E-Consent Phase 1

Study ID

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VUMC Institutional Review Board
Informed Consent Document for Research

Study Title: The Effect of SGLT2 Inhibition on Adipose Inflammation and Endothelial Function
Version Date: 5/12/21 Phase 1
PI: Mona Mashayekhi, M.D., Ph.D.

Name of participant:

_____

Age

_____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:

The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:
The purpose of this study is to determine whether empagliflozin, a drug approved by the Food and Drug Administration to treat type 2 diabetes, can have anti-inflammatory effects throughout the body. This study involves taking empagliflozin for 12 weeks and coming to the Clinical Research Center (CRC) for three study days for testing. There will be 6 people in this phase of the study.

Detailed Information:

The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you are an adult with a body mass index (BMI) over 30 and have pre-diabetes.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

Inconveniences
Not eating or drinking after midnight on the night before each study day
Not having alcohol or caffeine 12 hours before the study day
Coming to the CRC for study days
Taking daily medication
Giving a urine sample

Questionnaires
Answering the questionnaires may be boring.

Blood Draws
Pain, redness, soreness, bruising, or infection may occur at the needle stick site. Rarely some people faint.

Flow-Mediated Dilation
The blood pressure cuff may cause some discomfort or brief numbness in your hand and fingers while it’s inflated. This will resolve as soon as the cuff is released.

ECG
The sticky patches on your chest may irritate your skin.

Glucose
The oral glucose (sugar solution in water) that you will need to drink may not taste good.

Pregnancy Risks
The drugs used in this study may hurt an unborn child. If you take part in this study, you and any person you have sex with must use birth control while you are in this study. If you become pregnant while you are in this study, you must tell your doctor at once. Also, women must not breast feed while in this study. If you are a woman and are able to become pregnant, you will have a urine test to make sure that you are not pregnant before you receive treatment in this study.

Liver Ultrasound (FibroScan)
You may experience itching or skin irritation from the vibration of the probe or from the water-soluble gel needed for this procedure.

Radiation Risk
This research study involves exposure to radiation from 2 DEXA whole body scans. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive by participating in this study is equal to your body receiving 17 days of radiation from your natural surroundings or less than 1% of the amount of radiation allowed for persons exposed to radiation as part of their work.

Fat Sampling
The fat sampling could cause bleeding or infection. We will number use sterile technique and only an experienced doctor or nurse practitioner will do the sampling.

Endothelial Cell Sampling
Sliding the tiny wire into your vein to collect cells from the walls may increase the chances of transient pain, bleeding, bruising, infection, or vessel damage. The end of the wire is soft and curved to prevent damage. A doctor or nurse practitioner experienced in collecting cells from your vein will perform the procedure.

Nitroglycerin
Nitroglycerin may lower your blood pressure, increase or decrease your heart rate, or cause you to feel dizzy, faint, lightheaded, weak, hot, nauseated, or have a headache. If your blood pressure or pulse is too low, the study physician may not perform this part of the study.

Lidocaine
We will use lidocaine to numb your skin prior to the fat sampling. Very rarely, lidocaine used to the numb the skin can be absorbed and cause drowsiness, slow heart beats, or slow breathing.

Empagliflozin
Dizziness, lightheadedness, or fainting may occur with this medicine. This is more common if you have kidney disease, low blood pressure, or if you are taking a diuretic (water pill). Taking plenty of fluids each day may help. Drink plenty of water during exercise or in hot weather. Check with your doctor if you have severe nausea, vomiting, or diarrhea that does not stop. This may cause you to lose too much water.

This medicine may cause hypoglycemia (low blood sugar) when taken together with other diabetes medicines (e.g., insulin, glipizide, or glyburide). Some symptoms of low blood sugar include: behavior changes that are similar to being drunk, blurred vision, cold sweats, confusion, cool, pale skin, difficulty with thinking, drowsiness, excessive hunger, a fast heartbeat, headaches that continue, nausea, shakiness, slurred speech, or unusual tiredness or weakness. Talk to your doctor about how to treat low blood sugar.

