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MUGGLE

Stimulated glucagon as a biomarker of hypoglycaemia risk in Type 1 diabetes

A research project helping scientists to understand whether a simple blood glucagon measure could be a useful marker of hypoglycemia risk in Type 1 diabetes

Could you spare some time to help researchers better understand whether blood glucagon measurement helps predict risk of hypoglycaemia in people with diabetes?

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Chief Investigator: Professor Richard Oram

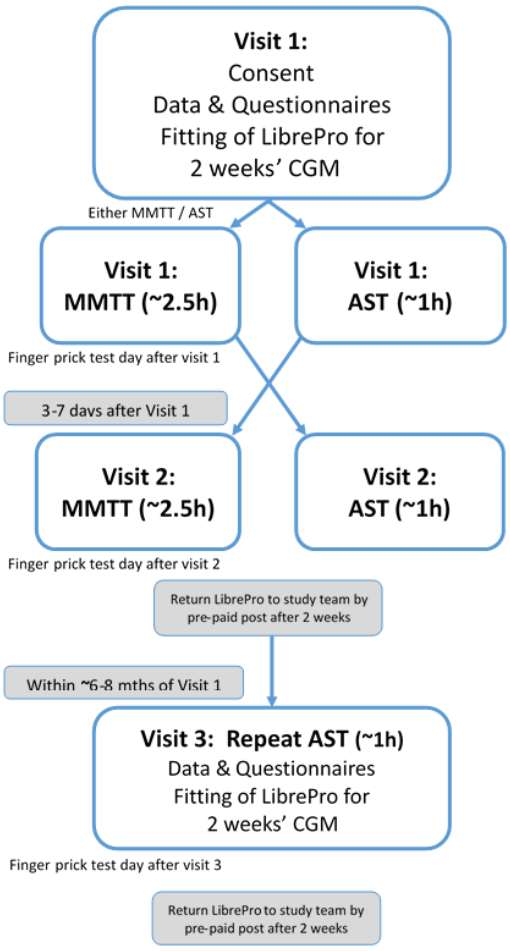
Why are we doing this research?

Normally blood glucose (sugar) levels are controlled by insulin, a hormone that lowers high blood glucose levels, and glucagon which is released into the blood to raise glucose when levels are low. For people with Type 1 diabetes (T1D), taking insulin medication to lower glucose levels, delayed meals and exercise can all result in dangerously low blood sugar levels (hypoglycaemia). The ability to release glucagon and correct blood glucose can vary, particularly in people who have had Type 1 diabetes for years. For some people, glucagon levels may not be able to rise quickly, reflecting an impairment in glucagon production.

The aim of this study is to find out how blood glucagon levels (after a stimulus) compare to a person's own experience of hypoglycaemia, and hypoglycaemia as measured by flash glucose monitoring in T1D. We hope this research will establish whether glucagon measured after a meal could be used as a blood marker of hypoglycemia risk and help to identify individuals at high risk, potentially identifying some people who could benefit from treatments targeting glucagon.

Why have I been invited?

You have been invited into this study because you have been diagnosed with T1D and have had your insulin production assessed as part of a previous research project (the TIGI study) or during routine care.



What does participation involve?

You will be invited to the NIHR Exeter Clinical Research Facility (Exeter CRF) for three morning visits over approximately 6 months. The first two visits will be a few days apart, with the third visit approximately 6-8 months later. Each visit will take up to 2 or 4 hours, depending on the visit type and test performed. You will have your visit type explained in advance so that you know what to expect. You will be asked to sign a consent form at the first visit to say you are happy to take part in the study and for your blood samples to be used for research purposes (please see the back page of this leaflet for the consent statements you will be asked).

We will ask you to fast overnight (nothing to eat or drink, except water for at least 10 hours before your appointment time) before each visit and will advise you about your insulin dosing. We will ask you some questions about your diabetes and health and measure your height and weight. At each visit, we will insert a small cannula (thin plastic tube) into your arm to make the collection of blood samples more comfortable. Samples will be collected at specific times to measure your body's own insulin and glucagon production and other factors associated with T1D (e.g. immune system) before (fasting samples) and after food/ stimulation. We will provide kits for you to collect a finger prick blood sample at home (similar to a routine finger prick glucose test) the day after each visit and return it to our Exeter lab using the prepaid envelope provided. These optional samples will help to establish if home blood spot C-peptide measurement is a practical alternative to MMTT and could be an indicator of risk of hypoglycaemia.

