Contribution of Hyperinsulinemia vs. Hyperglycemia to Insulin Resistance in Type 1 Diabetes and Maturity Onset Diabetes of the Young, Type 2 (MODY2)

NCT02971202

October 10, 2016

**Institutional Review Board**
**Informed Consent Document for Research**

**Principal Investigator: Justin M. Gregory, M.D.** **Revision Date: 10Oct2016**
**Study Title: A NOVEL CROSS-SECTIONAL ANALYSIS OF INSULIN SENSITIVITY AMONG ADOLESCENTS AND YOUNG ADULTS WITH TYPE 1 DIABETES, MODY2, AND NORMAL CONTROLS: THE CONTRIBUTION OF HYPERINSULINEMIA VS. HYPERGLYCEMIA TO INSULIN RESISTANCE**
**Institution/Hospital: Vanderbilt University Medical Center**

This informed consent applies to adults

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.**

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. This information may also be given to other healthcare providers if your medical record is released to them for treatment purposes.

## 1. What is the purpose of this study?

You are being asked to take part in this research study because you have type 1 diabetes (T1DM) or monogenic diabetes, type 2 (MODY2). If you do not have diabetes, you may also qualify to be a control subject.

Individuals 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.

Someone with MODY2 has a change in a chemical called glucokinase. This chemical plays an important role in recognizing how high sugar is in the body. This change causes the pancreas to release insulin to keep blood sugar at a higher “target” compared with people who do not have diabetes. People with MODY2 have insulin levels that are usually similar to people without diabetes.

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 heath disorders including heart disease, therefore the purpose of this study is to determine:

- Why some patients with diabetes have more insulin resistance than others
- If some parts of the body are more resistant to insulin than other parts of the body

We want to learn more about whether levels of insulin in the blood influence insulin resistance.

## 2. What will happen and how long will you be in the study?

If you decide to participate, there will be two study visits. These two study visits will be approximately 2 weeks apart. Each study visit will be at the Vanderbilt Clinical Research Center (CRC).

Visit 1: Screening visit

The first visit is to test whether you qualify to be in the study. It is also to measure some factors that influence insulin resistance in the body.

You will be asked to have nothing to eat or drink except plain water after midnight on the night before the visit. If you have T1DM, you should continue your normal insulin regimen. If you have low blood sugar while you are not eating or drinking it is okay to have 15 grams of carbohydrates to bring your blood sugar back up to normal.

Here is what will happen at Visit 1:

- 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 be given 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: a doctor will review your medical history with you. A physical exam will also be done.
- Resting metabolic rate: this test will measure chemical changes in your body which provide energy. You will lie quietly in bed with a special face tent placed over your head for 30 minutes or less.
- 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 to assure that it is safe to collect multiple blood samples. Approximately one tablespoon of blood will be taken at this first 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. He or she will lie on a table for 10-15 minutes while the machine takes measurements.
- Peripheral Arterial Tonometry: the EndoPAT test: this test measures the way the lining of your blood vessels work. This gives us a way to look for early signs of disease in the blood vessels that might lead to high blood pressure of heart disease. You will rest on your back or recline in a chair while we do this test. We will put a blood pressure cuff on your arm and a small fingertip probe on two of your fingers that allow us to measure blood vessel function without drawing blood or sticking you with a needle. After a resting period, the blood pressure cuff will be tightened for 5 minutes then rapidly releases. While the cuff is tightened, your arm may feel as though it has fallen asleep. This will resolve on its own shortly after the test is over.
- Exercise test: : We will perform a fitness test called the $VO_2$ max. You will walk on a treadmill for approximately 10-15 minutes until you are too fatigued to continue. You will wear a mouth piece and breathing device that measures air going in and out of your lungs. We will monitor the electrical tracing of your heartbeat using an EKG. At the beginning of the test, the treadmill speed will be slow and the elevation will be slight. Every 3 minutes, the speed and elevation will increase. When you become fatigued to the point you cannot keep exercising, you will put your hands on the treadmill handlebar. The speed and elevation will be reduced to a low level. You will be asked to “cool down” from this exercise for another 5-10 minutes. A doctor will be present.
- Meal: after exercising, you will be provided with a meal before going home.

