GLP-1 Therapy: The Role of IL-6 Signaling and Adipose Tissue Remodeling in Metabolic Response

NCT04387201

Version Date: 04/06/2023

Contact Name: Michelle Mayon
Telephone: [redacted]

UTHealth Houston
IRB NUMBER: HSC-MS-19-0787
IRB APPROVAL DATE: 04/06/2023

UTHealth Houston

CONSENT TO TAKE PART IN RESEARCH

Simple Study Title: GLP-1 and IL-6

Full Study Title: GLP-1 Therapy: The Role of IL-6 Signaling and Adipose Tissue Remodeling in Metabolic Response

Study Sponsor: National Institutes of Health – National Institute of Diabetes and Digestive and Kidney Diseases

Principal Investigator: Absalon D. Gutierrez, MD, Associate Professor, Internal Medicine/Division of Endocrinology, Diabetes and Metabolism, UTHealth

Study Contact: Michelle Mayon, Study Coordinator, [redacted]

The purpose of this study is to see if dulaglutide - a diabetes drug composed of a protein called "glucagon-like peptide-1" (GLP-1) – helps lead to the formation of "brown fat" in humans with prediabetes or at risk for prediabetes. "Brown fat" is a type of fat which lowers blood sugar and promotes weight loss. You have been invited to join this research study because you may have a clinical diagnosis of prediabetes or are at risk for prediabetes.

If you choose to participate in this study, you will be asked to take study medications, participate in radiological imaging, and undergo two small biopsies from the area above and behind your collarbone. The total amount of time you will be in this study is approximately four to six months.

There are potential risks involved with this study that are described in this document. Some known risks include nausea, diarrhea, bleeding, bruising, and mild radiation exposure. There may be potential benefits to you such as learning more about your prediabetes and/or weight status.

The only alternative to participating in this research study is to not take part in the study.

Participation in this research study is voluntary. You may choose not to take part in this research study or may choose to leave the research study at any time. Your decision will not affect the clinical care you receive at the University of Texas Health Science Center at Houston (UTHealth) or Memorial Hermann Health System.

If you are interested in participating, please continue to read below.

What is the purpose of this research study?

The purpose of this study is to see how well dulaglutide - a diabetes drug composed of a protein called "glucagon-like peptide-1" (GLP-1) - stimulates the secretion of another protein called interleukin-6 (IL-6). Together, these two proteins may lead to the formation of "brown fat" in humans with a clinical diagnosis of prediabetes or at risk for prediabetes. "Brown fat" is a type of fat, which lowers blood sugar and

promotes weight loss. This study is not being conducted for the treatment of prediabetes or obesity.

The National Institutes of Health is paying UTHealth for their work on this study.

A description of this clinical trial will be available on http://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.

Who is being asked to take part in this study?

You are being asked to take part in this research study because you have a clinical diagnosis of prediabetes or are at risk for prediabetes. This study is being conducted at UTHealth and Memorial Hermann Hospital at the Texas Medical Center. About 26 people will take part in the study in this city at UTHealth and Memorial Health System.

What will happen if I take part in this study?

If you agree and are able to take part in this study, you will undergo the following procedures:

• **Visit 1 (Screening Visit):** The purpose of this visit (which will take place in our Clinical Research Unit) is to see if you qualify for the study. You will have a complete physical examination. We will ask questions about your medical history, current illnesses, and current medications. You must not be taking any diabetes medication that can lower your blood sugar in order to qualify for this study. Tell the study staff about any medications you are taking during the study and any changes in your diet and exercise habits. This includes prescription or over-the-counter medicines and vitamins. If not already completed, we will arrange for lab testing, where you will have about 2 tablespoons of blood drawn for routine blood tests, including complete blood count, and blood chemistry including liver and kidney function tests. We will test you for pregnancy (with a urine sample) if you are a woman who can have children.

If you qualify for the study, you will be asked to briefly come to the Endocrinology Clinic at UT Physicians Professional Building (6th floor) to pick up the first study medication, which is weekly vitamin B12 ("also known as "cyanocobalamin") injections. It is not known whether the study drug itself (dulaglutide) will be of benefit. For this reason, all study participants must also receive cyanocobalamin (believed to be inactive) as a comparator. This will allow a careful comparison to study the benefits of dulaglutide. Dulaglutide and cyanocobalamin are each injected under the skin. Cyanocobalamin will be given at this time. We will review dosing and storage instructions with you. You will finish the rest of the injections at home on a weekly basis for a total of 6 weeks. After Visit 3, you will begin dulaglutide injections weekly for a total of 6 weeks(describedfurtherbelow). You and your study team will know if you are receiving cyanocobalamin or dulaglutide.

