COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT 200 FR. 4 (2014-4)

YALE UNIVERSITY SCHOOL OF MEDICINE - YALE-NEW HAVEN HOSPITAL

Title: The Effects of Glucagon on Rates of Hepatic Mitochondrial Oxidation and Pyruvate Carboxylase Flux in Man Assessed by Positional Isotopomer NMR Tracer Analysis (PINTA)
Part 4A: The Effects of Glucagon

Principal Investigator: Kitt Falk Petersen, M.D.
Funding Source: Merck, Sharp & Dohme Corp.

Invitation to Participate and Description of Project

You are invited to participate in a clinical research trial to look at how the liver regulates sugar (glucose) and fat (lipid) metabolism in healthy people. It is the hope that these studies will help us understand how the liver of healthy people switches from burning glycogen (starch) to fat after an overnight fast and how glucagon regulates this process.

This is a test of 'normal' physiology, which will help us understand the regulation of sugar and fat metabolism by the liver and why this is altered in people with fatty liver and diabetes.

In order to decide if you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research, which a member of the research team also will discuss with you. This discussion should go over all aspects of this research: The purpose, the procedures, the risks and possible benefits. Once you understand the study, you will be asked if you wish to participate. If you decide to do so, you will be asked to sign this form.

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.

Description of Procedures: You have been invited to take part in this research because you are healthy and between 18 and 64 years old. You have completed our research study with Oral Glucose Tolerance Test and MRS measurements of liver and muscle fat content (HIC protocols 9013 and 7883) and these tests have shown that you are healthy and do not have diabetes or lipid abnormalities. You will be one of about 12 healthy persons who will be part of this study. To be part of this research, you must be in good health, non-smoking and not taking any medications other than birth control pills. You must not be pregnant during this research because of the unknown risks to the fetus. If you have kidney, liver, heart disease, diabetes or a mental illness you may not take part in this research.

The study has two parts and you will be asked if you would like to take part in both of these study parts.

Screening Visit: If you agree to be in the study, you will be asked to come to the Yale Center for Clinical Investigation – Hospital research Unit (HRU) in the Yale - New Haven Hospital for to meet with the investigators and study personnel and hear more about this research study. This visit will take about one hour.

You will be given a consent form to read and afterwards decide if you want to be come part of this research. You may take the consent form with you so you can think about it and discuss it with others before you decide if you would like to be part of this research.

If you have AIDS or are HIV positive (have the virus which causes AIDS), have hepatitis or have been in close contact with people who have AIDS or hepatitis, please let us know since this means that you may not be part of this research.

If you decide to take part in this research the study coordinator will find a date that fits your schedule for each of the two parts of the study.

I have decided to take part in:

Part 1: 12-Hour overnight fast ☐

Part 2: 12-Hour overnight fast with glucagon ☐

PART A (12-Hour Overnight Fast Study).

This part will be a test of how your body burns glucose and fat as energy in the morning after an overnight fast. You will be asked to come to the HRU at 7 AM, the study will take approximately 5 hours and you will leave the HRU in the early afternoon after a regular lunch.

Body Weight and Fat Mass: In order to measure your weight and how much body fat you have, we will weigh you on a scale, which also measures how much body fat you have. Body fat is measured with a small amount of an electrical current (bioelectrical impedance). The scale we use for this is safe and available in most stores for home use.

Liver Lipid Content: We will measure the amount of fat in your liver using an instrument called 'Fibroscan'. This test is done in your room in the HRU. After a small amount of gel is spread on the right side of your abdomen over the liver an ultrasound head (probe) will be placed on this part of your abdomen and moved around in circles while a small amount of ultrasound is given through the probe. The ultrasound bounces off your liver and sends a signal back to the computer, which then can calculate the amount of fat in your liver. This test is commonly used in clinics and hospitals to detect and measure liver fat. The test in not using any radioactivity and is safe and painless and will take about 10 min.

We will place two IV lines (tube or catheter) into a vein in your arm and one in your hand. This will allow us to infuse the study substances into the IV line in your arm and draw small amounts of blood from the IV line in your hand during the test.