Our team will contact you as soon as the results from Visit 1 are available. If you qualify, you will be asked to return for Study Visit 2 in approximately two to three weeks (rarely even sooner).

Visit 2: Insulin resistance study

The second visit will measure how effectively your body uses insulin. The test is sometimes called a "clamp study." You will return to the Clinical Research Center for an overnight visit. While at home for 3 days before the visit, we will ask you to:

- Eat only a certain number of calories each day. We will tell you this amount.
- If you have T1DM, continue your usual medication regimen.
- If you have T1DM or MODY2, we will ask you to check your glucose 8 times a day for 3 days (before the 3 meals, 2 hours after each meal, bedtime, and at 2 AM). It is possible we may ask you to wear a continuous glucose monitor instead. These numbers will be written down on a "glucose log" we will provide. Please bring this glucose log with you when you return.
- Refrain from vigorous exercise.

We will ask you to arrive in the late afternoon or early evening. You will eat a specific meal for supper in the CRC. After 10 PM you will be asked to stop eating and drinking except for water. Women will have a second urine pregnancy test. If you have T1DM or MODY2, we will place an IV (a tube for withdrawing or giving fluids) in each arm. The IV in one arm will be used to give insulin during the night to control your blood sugar. We will check your blood sugar every hour overnight to help control your blood sugar. If you are a control subject, the IVs may be placed in the morning.

After sleeping in the hospital overnight, the clamp study will begin. You will be asked to lie in bed for 8 hours except to use the bathroom. One IV will be used to give you insulin, dextrose (sugar water), saline. Two other chemicals that are in the body called hormones will also be given. They are glucagon and somatostatin. These two hormones work with insulin to keep blood sugar under control. Glucagon is also a drug used to treat low blood sugar. Somatostatin is not a Food and Drug Administration (FDA)-approved drug, but has been used for the same investigational purpose in many similar studies. Finally, we will also give labeled glucose, which we call "tracer." The labeled glucose has a "tag" attached to it that helps to tell the difference between the sugar your body makes and what we give you. This labeled sugar has no side effects at the doses you will be given. The second IV will be used to draw blood from your arm.

When we are ready to begin the study we will draw a blood sample. We will then begin infusing the tracer. After 1½ hours, we will draw blood 3 times over ½ hour. The next ½ hour is for taking a sample of muscle tissue from your leg. This is called a muscle biopsy.

Muscle biopsy

You have the option to agree to do the muscle biopsy as an additional part of this study. The purpose of the muscle biopsy is to understand the reason why some people with diabetes are resistant to insulin. Understanding what is going on inside a muscle cell in diabetes will help us design new treatments to reduce insulin resistance. Reducing insulin resistance will likely lead to improvements in heart disease in diabetes.

If you agree to do the muscle biopsy we will clean the skin on your leg. We will then give an injection of numbing medicine (lidocaine) in the skin. We will make a tiny cut (about ¼ inch) in your skin and take a sample of your muscle. We will then place a clean bandage on the wound and apply pressure for ten minutes. Finally, we will place a special bandage called Steri-Strips to close the wound.

Once the muscle biopsy period is complete, we will begin infusing the hormones used in the clamp. During this time, we will draw a small amount of blood every 5-10 minutes to measure your blood sugar. We will also give you dextrose through your IV to keep your blood sugar levels normal. After 2 hours, we will have another ½ hour blood

sampling period. Following this, a second 2 hour period will begin where more insulin will be given. We will continue giving you dextrose to keep your blood sugar levels under control. Then, there will be a final ½ hour blood sampling period. Finally, there will be a ½ hour period to take a second muscle tissue sample. After the second muscle tissue sample, we will turn off the hormones and the tracer. We will give you a meal and continue monitoring your glucose until it is stable. Once the blood sugar is stable, you can eat and then be discharged home. The total amount of blood drawn during study visit 2 is approximately 10 tablespoons.

Participants with T1DM should resume their home insulin regimen. During the evening following the study, blood glucose should be checked before dinner, bedtime, and at 2 AM. If glucose is < 120 at any of these checks, they should eat an extra 15-30 gm of glucose 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. This will help to prevent low blood sugar.