If you participate in the study, Visits 2 through 5 will each involve at least one of the following procedures:

a) Computed tomography (CT) scan: This is imaging study which uses a special kind of X-ray machine. It will send several beams simultaneously from different angles to take pictures of your anatomy. The computer processes the results, displaying them as a two-dimensional picture shown on a monitor. We will not use contrast solutions for these scans.

The CT scanner is a large machine with a hole in the middle. It looks like a donut with a table in the middle. When directed by your nurse, you will be asked to go to the bathroom (to urinate) and then lie on a partially enclosed scanning table. The table will slide into the machine. You will be asked to remain still during the scan. You will hear buzzing or clicking sounds during the scan, which will last 1-2 minutes. The size of the opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner. If you feel any anxiety over being in enclosed spaces, let your study doctor know.

b) F 18-fluorodeoxy glucose-Positron Emission Tomography (FDG-PET) Scan: This is a nuclear medicine medical imaging technique that produces a 3-D image of metabolic processes in the body. This is done in combination with a CT scan (same as the one described above). For this reason, it usually referred to as FDG-PET/CT scan. This allows images of both anatomy (CT) and metabolism (PET) to be taken during the same examination. The FDG-PET/CT scan has the benefit of combining the PET scan information about organ metabolism with the CT scan information about the size and shape of specific bodily organs. Alone, each test has its limitations but when the results of the scans are fused together they provide the most complete information on brown fat tissue function and location. You will be injected with F-18 FDG (small radioactive dose) intravenously approximately 60 minutes before the scan and then wait in a quiet room before scanning.

The PET/CT scanner is also a large machine with a hole in the middle. It looks like a donut with a table in the middle. When directed by a technologist, you will be asked to go to the bathroom (urinate) and then lie on a partially enclosed scanning table. The table will slide into the machine which is quiet. You will be asked to remain still during the scan. You will need to lie still for about 20-40 minutes before coming off of the scanning table. The size of the opening is 27 to 30 inches. How much space you feel you have around you will depend on your body size and the scanner. If you feel any anxiety over being in enclosed spaces, let your study doctor know.

c) Adipose Tissue Biopsy: Under the guidance of a CT scanner, we will use a biopsy needle to take adipose (fat) tissue from area above and behind your collarbone. This area of the body has the highest amount of brown fat.

You will be taken to a procedure room that also has a CT scanner. CT images will be taken of the lower neck, to visualize the best biopsy site. An interventional radiologist will identify the location of the brown fat via the CT images combined with the previous PET/CT images. If no brown fat is visualized, then the interventional radiologist will plan for a white fat biopsy in the same area. The skin over the area of the biopsy will be cleaned using an antiseptic solution and covered with a sterile drape. Local anesthesia (approximately 5 mL of 2% lidocaine) will be injected in the deep skin biopsy site and in the fat tissue. This injection will be advanced in the targeted fat tissue area and an additional CT scan will be performed to ensure the correct placement of the needle at the biopsy site, avoiding any nearby blood vessels. The interventional radiologist will determine the depth of the fat tissue and plan for the advancement of the biopsy needle.

Afterwards, an incision (less than 1 cm) will be made the skin using a scalpel and a 6-mm biopsy needle will be inserted through the incision and advanced into the depot of fat tissue. After proper positioning of the needle, the nurse will apply suction using a syringe and a suction catheter. The biopsy needle will be rotated to collect a sample of fat tissue, which will be about the size of a pea. Up to three attempts will

be made to obtain tissue. After procedure is completed, the radiologist or nurse will apply manual compression for 3–5 min to minimize bleeding. A small adhesive bandage will be placed over the incision, which you can remove at home the next morning. You can also shower with the bandage when you are at home. The duration of the procedure is approximately 30–40 minutes.