This medicine may cause vaginal yeast infections in women and yeast infections of the penis in men. This is more common in patients who have a history of genital yeast infections or in men who are not circumcised. Women may have vaginal discharge, itching, or odor. Men may have redness, itching, swelling, or pain around the penis, or a discharge with a strong odor from the penis. Check with your doctor right away if you have any of these symptoms.

This medicine may increase your risk of having urinary tract infections. Check with your doctor right away if you have bladder pain, bloody or cloudy urine, difficult, burning, or painful urination, or lower back or side pain.

This medicine may cause a rare but serious bacterial infection, called necrotizing fasciitis of the perineum or Fournier's gangrene, which can cause damage to the tissue under the skin in the area between and around the anus and genitals (perineum). Fournier's gangrene may lead to hospitalization, multiple surgeries, or death. Check with your doctor right away if you have fever, unusual tiredness or weakness, or pain, tenderness, redness, or swelling of the area between and around your anus and genitals.

Ketoacidosis (high ketones and acid in the blood) may occur while you are using this medicine. This is an extremely rare complication seen in type 1 or type 2 diabetic patients and has not been reported in pre-diabetic or non-diabetic patients. This can be life-threatening and requires immediate medical attention. Tell your doctor right away if you have nausea, vomiting, trouble breathing, increased thirst or urination.

Make sure any doctor or dentist who treats you knows that you are using this medicine.

Risks that are not known:
Because this treatment is investigational, meaning non-FDA approved for pre-diabetics, there may be risks that we do not know about at this time.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study: we may learn more about how inflammation in obesity contributes to heart disease and discover how to treat that inflammation to prevent heart disease.

Procedures to be followed:

Screening Day
If you agree to be in the study, you will come to the CRC having had nothing to eat or drink since midnight. We will

review the study procedures and answer any questions you may have.

We will complete a medical history and perform a physical exam. We will measure your height and weight. We will place a catheter (small tube) in a vein in your arm. We will take a blood sample (about 1 ½ tablespoons) and ask for a urine sample.

We will place sticky patches on your chest to measure your electrocardiogram (ECG, a measure of your heart's electrical function.)

We will have you perform an oral glucose tolerance test (OGTT). This test shows how well one's body handles sugar. We will take a blood sample to test the starting blood sugar level. You will then drink 300 milliliters (about 1 ¼ cups) of a liquid that contains 75 grams of glucose in water within 10 minutes. Blood will be drawn again 30, 60, 90, and 120 minutes later. At the end of the study, you will be provided a snack.

Study Day 1
We will ask that you refrain from taking a PDE5 inhibitor (Viagra, Cialis, Levitra, or Stendra) for at least one week before the study day.

At least 24 hours after your screening visit, we will ask you to come to the CRC having had nothing to eat or drink after midnight and no alcohol or caffeine for 12 hours before the study day.

We will ask you to complete a questionnaire about your weight history. If you are a woman who could become pregnant, we will test whether you are pregnant. If you are pregnant, you will not be allowed to be in the study. We will measure your weight, and your hip and waist circumferences. We will place a catheter in the vein in your arm to take blood (about 5 tablespoons during the whole study day). The following tests will be performed:

DEXA scan: We will measure your body composition (the percent of your body that is fat, muscle, water, and bone) by giving you a DEXA (dual energy X-ray absorptiometry) scan. To have this scan, you will lie down on a table for 5-10 minutes while the machine scans your whole body.

Liver ultrasound (FibroScan): The FibroScan is a special type of ultrasound that estimates the stiffness and fat content of your liver using sound waves. You will lie on your back with your right arm resting beside your head. Your upper abdomen and lower ribcage will be exposed, and a water-soluble gel will be placed on your skin. A FibroScan probe will be placed on the skin. You may feel vibrations from the probe. At least ten measurements of your liver will be collected. The procedure usually lasts less than 15 minutes, but can last up to 45 minutes.

Flow-Mediated Dilation: We will do an ultrasound scan of the artery in your arm. We will do this for about 30 seconds. We will then place a blood pressure cuff on your arm and inflate it for 5 minutes. When we release the cuff, we will again use the ultrasound to measure your artery for 3 minutes. This test is called flow-mediated dilation (FMD). As part of this test, we will give you a tablet of nitroglycerin, a medication approved by the FDA to treat angina, to dilate your blood vessels.

