITLE: RESTORING VASODILATOR ACTIONS OF INSULIN IN PATIENTS WITH TYPE 2 DIABETES: (ROLE OF PHYSICAL ACTIVITY IN RESTORING VASCULAR INSULIN SENSITIVITY IN SKELETAL MUSCLE OF PATIENTS WITH TYPE 2 DIABETES).

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 lower body heating 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 40 people will take part in this study at the University of Missouri.

<u>If you have Type 2 diabetes:</u>

- The study involves two ~4 hour experimental visits that all take place at the University of Missouri Physical Activity and Wellness Center (MUPAW) in the Department of Nutrition and

Exercise Physiology. During the experimental visits we will be performing various measures of arterial and metabolic health. We will explain these procedures in this form. These visits will take place approximately 8 days apart during which you will undergo lower body heating for 60 min, for 7 days at the MU Physical Activity and Wellness (MUPAW) center in the Department of Nutrition and Exercise Physiology. Between your visits, we will also provide you with supplies to use at home that assess your physical activity and dietary intake.

- The total amount of time you could be in this study is about 2 weeks.

If you do not have Type 2 diabetes:

- The study involves a single ~4 hour experimental visit. This will take place at the University of Missouri Physical Activity and Wellness Center (MUPAW) in the Department of Nutrition and Exercise Physiology. Before your visit, we will also provide you with supplies to use at home that assesses your physical activity and dietary intake.
- The total amount of time you could be in this study is about ~1 week.

Overall:

- 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.

Prior to participating in the study, you will provide written informed consent and complete a medical health history questionnaire. You will be scheduled to come to MUPAW for the experimental visits. On testing days, you will arrive in the morning after an overnight fast, having not taken medications, and not exercised for 24-48 hrs. Between your visits we will give you an accelerometer that fits on your waistband to wear for 7-day periods so we can quantify your physical activity. We will also give you 3-day food diaries to fill out.

If you have type 2 diabetes, you will undergo lower body heating for 60 min, for 7 days at the MU Physical Activity and Wellness (MUPAW) center in the Department of Nutrition and Exercise Physiology. Lower body heating will be accomplished via water bath immersion at a temperature of 40.5°C (105 F), using an inflatable hot tub. During the lower body heating, you will be seated, and water will reach a level between your naval (belly button) and armpit. The purpose of the lower body heating is to increase leg blood flow. This water temperature is below the threshold for pain sensation or burning. Your experimental visits will be scheduled for before and after the 7 days of lower body heating sessions.

Between your visits, we will provide you with supplies to use at home that assesses your physical activity and dietary intake.

If you do not have Type 2 diabetes you will participate in a single experimental visit. On the testing day, you will arrive in the morning after an overnight fast, having not taken medications, and not exercised for 24-48 hrs. Before your visit, we will provide you with supplies to use at home that assesses your physical activity and dietary intake.

Experimental Visit: This visit will last approximately 4 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 below the knee. This cuff will be inflated (250 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 superficial femoral artery (upper 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.

Oral glucose tolerance test: The oral glucose tolerance 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 a arm. During the entire test you will lay comfortably in a bed. The total volume of blood drawn per test will be 45mL (~10 teaspoons). During this time, we will perform repeated measures of blood flow in a leg using an ultrasound probe, measures of blood pressure, and measures of heart rate via ECG.

Endothelial cell collection: Cells will be collected from the inside of your vein in which the catheter for the oral glucose tolerance test is placed. Briefly, after the catheter is placed a small wire is inserted to rub the side of the vessel for us to collect these cells. Any discomfort you will feel will be from the initial stick normally felt when the needle goes into the arm to place the catheter; the inside of the vessels will not feel the collection of the cells when we insert the small wires.