• **Visit 2:** This visit will take place approximately 1-10 days after last dose of study medication. You will be asked to fast (not eat or drink anything except water from midnight of that day) at home. Visit 2 must take place before Visit 3, and may be done in the morning or afternoon. Visit 2 may also be done on the same day as Visit 3 if Visit 2 is done in the morning. At approximately 8 am or 12 pm, you will check in with Nuclear Medicine at Memorial Hermann. We will test you for pregnancy (with a urine sample) if you are a woman who can have children (i.e., if pregnancy test is positive, you will not receive study medications or procedures that day). You will then change into a hospital gown. At 9 am or 1 pm, a nurse will direct you into a room with temperature controlled to approximately 72 degrees F. Vital signs will be measured and you will have one IV (small plastic catheter (tube) inserted into your vein) placed on the inside of your arm near the elbow. At 10 am or 2 pm, we will draw about 2 tablespoons of blood through this IV. This blood will be used to measure markers of inflammation, sugar, and insulin in your blood. Then you will be given an injection of a small amount of a radioactive drug/tracer (a chemical similar to sugar which is called FDG) into the IV. The amount of radiation is no more than what you would have during a whole body CT with contrast. It only stays in your body for a few hours and there are no special precaution required after the scan is completed. The FDG will travel to particular parts of your body. It travels to places where glucose is used for energy. At 11 am or 3 pm, you will be taken to separate room complete the PET-CT scan. Upon completion, we will remove the IV and provide you with a small snack. You may then leave.

• **Visit 3:** This visit will take place approximately one week after (±3 days, and after completing Visit #2) last dose of study medication. You will be asked to fast (beginning from midnight of that day) at home. At approximately 12 pm, you will check in with Interventional Radiology at Memorial Hermann. We will test you for pregnancy (with a urine sample) if you are a woman who can have children (i.e., if pregnancy test is positive, you will not receive study medications or procedures that day). You will then change into a hospital gown. At 1 pm, a nurse will direct you into a room with temperature controlled to approximately 72 degrees F. Vital signs will be measured and you will have one IV (small plastic catheter (tube) inserted into your vein) placed on the inside of your arm near the elbow. At 3 pm, you will be taken to the procedure room, which will include a CT scanner. You will have an adipose tissue biopsy, as per the procedure described above. Also as noted above, a small adhesive bandage will be placed over the biopsy site, which you can remove at home the next morning. The study team will provide you with a small snack. You may then leave.

In at least three weeks, you will be asked to briefly come to the Endocrinology Clinic at UT Physician Professional Building (6th floor) to begin the next study medication, which is dulaglutide. We will review dosing and storage instructions with you. You will finish the rest of the injections at home on a weekly basis for a total of 6 weeks.

• **Visit 4:** This visit will take place approximately 1 - 10 days after completion of study medication, with procedures identical to those described in Visit #2.

Visit 5: This visit will take place approximately one week after (±3 days, and after completing Visit #4) last dose of study medication., with procedures identical to those described in Visit #3. The only exception is that the study will be completed and no more study medication will be given.

Contact Name: Michelle Mayon
Telephone: [redacted]

How long will you be in the study?
If you agree to take part, your participation will last for four to six months and will involve five study visits.

What choices do you have other than this study?
The only alternative is not to take part in this study.

What are the risks of taking part in this study?
There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Medication
If you choose to take part in this study, there is a risk that that dulaglutide and/or cyanocobalamin (vitamin B12 injections) may not be as good as diet and exercise in treating your condition.

There is also a risk that you could have side effects from the dulaglutide. These side effects may be worse and may be different than you would get with the usual treatment.

Some of the most common side effects that the study doctors know about are:

- Nausea
- Vomiting
- Headache
- Diarrhea
- Stomach irritation

Some of the less common side effects that the study doctors know about are:

- Dizziness
- Hypoglycemia
- Injection site rash
- Nasopharyngitis
- Pancreatitis (very rare, less than 1%)

There is also a risk that you could have side effects from the cyanocobalamin (vitamin B12 injections). These side effects may be worse and may be different than you would get with the usual treatment.

Some of the most common side effects that the study doctors know about are:

- Headaches
- Mild loss of strength

Some of the less common side effects that the study doctors know about are:

- Paresthesias (numbness)
- Nausea
- Rhinitis
- Injection site redness

There may be some risks that the study doctors do not yet know about.

Study Procedures

Study procedures are completed during study visits. Each procedure has the following potential side effects:

A) Blood Draw and Catheter Insertion:

The insertion of the catheter (used to draw blood) may cause some discomfort, feeling lightheaded, fainting, bruising, clotting and bleeding from the site of the needle stick and, in rare cases, infection.

