# CONSENT FORM
# (Revised April 8, 2014)
## Measurement of Glucose/Glycogen Metabolism in Humans Using Magnetic Resonance at 4 or 7 Tesla

You are invited to participate in a protocol designed to investigate the effects of diabetes mellitus and high blood insulin on the brain, heart and skeletal muscle using magnetic resonance. Some participants will also be asked to be part of a teaching program designed to prepare people for protocols done in a magnetic resonance scanner. You were selected as a possible participant because you are healthy, are not pregnant and you have no known medical disease and therefore your glucose metabolism will be typical of a normal person. Alternatively, you may have been asked to participate because you have diabetes.

We ask that you read this form and ask any questions you may have before agreeing to be in the protocol. This protocol is being conducted by:


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**Background Information**:

The blood sugar called glucose is a major fuel for most organs in the human body, particularly the brain. How and where the body uses glucose is regulated by a number of hormones, for instance insulin and glucagon, which regulate how glucose is stored in tissues as glycogen. In a number of diseases, in particular diabetes mellitus, the glucose supply to the brain may be different than in normal subjects and brain glycogen metabolism may be deranged, which may be a cause for reduced awareness of low blood sugar.

The purpose of this protocol is to determine the effects of altered glucose metabolism on the brain. For example, patients with long duration diabetes mellitus lose their ability to secrete the hormones necessary to protect them against hypoglycemia (low blood sugar), which may be due to alterations in glucose availability to the human brain.

To measure these effects, we will use intravenous infusions of glucose and insulin (both of which occur naturally and are made by your body) and a magnetic resonance 4 Tesla or 7 Tesla scanner.

**How the Protocol is Performed:**

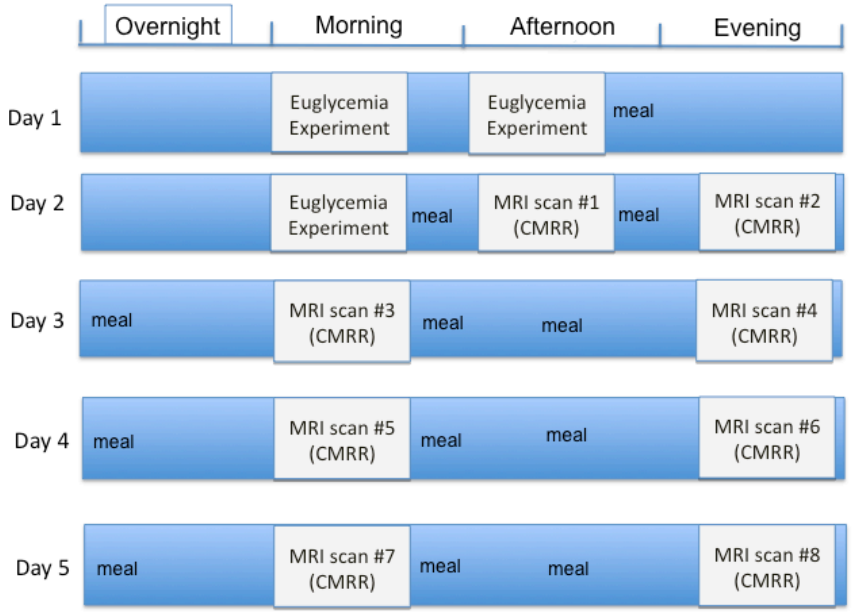
If you agree to participate, you will be asked to come to the Center for Magnetic Resonance Research (CMRR) for a tour of the facility in the days before the actual experiment. While at the CMRR, one of the investigators will talk with you about the protocol and provide you with information about magnetic resonance scanning.

Before participating in the protocol we will ask you not to use cigarettes, alcohol, or caffeine for at least 8 hours before the start time of the visit. In addition you will be asked not to engage in heavy exercise or strenuous physical activity 24 hours prior to testing. All subjects will be asked to fast for a minimum of 8 hours before arriving at the center on Days 1 and 2. Healthy volunteers will be asked to participate in the protocol up to 5 days, and volunteers with diabetes will be asked to participate up to 4 days.