During Visits 1 and 3, you will be fitted with a Libre Pro device (https://www.freestyle.abbott/in-en/products/freestyle-libre-pro.html) for 2 weeks of continual glucose monitoring (CGM) and will be given training and advice for this.

Visits 1 & 2 tests: The test undertaken at Visit 1 will mean you will have the other test at Visit 2.

Mixed Meal Tolerance Test (MMTT): involves a liquid meal (a bit like a milkshake) with samples collected before this is given and then at 30 minute intervals over the next 2 hours.
Arginine Stimulation Test (AST): you will be given a small amount of a natural amino acid called Arginine (via a cannula in your non-sampling arm) which stimulates glucagon secretion (release). Samples will be collected before this is given and then at 6 specific intervals over the next 30 minutes.

Visit 3 test: this will be either a shorter 'Light MMTT' (approx 1.5h) involving fewer sample time points, or a repeat AST. The results from Visits 1 and 2 will inform which test you will have.

At the end of each visit, we will provide a light meal and make sure you are comfortable before going home.

Please see the flowchart opposite for more information about your appointments.

Are there any risks or benefits in taking part?

Donation of blood samples can be uncomfortable but an experienced nurse / researcher will perform this procedure to minimise any discomfort and will monitor you closely and regularly check your glucose levels throughout the whole procedure. The project gives insights into risk level of hypoglycaemia but won't change your treatment. However, if we unexpectedly identify anything that could impact on your clinical care, we will inform your clinician/GP who may then want to follow this up with you.

Study Visit Flowchart

What will happen during my research appointments?

VISITS	What does this involve?	Are there any risks?
VISIT 1 at the Exeter CRF **Give consent to participate** **20-30 mins**	To minimise risk of COVID-19 infection to participants, the research team will follow local NHS Trust policy and procedures based on the current UK government guidance. A member of the study research team will discuss the study with you and answer any questions both in advance and during the visit. We will ask you to fast overnight (nothing to eat or drink, except water for at least 10 hours before your appointment time) before each visit and will advise about your insulin dosing. If you are willing to take part, you will be asked to sign a consent form. You will then be asked some questions about your general health, medical history and diabetes, and your height and weight will be measured. We may need to contact your clinician/GP to verify information about your health/ treatment. You will be fitted with a Libre Pro device for 2 weeks of continual glucose monitoring (CGM) and given training and advice for this.	No. Participation is entirely voluntary and it is up to you whether to join the study and you can withdraw at any time without giving a reason and without affecting your legal rights. We have provided you with as much information as possible to help you to make an informed decision about taking part or not, and your right to withdraw.
VISITS 1 & 2 at the Exeter CRF within 5 days of Visit 1. **VISIT 3** at the Exeter CRF within 8 months of Visit 1	The first two visits will be a few days apart, with the third visit approx 6 months later. The visit types are: a Mixed Meal Tolerance Test (MMTT) and an Arginine Stimulation Test (AST) – see below for more detail. You will have your visit type explained in advance so that you know what to expect. **If** Visit 1 is the MMTT test, Visit 2 will be the AST test. **If** Visit 1 is the AST test, Visit 2 will be the MMTT test. Visit 3 will be a repeat AST. We will provide kits for you to collect a finger prick blood sample at home the day after each visit and return to our Exeter lab using the prepaid envelope provided. This test is similar to a routine finger prick glucose test and is optional.	See below.
Mixed Meal Tolerance Test (MMTT) **Approx 2.5 hours** **At VISIT 1 <u>OR</u> 2**	This is a test to assess how much insulin and glucagon the body can make and how well the body responds to these hormones. The test is carried out by placing a small cannula (thin plastic tube) into one arm for the duration of the test to collect blood samples before the liquid meal 'milkshake' is consumed and then every 30 minutes afterwards for 2 hours. The exact number of blood samples may vary but the total amount of blood we will take over your visit will not exceed 150 millilitres (ml).	There may be slight discomfort and bruising from the insertion of the cannula(s) into the vein. These risks will be minimised by the procedures being performed by a qualified research nurse who will monitor you closely and regularly check your glucose levels throughout the whole procedure.