B) CT Scan:

Targeted CT scan images will be obtained during Visit #3 and Visit #5. The amount of radiation exposure you will receive at each visit is about the same as that of an intercontinental jet flight. There is might be a very slight chance of cancer from exposure to this radiation. However, this is unlikely given the small doses used in this protocol. No contrast dye will be used for these CT images. Prior to each of these visits, each female subject of childbearing potential will receive a urine pregnancy test to ensure there is no pregnancy prior to participation.

C) FDG-PET/CT Scan:

FDG-PET-CT will be obtained at Visit #3 and Visit #4. An intravenous small amount of radioactive glucose will be given one hour prior to obtaining images. Because the dose of radiotracer administered is small, there is a relatively low radiation exposure to the patient. Nuclear medicine diagnostic procedures (including PET-CT) have been used for more than three decades, and there are no known long-term adverse effects from such low-dose exposure. Allergic reactions to radiopharmaceuticals may occur but are extremely rare and are usually mild. Injection of the radiotracer may cause slight pain and redness which should rapidly resolve within a few days. As these procedures are not safe during pregnancy, a urine pregnancy test will be collected on the day of the exam (only in female subjects of childbearing potential), to ensure there is no pregnancy prior to participation.

D) Adipose Tissue Biopsies:

Per biopsy, we will obtain 100-200 mg of subcutaneous supraclavicular adipose tissue (Visit #3, Visit #5), as described above. Risks and side effects related to these biopsies are as follows:

Less likely and not serious:

- Bleeding and/or bruising and/or mild swelling at site of biopsy. As the incision is small (less than 1 cm), you will not require sutures. A small adhesive bandage will be placed over the incision, which can be removed the next morning. If there is any swelling or bruising, it usually goes away with rest after a few days, although sometimes it may take a week. The bruising is helped by using hot packs.

Rare and Serious:

- Rarely, bleeding from a subcutaneous biopsy may be severe enough to require hospitalization.

- Very rarely, some subjects may experience numbness or tingling at the biopsy site. This is usually temporary and goes away in a few days.
- There is a small risk of infection at the site of the biopsy. Infections can be usually treated effectively with oral antibiotics.
- Allergic reactions to the local anesthetic we use for the biopsy are extremely rare, but could include a skin sore, swelling, or hives.

Safety Measures:

- Furthermore, you will be instructed to inspect the wound daily, and inform the study team if you experience bleeding or worsening redness, pain, or discomfort.

As CT images will be obtained during this procedure, a urine pregnancy test will be collected on the day of the exam (only in female subjects of childbearing potential), to ensure there is no pregnancy prior to participation.

Women and Pregnancy

If you are a woman able to become pregnant, a urine pregnancy test will be done, and it must be negative before you can take part in this study. The medication, CT scans, and FDG-PET-CT scans used in this study could be harmful to an unborn baby. These interventions may hurt an unborn baby in ways we do not currently know. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for one week afterward. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for one week after you have completed the study. If you become pregnant while taking part in this study or if you have unprotected sex, you must inform the study doctor immediately.

What are the benefits to taking part in this study?

The benefits of participating in this study may be: learning more information about your pre-diabetes and/or overweight health status. Information from laboratory studies and procedures will be available when the study ends. You may also help the investigators find better alternatives for treatment and prevention of prediabetes and obesity. However, you may receive no benefit from participating.

This study may help the study doctors learn things that may help other people in the future.

Can you stop taking part in this study?

You may decide to stop taking part in the study at any time. To withdraw from the study, please contact Absalon D. Gutierrez, MD, at [redacted].

Your doctor or the sponsor can stop the study at any time. Your doctor or the sponsor may stop your participation in the study if your condition worsens, the study is stopped, the study drug is no longer available, you do not meet all the requirements of the study, or the study is not in your best interest. If your participation in the study is stopped, your doctor will discuss other options for your treatment.

If you stop participating in this study, the information already collected about you will still be used in the data analysis. However, no further information will be collected without your permission.

While taking part in this study, the study team will notify you of new information that may become available and could affect your willingness to stay in the study.

What happens if you are injured during the study?
If you suffer an injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, necessary facilities, emergency treatment, and professional services will be available to you, just as they are to the general community. You should report any such injury to Absalon D. Gutierrez, MD, at [redacted]. You will not give up any of your legal rights by signing this consent form.

