VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
Version Date:	6/16/2022
PI:	Justin M. Gregory M.D., MSCI

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.

What is the purpose of this study?
You are being asked to take part in this research study because you have Type 1 Diabetes Mellitus (T1DM). This study will help us learn how insulin affects heart health. This study will enroll approximately 40 participants.

People who do not have diabetes make insulin in their pancreas. Insulin works to keep sugar in the blood at a normal level. This insulin then goes directly from the pancreas to the liver. The liver removes much of the insulin. The insulin that remains goes into the blood that travels around the rest of the body. This brings insulin to muscle and fat. There, insulin allows sugar to be taken into these tissues.

People with type 1 diabetes do not make their own insulin. As a result, they must give themselves injections of insulin into fat tissue. This keeps their blood sugar under control. The injected insulin reaches muscle and fat before it can be removed by the liver. This results in higher levels of insulin at the muscle and fat for people with type 1 diabetes compared to those who do not have the condition.

Many patients with diabetes have insulin resistance, a condition where the body does not use insulin to take sugar into tissues as well as normal. Insulin resistance is linked to a variety of health disorders including heart disease. Therefore, the purpose of this study is to determine:

- How insulin levels in the blood affect your blood vessels.
- How well the body uses insulin.
  AND
- If nutritional factors can improve how your body uses insulin.

Our goal is to learn more about whether levels of insulin in the blood increase risk of heart disease.

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:

The following risks associated with this study are considered to be minimal or low:

Venipuncture and placement of IV: the placement of a small tube into a vein for drawing blood and giving medicine can cause bruising, bleeding, pain, and infection. Sometimes people may feel nauseous, lightheaded, or even faint during this procedure. We will attempt to lessen these possibilities by cleaning the skin and having you lie down or sit during this procedure.
Hypokalemia: Insulin infusions can cause lowering of potassium levels in the blood. If the potassium drops severely and is left untreated, a change in heart rhythm can occur. We will monitor potassium levels in the blood during the study. If the level becomes low, we will provide a tablet which has potassium called potassium chloride. Oral potassium may cause abdominal discomfort, diarrhea, nausea, or vomiting.
DEXA scan: This research study involves exposure to radiation from a DEXA whole body scan. This radiation exposure is not necessary for your medical care and is for research purposes only.

Risk of loss of confidentiality: our study team believes our participants are entitled to privacy and confidentiality. Blood and tissue samples taken during the study will not use your name. Instead, a specific participant code will be used that does not reveal your identity. Only the study team will be able to link your identity to the study code.

A higher level of risk exists with the following:

- Low blood sugar: study participants with T1DM are at increased risk for low blood sugar during testing.
    - They are asked not to eat after 7pm before each study visit and to take their usual home insulin regimen. If low blood sugar occurs overnight before study visit one it is okay to correct the low glucose using the "Rule of 15."
        - If you feel like you have low blood sugar, check your blood sugar.
        - If your blood sugar is less than 70 mg/dL, you have low blood sugar

- Eat 15 grams of carbohydrates. This could be 4 glucose tablets or ½ cup of juice.
- Wait 15 minutes.
- Test again to see if blood sugar is safely up to 100 mg/dL or above.
- If not, take a second dose of 15 grams of carbohydrates and test again in 15 minutes.
- Keep repeating until blood glucose is safely up to 100 mg/dL or above.

  - During STUDY visits the insulin that will be given into the IV may cause low blood sugar. To protect against this, we will check glucose hourly in the participants who get insulin overnight and adjust the insulin dose accordingly.
  - All subjects will receive insulin during the clamp study. We will check glucose every 5-10 minutes. We will adjust the amount of dextrose (sugar) going into the IV to prevent low blood sugar. Giving dextrose into an IV can irritate the vein and the area around the IV site. In rare cases, dextrose can be infused into the tissues surrounding the venipuncture site, rather than the vein. This can potentially cause blistering. After the study is over it is possible low blood sugar may occur. To protect against this, you will eat as soon as the study is over. We will continue to monitor your blood sugar for approximately 1 hour after the study is over. You will also need to check your blood sugar at dinner, bedtime, and 2 AM after the study. If your blood sugar is < 120, you should eat extra 15-30 gm of carbohydrates with 5-15 gm of protein to prevent low blood sugar. As an example, one Luna bar has 26 gm of carbohydrates and 9 grams of protein. A package of 6 peanut butter and crackers has 24 grams of carbs and 5 grams of protein.