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.

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.

**3. Costs to you if you take part in this study:**

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

**4. 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 insertion of a small tube into a vein for withdrawing blood and giving medicine during Study Visits 1 and 2 can cause bruising, bleeding, discomfort, and infection. Sometimes participants may experience nausea, lightheadedness, or even faint during this procedure. We will attempt to minimize these possibilities by cleaning the skin and having you lie down or sit during this procedure.
- Lidocaine: this numbing medicine may burn or cause a rash, redness or soreness where you get the shot. There is a risk that this drug may cause problems with heart rhythm.
- DEXA scan: this research involves exposure to radiation from 1 DEXA whole body scan. 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 about 9 days of radiation from your natural surroundings.
- Exercise test: exercise can be associated with heart rate and blood pressure abnormalities, chest pain, lightheadedness, and breathing difficulty. Very rarely, it can cause heart attack and death. Patients taking insulin are at risk of low blood sugar during exercise. We will make every effort to minimize these risks. We will check your blood sugar before exercising if you have T1DM. Sugar will be given if needed. You will be monitored during the exercise test by a study doctor.
- 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 overnight before study visit 1 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 the exercise study blood sugar may become low. We will check your blood sugar before exercising and give sugar if needed to prevent a low blood sugar. You will eat a meal right after this.
  - During Visit 2 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. 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.
- Muscle biopsy: having a muscle sample taken may cause pain, soreness, or a skin infection at the biopsy site.
  - After the numbing medicine is given, you may feel some pressure or a "tugging" sensation during the procedure.
  - To prevent infection, we clean the skin and use "sterile" technique.
  - Once the numbing medicine (lidocaine) wears off, you may experience soreness that can last for up to a week.
    - You may take acetaminophen (Tylenol) as needed for pain or discomfort. **No more than 2,000 mg in a 24 hour period should be taken**.
  - Do not take a bath, swim, or use a sauna for 48 hours after the biopsy. It is okay to take a shower or sponge bath.

**5. Risks that are not known:**

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

**6. 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.

**7. 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.

**8. Other treatments you could get if you decide not to be in this study:**

If you decide not to be in the study, it will not affect your care at Vanderbilt.

**9. 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 check equal to the dollar amount below.

- Screening visit: the initial screening visit will last approximately 3 hours. Participants who complete their screening visit will be compensated $25.
- Clamp study: participants who complete the clamp study will be compensated $200.
- Muscle biopsy: subjects who participate in the muscle biopsy will be compensated an additional $100.

Some participants may be eligible for a travel allowance.

**10. 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.

**11. 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.

**12. 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 [redacted]. If you cannot reach the research staff, please page the study doctor at [redacted].

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 [redacted] or toll free at ([redacted]

**13. 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.

**14. Confidentiality:**

Only research associates in our laboratory or individuals directly involved in the study will have access to data or protected health information. Blood and muscle tissue 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.

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.

**15.** Authorization to Use/Disclose Protected Health Information

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Gregory and his study team may share the results of your study and/or non-study linked tissue samples, DEXA scan results, exercise study results, clamp study results, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, the Food and Drug Administration, or the National

Institute of Health. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

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.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Gregory in writing and let him know that you withdraw your consent. His mailing address is:

Dr. Justin M. Gregory
Division of Pediatric Endocrinology
[redacted]

At that time, we will stop getting any more data about you. But, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

**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.**

**Principal Investigator: Justin M. Gregory, M.D.** **Revision Date: 10Oct2016**
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**Institution/Hospital: Vanderbilt University Medical Center**

## 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.**

**Check one:**

- ☐ **I choose to take part in the study, including taking part in the muscle biopsy. I understand that if I wish to change my mind and not take part in the biopsy, I will notify the study team.**
- ☐ **I choose to take part in the study, but do not wish to take part in the muscle biopsy.**

| Date | Signature of patient/volunteer |
|---|---|

Consent obtained by:

| Date | Signature |
|---|---|

| Printed Name and Title | Time |
|---|---|