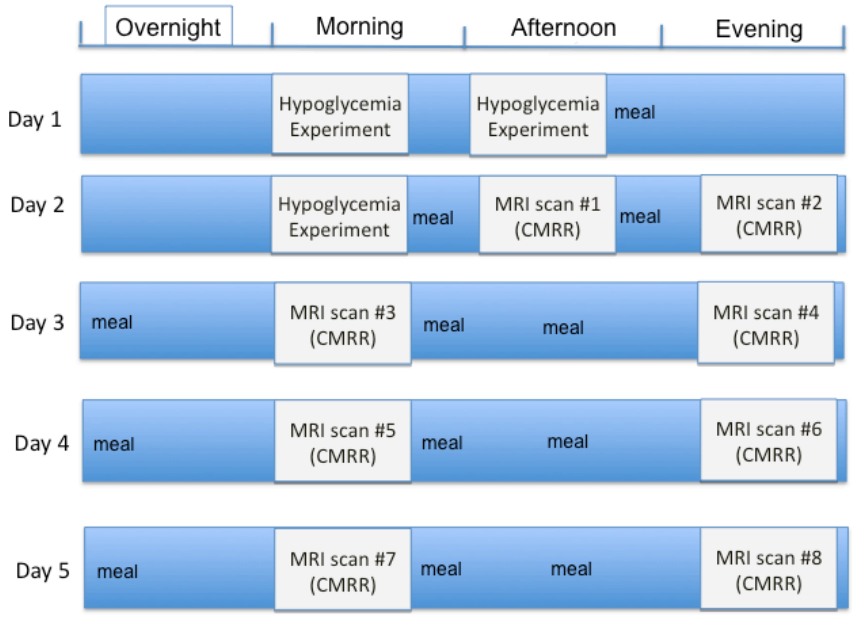
**Healthy controls**

If you are a healthy control you will first be asked to participate in 3 experiments involving either episodes of or euglycemia (normal blood glucose – Protocol A in the Figure) hypoglycemia (low blood glucose – Protocol B in the Figure). These experiments will be done over 2 days. You will be asked to participate in both protocols A and B as illustrated in the Figure The protocols will be separated by minimum of 6 weeks. From the day before each protocol starts until the conclusion of each protocol, we will ask you to avoid strenuous exercise. On the days 1 and 2 you will be asked to not eat anything after midnight. Both protocols will be done at the Masonic Clinical Research Center (MCRU) and CMRR.

**Protocol A (to be done 6+ weeks before or after Protocol B):**




**Protocol B (to be done 6+ weeks before or after Protocol A):**



On day 1 for each protocol you will arrive at the MCRU at 7 AM. On Day 1 in the Protocol A you will undergo two 120 minutes experiments in which blood glucose will be maintained in the normal range. In Protocol B, there will be two 120 minutes experiments of hypoglycemia on day 1. To prepare for each protocol, a small intravenous catheter will be placed in your arm for infusion of insulin, potassium and glucose. Insulin is a hormone that your body makes naturally and it causes your blood sugar to decrease. Glucose is a sugar and it is used to carefully regulate your blood sugar level and to ensure that your blood sugar level does not go too low. Potassium is a salt-like substance that is present in the blood. A second catheter will be placed in your other arm for venous blood sampling. This arm will be wrapped in a heating pad to ensure adequate blood flow and accurate laboratory results. Blood will be drawn every 5 minutes for measurement of glucose and other hormones. Insulin and glucose will be infused in calculated doses to maintain your blood sugar level in the target range. At the end of the euglycemic/hypoglycemic experiment all infusions will be discontinued and the blood sugar level allowed to normalize. At this time you will be given a meal and when the blood glucose returns to normal you will be allowed to go home.

On day 2, you will again arrive at the MCRU at 7 AM and the same protocol will be followed as in the morning on day 1. On day 2 there will be one 120 minute experiment of euglycemia in protocol A and one 120 minute experiment of hypoglycemia in protocol B. After arriving, a small intravenous catheter will be placed in your arm for infusion of insulin, potassium and glucose. A second catheter will be placed in your other arm for venous blood sampling. This arm will be wrapped in heating pad to ensure adequate blood flow and accurate laboratory results. Blood will be drawn every 5 minutes for measurement of glucose and other hormones. Insulin and glucose will be infused in calculated doses to maintain your blood sugar level in the target range. At the end of the euglycemic/hypoglycemic experiment all infusions will be discontinued and the blood sugar level allowed to normalize. You will then be given a small dose of glucose enriched with $^{13}C$ label via the catheter. This infusion will continue until the evening of day 5 and is necessary for us to measure how your brain is using glucose. Small plastic catheters will remain in two veins in your arms for infusion of glucose and for measuring your blood glucose levels every 15-120 minutes. During the protocol we will also ask you to give a urine sample every 1-4 hours. The urine sample and some of the blood samples will be saved for studies of metabolism without any information that identifies the samples as yours. You will spend most of your time in a hospital bed, but will be allowed to use the restroom and walk around briefly. Meals will be provided throughout each day as shown in the Figure, but will be very low carbohydrate in order to minimize your own insulin release. Snacks without carbohydrate will also be available. IV catheters will be kept in place from the start of day 2 until the end of the protocol on day 5.