Part A1: In this study we can measure how much glucose your liver makes from lactate and how much fat your liver burns for energy. During the study we will give small amounts of glucose, lactate and beta-hydroxybutyrate (BHB) into the IV line in your arm. These are normally present in your bloodstream and are part of the body

energy sources. The small amounts of glucose, lactate and BHB we give have a 'tag' on them so we can measure them in the blood sample we collect from the IV line in your hand. The 'tags' we use are stable, non-radioactive isotopes called deuterium (1H) and carbon-13 (13C).

Part 2: In this part of the study we will add an infusion of a small amount of the hormone glucagon in the IV line in your arm. Glucagon is a hormone, which normally is present in your blood stream, which helps the liver produce glucose by breaking down the glycogen (starch) depot in the liver during a normal overnight fast. Glucagon also increases the amount of fat used (or burned) by the liver. In this study we will measure how much fat is being burned when we raise you blood glucagon levels.

Indirect Calorimetry: During the study we will check how many calories your body uses. This is done while you have a large plastic hood over your head. The hood is made of clear plastic and it has fresh air coming into it. The hood collects the air you breathe out, sends it to a computer, and the computer calculates how many calories you use. This calorimetry test takes about 15 to 20 minutes. If you feel uncomfortable or anxious during the calorimetry we will stop this test.

At the end of the 3 hour study infusions after the final blood draws the infusions will be stopped, the IV lines will be removed and you will be given a regular lunch. After lunch you can leave as soon as you are ready.
The total amount of blood we will draw during each study will be about 100 mL or 7 tablespoons. This part of the study will take approximately a total of 7 hours. During this test you will be in a bed and you may read, sleep or watch TV.

Risks and Inconveniences:
The risks of being part of this study include those related to a glucagon infusion, IV lines and blood drawing.
If you are pregnant or breast feeding, you cannot be part of this study. You will be tested for pregnancy before the each study part and the pregnancy test must be negative (show that you are not pregnant).

Body Fat: The bioelectrical impedance used to measure body fat is a weak current, which is considered safe. Scales using this technique are available for home use.

Liver Fat: The small amount of ultrasound used to measure liver fat is considered safe and is commonly used in clinics and hospitals to quickly and safely measure and monitor liver fat content in people.

Blood draws and IVs: Risks of blood draw and IV lines (tube or catheter) in arm veins are small. Other than the needle stick this is painless. You may get some black or blueness in the skin where the IV was sitting. Very rarely, the vein may become infected or you may get a bruise; this is not dangerous and it will go away by itself or when you wrap a warm towel around the arm for a few hours. Infections can be treated with antibiotics. The total amount of blood that will be drawn for this study during both Part 1 and Part 2 is about 14 tablespoons (or 200

mL), which is less than half of a typical blood donation. You cannot donate blood for two months before you start or after the end of the study.

Deuterium and carbon 13-labeled (2H/13C) compounds: Deuterium and carbon 13 are natural, stable (non-radioactive) forms of hydrogen and carbon that are normally present in your body and there are no side effects or dangers with the small amounts of these stable isotopes that you will be given in this research study. The glucose, lactate and ketone given during the infusion are natural sugars, milk acid and fats that are also normally present in your body.

Glucagon: This is hormone, which is normally present in the blood. Glucagon works to stimulate the liver to break down the liver glycogen stores and make glucose from this glycogen. Glucagon also speeds up fat oxidation (fat burning) in the liver and may help lower liver fat in people who have fatty liver. In this study we will measure how much fat the liver is using when we give small amount of glucagon. The amount of glucagon you be given in this research in Part A2 is very small and will not cause you any discomfort. Your blood glucose levels will increase like you were eating a regular meal.

Indirect Calorimetry: There are no side effects of indirect calorimetry. Very rarely, some individuals may feel claustrophobic (fearful and anxious about being in an enclosed space). If this happens to you, the test will be stopped immediately.

Problems and side effects, which are not known at this time, could occur. You will be told of any changes in the way the study will be done and of any newly identified risks in this research.