- Anemia (too few red blood cells in the blood): We will be making multiple blood draws over the course of approximately one month. During the screening visit, we will make sure you do not have anemia before you can be in the study. We will also limit the amount of blood we take in each STUDY visit. If you notice recent onset of
  - Becoming tired easily
  - Lack of energy
  - Muscle cramps
  - Dizziness with standing
  - Onset of shortness of breath

Please let our study team know.

- Low blood pressure: A medicine called nitroglycerin will be used when we measure your blood vessel health. Nitroglycerin is routinely given before measuring blood vessels in the body. There is a small risk of allergic reaction and low blood pressure. To avoid symptoms of low blood pressure, we will only give nitroglycerin after making sure your blood pressure is not already low. Nitroglycerin may cause dizziness, lightheadedness or headaches.

Risks that are not known:

There may be risks that we do not know about at this time.

Good effects that might result from this study:

a) The benefits to science and humankind that might result from this study:

Insulin resistance is a key risk factor for heart disease in patients with diabetes. This study will shed new light on what causes this insulin resistance. Once the cause of the insulin resistance is better understood, diabetes therapy can be developed to improve the insulin resistance. This is expected to lead to less risk of heart disease for patients with diabetes.

b) The benefits you might get from being in this study:

There is no guarantee that you will directly benefit from being in this study.

Procedures to be followed:

Screening

The first visit is to test whether you qualify to be in the study. Screening visits will take place in either the Vanderbilt Clinical Research Center (CRC) or a room in the Eskind Diabetes Center.

During the screening visit the study team will do the following:

Consent: We will review this form and the study with you. We will answer any questions you may have about being in the study. This discussion will be in private. At the end of this discussion, you will have

the opportunity to agree to participate in the study (consenting). You also may decide to not be in the study. At any point in the study, you may decide to not continue participating.

Exam: The Primary Investigator (PI) or research team member will review each person's clinical history and perform a physical exam.

Blood and urine tests: a small amount of blood will be taken. This will measure several chemicals in your blood related to diabetes and insulin resistance. This includes hemoglobin A1c, a measure of your long-term glucose levels. It will also include tests to make sure you are safe to participate in the study. This includes a urine pregnancy test for females. We will test for anemia (too few red blood cells in the blood) to see if there is any reason we should not collect multiple blood samples from you. Approximately 2 tablespoons of blood will be taken at this first visit.

Insulin Pump Review: We will review features of your insulin pump that we will use to monitor how much insulin you are receiving.

Continuous Glucose Monitor education: The study team will teach you to use a continuous glucose monitor (CGM). The team will then show you how to upload both CGM data and insulin device data into a data collection program.

Diet instructions: We will formulate a diet plan for the week prior to each STUDY visit. We will also show you how to record your food intake in a diet log. We will provide you with all the food you will eat on the day before each STUDY visit.

DEXA scan: this measures the amount of lean tissue (like muscle), fat, and bone in your body. It uses a low-dose x-ray. Your will lie on a table for 10-15 minutes while the machine takes measurements.

STUDY B-C

After the screening visit, eligible volunteers will participate in STUDY B and STUDY C. For these study visits, you will eat a certain diet during the week prior to the visit at the Clinical Research Center (CRC). Then, STUDY visits will show how blood vessels react to insulin levels in blood.
STUDY visits will also determine how well the body uses insulin. This test is sometimes called a "clamp study."

You may be eligible for this study if you meet the following criteria:

- You are an adult with Type 1 Diabetes Mellitus (T1DM).

Study Title: Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
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Study Diet:

You will be asked to take part in 2 separate study visits over a period of approximately one month (STUDY B and STUDY C). This study will help determine if insulin sensitivity improves through the use of a diet designed by the study team. You will be asked to closely follow the diet instructions. . We will give you all the food to eat on the day before STUDY B and STUDY C. You will be required to use your insulin pump and continuous glucose monitor.

STUDY visits:

For each of the STUDY visits (STUDY B and STUDY C), you will return to the Clinical Research Center on the morning of the test. We will measure how effectively your body uses insulin. We will also see how the levels of insulin in your blood affect your blood vessels.