Starting on day 2 in each protocol, you will be asked to transfer to the Center for Magnetic Resonance Research twice a day. On day 2 the transfer will be in the afternoon and the evening. On days 3, 4, and 5 transfer will be in the mornings and evenings. At the CMRR you will be asked each time to conduct an MRI scan as follows: You will be placed on the patient bed in the magnet room for one-to-two hours. A nurse or researcher will stay with you at all times during this protocol. When the scan is completed you will be transferred back to your hospital room in the MCRU. After the final scan on day 5, the infusions will be stopped, the catheters will be removed, and you will be fed a normal meal.

You may also be asked several days prior to the protocol to report to the Clinical Research Center for a "mock" protocol to see if you are comfortable with the MRI scan and/or to test your body’s response to either protocol (as described above, but carried out at the Clinical Research Center). If you would like to try the MRI procedure in advance, this test will not exceed 2 hours. If we need to test your body's response to the infusion, this “pre-test” will involve only drawing blood and administering glucose and will be performed as described for either protocol above, but will last not more than 4 hours.

Magnetic resonance measurements performed in the magnet are very similar to magnetic resonance imaging exams used for diagnosis. The researcher will be watching you at all times. You will be given a bulb to hold during the measurements, by squeezing the bulb, you can signal the researcher if you want to stop. The magnetic resonance measurements will be associated with regular loud clunking noises that you may find unpleasant. For your comfort, you will be given ear protection to wear while lying in the scanner.

The MRI scan being done is designed to answer research questions, not for diagnosis of a medical condition. The research MRI scan is not a substitute for one a doctor would order for diagnostic imaging. It may not show problems that would be picked up by a clinical MRI scan. However, if we believe that we may have found a medical problem in your MRI scan, we will ask a doctor who is trained in the reading of MRI scans (a radiologist) to help us review the scan. If the radiologist thinks there may be an abnormality in your MRI scan, we will contact you and, with your permission, help you contact a doctor to obtain medical follow-up.

The researchers will give you a questionnaire to complete after the protocol. This should take no more than 5 minutes to complete.

**Participants with diabetes**

Participants with diabetes will start the protocol in the MCRU on the afternoon of Day 2 and only participate in one 5 day protocol. Participants with diabetes will not undergo the euglycemic/hypoglycemic experiment on days 1 and 2, but will only do the MRI scans on days 2-5, The researcher will advise you on how to adjust your insulin regimen during the 1-2 days before the protocol starts so your blood sugar is in good control when you arrive at the MCRU. After arrival, an IV will be placed in each of your arms. This will allow for giving insulin, glucose and potassium during the test. This catheter will also allow us to collect blood during the test. You will then be given a small dose of glucose enriched with $^{13}C$ label via the catheter. This infusion will continue until after the last MRI scan on day 5 and is necessary for us to measure how your brain is using glucose. Small plastic catheters will remain in two veins in your arms for infusion of glucose and for measuring your blood glucose levels every 15-120 minutes. During the protocol we will also ask you to give a urine sample every 1-4 hours. The urine sample and some of the blood samples will be saved for studies of metabolism without any information that identifies the samples as yours. You will spend most of your time in a hospital bed, but will be allowed to use the restroom and walk around briefly. Meals will be provided throughout each day as shown in the Figure, but will be very low carbohydrate. Snacks without carbohydrate will also be available. IV catheters will be kept in place from the start of day 2 until the end of the protocol on day 5.

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The researchers will give you a questionnaire to complete after the protocol. This should take no more than 5 minutes to complete.

**Potential Risks and Benefits:**

The protocol has several risks:

1. Magnetic field: Magnetic resonance examinations have become a routine tool in today's medical diagnosis. Based on more than a decade of experience with these devices, appropriate guidelines exist for these exams:

We have taken measures to eliminate the potential risk of the danger of magnetic objects being attracted by the magnet. We have elaborate procedures to make sure that no one brings anything magnetic into the room. Another potential risk is presented by the radio waves used. However, these will be applied according to guidelines set forth by the Food and Drug Administration (FDA). The magnet we will use has a static field strength that is several times that used for clinical exams. There is a risk of unknown effects related to participation in 4 or 7 Tesla MRI research. Long term effects of exposure to high magnetic fields are unknown. Short term most people experience no ill effects from the strong magnetic field, but some people report dizziness, mild nausea, headache, a metallic taste in their mouth, or sensations of flashing lights. These symptoms, if present, subside shortly after leaving the magnet. If any sensations experienced during participation cause discomfort or pain, notify the researcher right away and your participation will stop and you will be taken out of the magnetic field.

2. Infusions/blood drawing: Occasionally individuals may have some bruises afterwards where the catheter was inserted. Rarely an individual may experience inflammation of the vein (phlebitis) but this usually goes away with local heat and elevation of the extremity. We would not wish to you to participate in the protocol if you have given or expect to give a similar amount of blood in the month before or after the clamp. We will draw at most 7 oz. of blood (approximately 200 ml). Infusion of insulin (a hormone made naturally by the human body) produces no side effects other than the potential risk of low blood sugar, which we will avoid as described below.