Benefits: This study will not be of direct benefit to you. You will, however, learn about your body composition during this study. We expect that this research will help us understand how glucagon regulates how the liver switches from burning glycogen (starch) to fat. This is important since people with fatty liver and diabetes may have alterations in the way the liver handles sugar and fat. The benefits for the US population are potentially large.

Economic Considerations: The costs of all tests, HRU visits, examinations and medical care that are part of the study will be free to you. You will be paid $200 for Part 1 (Overnight Fast) and $200 for Part 2 (Overnight Fast with Glucagon). You will be paid a stipend for your participation in the study up to a total of $400 if you complete both Parts 1 and 2. If you do not complete the study, you will be paid only for the part you do complete, either $200 for Part 1, or $200 for Part 2. If you do participate in the Overnight Fast, you will also receive a stipend in the form of a parking voucher valued at $4.50 for each Overnight Fast that you participate in, to cover your costs for parking while you are at the study site. You will receive payment by means of a check. You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

In addition to the stipends above, you will be provided with a meal following completion of each Overnight Fast.

Confidentiality: Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. In order to safeguard of your information, we use coding of your personal information, samples and study data are coded and our research materials are stored in locked cabinets and on password-protected computers. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by Merck, Sharp & Dome Company, Inc, which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, phone number, social security number and address. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the principle investigator and selected members of the research team. Any information that can identify you will remain confidential. In order to safeguard of your information, we use coding of your personal information, samples and study data are coded and our research materials are stored in locked cabinets and on password-protected computers. The research team will only give this coded information to others to carry out this research study. The link to your personal information will be kept for indefinitely.

The information about your health that will be collected in this study includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this study.
- The entire research record and any medical records held by YNHH created from: 2015 until the study ends.
- Records about phone calls made as part of this research
- Records about your study visits
- Physical exams
- Laboratory test results
- Diaries and questionnaires
- Records about the study drugs (natural isotopes) you received

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The U.S. Food and Drug Administration (FDA) - This is done so that the FDA can review information about the glucagon involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments.
- The Principal Investigator Dr. Kitt Falk Petersen.
- The study sponsor; Merck, Sharp & Dohme Corp.
- Health care providers who provide services to you in connection with this study.
- Co-Investigators and other investigators
- Study coordinator and members of the research team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study: List any separate or local committees not in the protocol, if applicable

Investigator Interest

Dr. Gerald Shulman, co-investigator on this study, has received compensation from the study sponsor, Merck Pharmaceuticals, for consulting services. You may speak with Dr. Shulman at any time regarding this interest.

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Hospital Research Unit (HRU) is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. This authorization to use and disclose your health information collected during your participation in this study will never expire.

In Case of Injury: This study is very safe and it is very unlikely that you will be hurt during this research. If you are hurt or injured during this research, you will be given the medical care that you may need, but you or your insurance company will be billed for the cost of this treatment. No financial compensation is available. You do not give up any of your legal rights by signing this form. Contact Dr. Kitt Falk Petersen, MD, Phone 203-785-5447.

Voluntary participation: Participating in this study is voluntary. You are free to choose not to participate. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). If you do become a subject you are free to withdraw from this study at any time during its course. However, you will not be able to enroll in this study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. it will not harm your relationship with your own doctors or Yale-New Haven Hospital. The study doctors may remove you from the study if they believe it is in your best interest.

Withdrawing Your Authorization to Use and Disclose Your Health Information:

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Kitt Falk Petersen, Yale University School of Medicine, Department of Internal Medicine, 333 Cedar Street, PO Box 208020, New Haven, CT 06520-8020. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions: Please take time to read this form and make sure you understand it. Feel free to ask any questions you may have. Your signature below indicates that you have read the above explanation of the procedure, that you give your voluntary consent to participate and that you have received a copy of the consent form.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

_____
Signature

_____
Date

_____
Signature of Principal investigator Telephone

or

_____
Signature of Person obtaining consent Telephone

If you have further questions about this project or if you have research-related problems, you may contact the study doctor Kitt Falk Petersen, M.D., Phone 203-737-6001. If you have any questions about your rights as a research subject, you may contact the Human Investigation Committee at telephone 203-785-4688.