Lower body heating sessions: During these sessions you will sit in an inflatable hot tub for 60-minutes with the water level between your belly button and armpit, and the water temperature set at 40.5°C (105°F). All sessions will be supervised. Before and after entering the hot tub, we will measure how hydrated you are by collecting a urine sample from you and from your body weight that you will record

will while not wearing any clothes. A digital scale will automatically record your weight while you are alone in a room getting changed. If the urine sample and body weights indicate that you are dehydrated, we will give you bottled water to drink. While in the hot tub you will be encouraged to drink provided bottled water. While in the hot tub we will measure your body temperature by using a digital ear thermometer that has single-use probes on its tip, that will be placed in your ear for 5-seconds. We will also record your heart rate and blood pressure by fitting you with wearable devices. We will also ask you how warm you feel using a visual scale. During the first and last heating sessions we will measure your core temperature by having you ingest an FDA-approved telemetry pill, 7-9 hours before your session. This pill is a single use device that will pass easily through your digestion system and it is often used in research involving hospital patients, firefighters, and military personnel. If you feel too warm while in the hot tub, you can exit the tub at any time.

HOW LONG WILL I BE IN THE STUDY?

If you have Type 2 diabetes you will be in the study for ~2weeks. If you do not have Type 2 diabetes you will be in the study for ~1 week. 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:

Lower body heating: While we do not expect any adverse events, the potential risks associated with the heating protocol is dehydration and/or the onset of heat stress. To prevent these risks, all sessions are supervised, and you are continuously monitored for signs and symptoms that include lightheadedness, dizziness, weak pulse, nausea, headache, feeling unbearably warm, or a body temperature above 39.5°C. To assess all of these you will have the following performed during each visit: urine sampling, nude body weight recordings, frequent recordings of body temperature, heart rate, blood pressure and perception of how warm you are. If you have signs or symptoms previously described, you are removed from the water bath, placed in a recovery chair with feet elevated, and cooled down with cold packs until body temperature returns to pre-immersion values. If signs or symptoms worsen such as fainting, agitation, confusion, seizures, inability to drink, or body temperature not falling below 39.5°C despite application of cooling packs, immediate medical attention will be sought. To keep your body temperature at 38.5°C, you are seated with the water level reaching between your belly button and armpit. To further prevent dehydration, you will be encouraged to drink provided bottled water while in the water bath. Additionally, if you feel too warm you will be allowed to exit the water bath.
The 40.5°C(105°F) water temperature is well below the threshold for pain sensation or burning. Temperature of the water will be continuously monitored.

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.

Oral glucose tolerance test: The risks of the OGTT are minimal. This is a regular glucose dose. Some people may feel nausea after drinking the glucose, rarely do people experience light headedness. Trained personnel conduct this study.

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.

Ingestible telemetry pill for core temperature: Manufacturer instructions detail that the CorTemp® pill should not be used by individual's that have any of the following: 1) someone less than 80 pounds, 2) someone diagnosed with but not limited to diverticulitis, inflammatory bowel disease, gag reflex disorders or impairments, previous gastrointestinal surgery, hypomotility of the gastrointestinal tract (such as Ileus), 3) someone undergoing Nuclear Magnetic Resonance (NMR) or MRI scanning while the CorTemp® is within the body,4) someone having a cardiac pacemaker or other implanted electro medical device, 5) people who have difficulty swallowing. Therefore, if you have anything from the previous list, you will be excluded from the study.

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 lower body heating 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?
If you are receiving the lower body heating sessions, you will be compensated $800 for completion of the duration of the study.

If you are part of the reference group participating in the single aerobic test and experimental visit you will be compensated $200.

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.

We will need your social security number in order to pay you. Any payment may need to be reported as income on your tax return. If you are not a resident/citizen (non-resident alien) of the United States, you will need to work with the MU Nonresident Tax Specialist at 573-882-5509.

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 want to talk privately about your rights or any issues related to your participation in this study, you can contact University of Missouri Research Participant Advocacy by calling 888-280-5002 (a free call), or emailing MUResearchRPA@missouri.edu.

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 _____

Are you participating in any other research projects? 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 Date

_____ _____

Witness (if required) 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.