What are the costs of taking part in this study?
The sponsor will pay for the special tests and examinations that are required by this study and not otherwise part of your standard medical care.

You should not receive any bills for this study. However, if you receive a bill that you believe is related to your taking part in this research study, please contact Absalon D. Gutierrez, MD, at [redacted] with any questions.

You will be paid for taking part in this research study. You will be compensated $40 for the screening visit (Visit 1), regardless of whether or not you ultimately qualify for the study. If you qualify for the complete study, you will be compensated $75 for Visit 2, $200 for Visit 3, $75 for Visit 4, and $200 for Visit 5. Your maximum potential compensation is $590. If you withdraw from study early you will be compensated for the study visits you completed.

In addition, there are also two brief appointments (after Visit 1 and after Visit 3) where you will come to the Endocrinology Clinic at UT Physician Professional Building (6th floor) to pick up the study medication. We will provide parking validation (for an approved nearby garage) for these two visits only. There is no additional compensation for these visits.

If you receive payment for taking part in this study, please be informed that you will be asked to complete a W-9 form that will be forwarded to the accounting department as a requirement by the Internal Revenue Service. You will also be issued a 1099-Misc form from this study for tax reporting purposes.

The University of Texas Health Science Center at Houston owns any data collected and the use of the data, results, treatments or inventions that can be made from the research. The University's ownership includes the right to license or transfer the use or ownership to other parties including without limitation, commercial entities contracting with UTHealth. There are no plans to compensate you for any patents or discoveries that may result from your participation in this research study. You will not be paid for any use of your data, samples, or results.

How will privacy and confidentiality be protected?
Your privacy is important and your participation in this study will be kept confidential. However, absolute confidentiality cannot be guaranteed.

If you sign this document, you give permission to UTHealth and Memorial Hermann Health System to use and disclose (release) your health information. The health information that we may use or disclose for

this research includes information in your medical record, results of physical examinations, medical history, lab tests, diagnostic tests, and biopsy results. Please understand that health information used and disclosed may include information relating to HIV infection, drug abuse, alcohol abuse, behavioral health, and psychiatric care.

Personal identifiers such as your name and medical record number will be removed from the information and samples collected in this study. After we remove all identifiers, the information or samples may be used for future research or shared with other researchers without your additional informed consent.

People who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect your health information and may share your information with others without your permission, if permitted by laws governing them. You will not be personally identified in any reports or publications that may result from this study. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

Representatives of the organizations listed below will see your name and other personal identifiers. Information released may include the dates of service/treatment, and date of birth. When they review your research records and medical records for the purposes of verifying study data:

- Representatives of UTHealth and/or Memorial Hermann Health System
- Representatives from the U.S. Food and Drug Administration (FDA)
- Representatives of the sponsor of this research including contract research organizations
- Companies engaged with the UTHealth for the commercialization of the results of the research study

Please note that you do not have to sign this Authorization, but if you do not, you may not participate in this research study. UTHealth and Memorial Hermann Health System may not withhold treatment or refuse treating you if you do not sign this Authorization.

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must contact Absalon D. Gutierrez, MD, in writing at [redacted].

This Authorization will expire 15 years after the end of the study.

Whom can you contact if you have questions about the study?

If you have questions at any time about this research study, please feel free to contact the study coordinator Michelle Mayon at [redacted], as she will be glad to answer your questions. You can contact the study team to discuss problems, report injuries, voice concerns, obtain information in addition to asking questions about the research.

The Committee for Protection of Human Subjects at the University of Texas Health Science Center has reviewed this research study. You may contact them for any questions about your rights as a research subject, and to discuss any concerns, comments, or complaints about taking part in a research study at [redacted].

Contact Name: Michelle Mayon
Telephone: [redacted]

SIGNATURES

Sign below only if you understand the information given to you about the research and you choose to take part in this research study. Make sure that all your questions have been answered. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

Printed Name of Subject	Signature of Subject	Date	Time

Printed Name of Person Obtaining Informed Consent	Signature of Person Obtaining Informed Consent	Date	Time

The Committee for Protection of Human Subjects at the University of Texas Health Science Center has reviewed this research study. You may contact them for any questions about your rights as a research subject, and to discuss any concerns, comments, or complaints about taking part in a research study at [redacted].