Endothelial Cell Sampling: We will slide a tiny wire into your vein through one of the catheters to collect cells from the walls of your vein. We will do this three times and then remove that catheter.

Fat Sampling: We will take a sample of fat from the area of your stomach near your belly button. We will numb the area with lidocaine and clean it well. We will then make a small cut in the skin and use a special needle to remove the tissue.

At the end of the study day, we will give you empagliflozin. You will begin taking it approximately 2 weeks after study day one. You will take it once daily by mouth.

You will then be finished for the day.

Study day 2
After you have been taking the study drug for two weeks, you will again come to the CRC, having had nothing to eat or drink after midnight. We will repeat all the procedures that were in study day 1 except for the DEXA scan and liver ultrasound.

You will continue taking the study drug for another 10 weeks.

Study day 3
After you have been taking the study drug for 12 total weeks, you will again come to the CRC, having had nothing to eat or drink after midnight. We will repeat all the procedures that were in study day 1.

At the end of the procedures, you will be done with the study.

Payments for your time spent taking part in this study or expenses:
If you complete the entire study, you will be paid $600. If you only complete a portion of the study, you will be paid $200 for each of the study days you complete.

We may ask you for your Social Security number and address before you are compensated for taking part in this study. You may receive up to $600 for taking part in this study. This amount may be taxable and will be reported to the Internal Revenue Service (IRS).

Costs to you if you take part in this study:
There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Mashayekhi at 615-208-5037.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Reasons why the study doctor may take you out of this study:
You may be removed from this study without your consent if staying in the study would be harmful to you or you no longer meet the requirements of the study, or if the study is stopped. If you are removed from the study, you will be told the reason.

What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

Confidentiality:
Any private information we have obtained from you will be stored in a secure database. Only Dr. Mashayekhi and members of her study team will have access to your identified information. Any information we share with other researchers or publish will not identify you and will not contain your name.

Dr. Mashayekhi and/or Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Mashayekhi, and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use of transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Study Results:
Your study results will not be shared with you.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this authorization?
You do not have to sign this authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Signature _____

Today's date _____

Time _____

With your permission, we would like to contact you for future studies in which you might be interested. May we contact you in the future?

◯ Yes
◯ No

Date of IRB Approval: 05/25/2021
Date of Expiration: 05/24/2022

Institutional Review Board

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Consent for Genetic Research

One purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for your body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a blood sample for genetic research. What we learn about you from this sample will not be put in your health record. Your test results will not be shared with you or your doctor. No one else (like a relative, boss, or insurance company) will be given your test results. Health insurance companies and group health plans may not request your genetic information that comes from this research.

A single blood sample of 2 teaspoons will be taken from your arm at the same time we are taking another sample. This will not take any extra time.

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. This may cause problems with insurance or getting a job.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that comes from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only Dr. Mashayekhi and members of her study team will have access to your name.

Your sample will be used to make DNA that will be kept for an unknown length of time (maybe years) for future research. The sample will be destroyed when it is no longer needed.

Your samples and information about you may be shared with others to use for research. To protect your privacy, we will not release your name.

You will not receive any benefit as a result of the tests done on your samples. These tests may help us learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Giving samples for research is your free choice and you may be in the study even if you do not want your samples used or stored for gene research.

At any time, you may ask to have your sample destroyed. You should contact

Dr. Mona Mashayekhi, Vanderbilt Diabetes Center, 7465 MRB IV, 2213 Garland Ave., Nashville, TN 37232

to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples. You will not be paid for the use of your samples.

Please check Yes or No to the questions below:

My blood/tissue sample may be used for gene research.	◯ Yes ◯ No
My blood/tissue sample may be stored/shared for future gene research in diabetes and heart disease.	◯ Yes ◯ No
My blood/tissue sample may be stored/shared for future gene research for other health problems (such as cancer, arthritis, etc).	◯ Yes ◯ No

Date of IRB Approval: 05/25/2021
Date of Expiration: 05/24/2022

Institutional Review Board

VANDERBILT

Signature

_____

Today's date

_____