3. Hypoglycemia (low blood sugar): Symptoms of hypoglycemia may occur when your blood sugar falls below 60 mg/dl and include sweating, shakiness, confusion, increased heartbeat and feeling "low". It is reversed within minutes by stopping the insulin infusion and by raising your body sugar by increasing the glucose infusion. If the blood sugar drops very low (lower than the level at which we will perform the protocol), seizures or abnormalities in heart rhythm can occur. To be certain that your blood sugar level does not drop too low, we will check your blood every five minutes during insulin infusion

and adjust the amount of sugar we give you by vein to keep your blood sugar at the correct level. With such careful monitoring, it is very unlikely that you will develop a blood sugar low enough to make you feel ill. Your blood sugar will be regulated to be in the normal range or higher during the magnet protocol.

4. $^{13}$C glucose: The stable isotope $^{13}$C is naturally present in your body and $^{13}$C glucose in its pure form has no known side effects different from that of regular glucose. This isotope is not radioactive. We have carefully established procedures to minimize the risk of impurities in the glucose infused. We will infuse glucose enriched with this isotope, which we will then measure using the magnet.

5. Urine collection: Some people find it difficult to provide a urine sample into a collection vessel. To make this as easy as possible for you, you will be given privacy during the collection.

**Potential Benefits:**

There are no direct benefits of participation to you other than the satisfaction you may have in helping us answer important as yet unanswered questions about human glucose metabolism.

**Alternatives to Participating in the Protocol:**

You do not have to participate in this protocol.

**Research Related Injury:**

In the event this research activity results in injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the protocol physicians know right away.

**Protocol Costs/Compensation:**

You will be paid $250 to help cover travel expenses and time lost from work for each day of the protocol. Subjects participating in a series of experiments over more than one day will be paid an additional $50 at the completion of the protocol. If you would like to test your comfort level with the MRI scan several days prior to the protocol, you will be reimbursed separately for this scan at a rate of $15/hour spent for the whole procedure.

**Confidentiality:**
The records of this protocol will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a subject. Your record for the protocol may, however, be reviewed by representatives of the Food and Drug Administration and by departments at the University with appropriate regulatory oversight. To that extent, confidentiality isn't absolute. Protocol data will be encrypted according to current University policy for protection of confidentiality.

**Voluntary Nature of the protocol:**

Participation in this protocol is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University or the CMRR. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

**New Information:**

If during the course of this research protocol there are significant new findings discovered which might influence your willingness to continue, the researchers will inform you of those developments.

**Notification of Significant New Findings:**

Personnel in the Center for Magnetic Resonance Research (CMRR), the site where you are participating in MRI research, maintain a list of the names and contact information of all participants included in research at this facility. This information is required and will be used by CMRR to notify participants of significant new information about the effects of MR on human health that develop over the course of MRI research. Participant's identifying information is stored securely and it is maintained in a confidential manner by persons with oversight of research conducted at the CMRR.

**Incidental Findings:**

The images or pictures created during this protocol are for research purposes only and are not intended to provide health care to you. However, if the results from the magnetic resonance imaging show something unusual in the pictures, a Radiologist trained in reading the pictures will look at them. The pictures will not contain any personal information except your age and pertinent medical history collected as part of the research. There will be no charge to you for having the Radiologist look at your pictures. The investigator will contact you if the recommendation of the Radiologist is to further investigate the unusual results of the pictures with your own physician. However, further medical follow up is not a part of this protocol and the protocol does not have funds set aside for this purpose. Therefore, if the results do show something unusual, any medical follow up cost will be your responsibility and/or the responsibility of your health insurance carrier.

**Contacts and Questions:**

The researchers conducting this protocol are Drs. Elizabeth R. Seaquist and Gulin Oz. You may ask any questions you have now. If you have any questions later, **you are encouraged** to contact them at (612) 626-4833 (E.R.S.), or (612) 625-7897 (G.O.)
If you have any questions or concerns regarding the protocol and would like to talk to someone other than the researchers, **you are encouraged** to contact Research Subjects' Advocate Line, D528 Mayo, 420 Delaware St. Southeast, Minneapolis, Minnesota 55455; (612) 625-1650.

**Statement of Consent:**

I have read the above information. I have asked questions and have received answers. I consent to participate in the protocol.

You will be given a copy of this form to keep for your records.

Signature: _____ Date: _____

Signature of Investigator: _____ Date: _____

**Statement of Consent for storage of blood and urine samples**

I agree that the investigators may store samples of my blood and urine for the protocol of metabolism and understand that they will be stored without any information that would identify the samples as mine.

Signature: _____ Date: _____

I do not want the investigators to store my samples.

Signature: _____ Date: _____