Before each visit, we will ask you to:

- Prior to STUDY B and C visits, we will ask you to get a SARS-CoV-2 (COVID-19) PCR test at a Vanderbilt associated clinic if you are not fully vaccinated and have not had COVID-19 within the past three months.
- Eat only the food we provide on the day before STUDY B and STUDY C.
- Eat the dinner we provide you between 5-7 pm on the night before STUDY B and STUDY C. Then you will begin fasting except for water.
- We will provide instructions for controlling your blood sugar on the night before STUDY B and STUDY C.
- If you are not using insulin lispro (Humalog © or Admelog ©), we will provide this insulin to be used to fill a new insulin pump cartridge between 24-48 hours prior to STUDY B and STUDY C.
- Record all food eaten in a digital food log on the week before STUDY B and STUDY C.
- Consume no more than one alcoholic drink per day on the week before STUDY B and STUDY C.
- Wear a continuous glucose monitor
- Continue your usual medication regimen.

Additionally, right before the STUDY visits we will ask you to:

- Refrain from vigorous exercise for 12 hours.
- Consume no caffeine for 12 hours
- Avoid aspirin for 3 days.
- Hold vitamin supplementation for 3 days
- Avoid non-steroidal anti-inflammatory drugs like ibuprofen for 1 day
  Refrain from smoking and avoid secondhand smoke exposure for 12 hours

Study Title:	Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
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We will ask you to arrive at the research center by 7am on the day of the study. Women will have a urine pregnancy test.

The clamp study will begin in the morning after arrival to the clinical research center. You will be asked to lie awake in bed for a few hours except to use the bathroom.

Tests involved in each STUDY visit include:

Flow-Mediated Vasodilation (FMD): A pillow will support your arm with the palm facing forward. A blood vessel in your arm will be measured over at least a 10-20 second period. A blood pressure cuff will be inflated for 5 minutes. After 5 minutes, the cuff will deflate, and we will measure the size of your blood vessel. After resting for about 10 minutes, we will measure the blood vessel again. The second time, we will give you a medicine under your tongue (nitroglycerin). We will measure how much your blood vessels widen in response to this medicine.

Clamp Study: We will place an IV (a tube for withdrawing or giving fluids) in each arm. One IV will be used to give you insulin and dextrose (sugar water) with saline. The second IV will be used to draw blood from your arm. Then, we will determine how well your body uses insulin by adjusting the amount of the insulin and dextrose going into the IV. The total amount of blood drawn in each STUDY visit will equal approximately 10 tablespoons.

Payments for your time spent taking part in this study or expenses:

You will be compensated for your participation in the study. We will ask for your social security number and address before you are compensated. You will be mailed a gift card equal to the dollar amount for the completed items listed below.

- Screening visit: the initial screening visit will last approximately 3 hours. Participants who complete their screening visit will be compensated a $50 gift card amount.
- Credit for using online software to log food intake: to participate in the study you will need to record all food intake into an online dietary log. This $50 gift card amount will cover costs that may come with certain features of the software program to record your dietary intake. This credit is also intended to help with costs related to internet connection, SmartPhone use, etc.
- Clamp study: participants will be compensated a $200 gift card amount for completing each clamp study.

Costs to you if you take part in this study:

There is no cost to you for taking part in this study.

Study Title: Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
Version Date: 6/16/2022
PI: Justin M. Gregory M.D., MSCI

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 Justin Gregory, M.D. at 615-322-7427. If you cannot reach the research staff, please page the study doctor at 615-835-9612.

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 Vanderbilt University 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 become pregnant
- If there is concern that staying in the study might be harmful to you
- You no longer meet the requirements of the study

If you are taken out of the study, you will be told why.

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. Deciding to not be part of the study will not change your regular medical care in any way.

Study Title: Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
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Clinical Trials Registry:

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

Confidentiality:

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.

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

Only research associates in our laboratory or individuals directly involved in the study will have access to data or protected health information. Blood samples will be stored in our locked freezers for an indefinite amount of time. Samples will be coded with a unique identifier. This unique identifier can only be linked to patient identity through a secure database. Research records and data with personal identifiers will be stored in our locked offices or on a secure data collection program (REDCap). Only the study doctor and key personnel on the research team will be able to access study patients' names or other identifying data. Data from the study will be maintained in HIPAA-compliant, password-protected databases. Urine samples from the pregnancy test will be immediately discarded.

Study Title: Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
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Privacy:

Your 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 learn more about the causes, risks, treatments, or how to prevent this and other health problems. If you wish, we will discuss the results from the clamp study.

Study Results:

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, and/or others. If this happens, there are no plans to provide money to 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.

Study Title: Determination of Iatrogenic Hyperinsulinemia's Contribution to Insulin Resistance and Endothelial Dysfunction in Type 1 Diabetes
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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.

Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Printed Name and Title _____ Time: _____