VISITS (continued)	**What does this involve?**	**Are there any risks?**
Arginine Stimulation Test (AST) **Approx 1 hour** **At VISIT 1 <u>OR</u> 2** **& VISIT 3**	This is a test to assess how much insulin and glucagon the body can make when fully stimulated and how well the body responds to these hormones. The test is carried out by placing a small cannula (thin plastic tube) into each arm for the duration of the test which minimises discomfort. One cannula is used to give the Arginine (a natural amino acid); the other is used to collect blood samples from the opposite arm before and after the Arginine is given. Samples post Arginine are collected at 6 specific intervals during the following 30 minutes. The exact number of blood samples may vary but the total amount of blood we will take over your visit will not exceed 150 millilitres (ml).	There may be slight discomfort and bruising from the insertion of the cannula(s) into the vein. These risks will be minimised by the procedures being performed by a qualified research nurse who will monitor you closely and regularly check your glucose levels throughout the whole procedure.
Refreshments	At the end of your appointment, we will provide you with something to eat and drink* and ensure that you are comfortable before leaving the Exeter Clinical Research Facility. *We can provide a range of options. However, if you have any special dietary needs, please discuss this with a member of the research team prior to your visit.	None.

What will happen to my samples?

Your samples will be divided into clinical and stored research samples. Your clinical samples will be sent for testing of HbA1c, insulin (C-Peptide) and glucose at the Exeter Clinical Laboratories at the Royal Devon & Exeter (RD&E) Hospital, following NHS laboratory requirements with three forms of identifiable information (name, DOB, NHS/CHI/hospital number) to ensure correct processing. Your HbA1c result will be made available to your clinician and/or GP, for your ongoing medical management.

We will conduct analyses of glucose, glucagon, insulin, and other biomarkers on stored research samples to study the function of your immune system and other factors that may play a role in the development of Type 1 diabetes. Research samples will be stored in the Exeter CRF and analysed using a unique study ID to protect your confidentiality. Surplus samples will be stored in the Exeter CRF for the duration of the study, after which they will be destroyed unless you consent to gift them to the Peninsula Research Bank (PRB), in which case they may be stored indefinitely for use in future research.

How will my information be kept confidential?

We will follow current ethical and legal practice and all information about you will be handled in confidence. The University of Exeter is the sponsor for this study. We will use information collected from you and from your medical records to undertake this research and will act as the 'data controllers' for this study. This means that we are responsible for looking after your information and using it properly. All information collected in this study will be kept strictly confidential and stored at the NIHR Exeter Clinical Research Facility on a secure password-protected study database held on an NHS server with NHS Firewall and back-up, and/or in a locked cabinet, and can only be accessed by the research team. You will be allocated a unique participant number to ensure your information will be protected and cannot be identified outside of the research team. Any personally identifiable information will be stored separately and securely from information obtained from the research. The University of Exeter will keep identifiable information about you for 15 years after the study ends to link information from your medical records to your study data unless you ask for this information to be deleted before that time. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. This information will include your name, date of birth, NHS number, and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

General Data Protection Regulation ('GDPR') and your rights

This information sheet gives you information that you have a right to receive under changes in the law. In 2018, regulatory changes in the way that data is processed came into force, with the EU General Data Protection Regulation 2018 (GDPR) and the Data Protection Act 2018 (DPA 2018). Since the UK left the EU, the key principles of EU GDPR have been adopted in the UK GDPR (a 'UK-only' version) and the DPA 2018 still applies. The University of Exeter terms its lawful basis to process personal data for the purposes of carrying out research as being in the 'public interest' and continues to be transparent about the processing of your personal data. The University continues to be transparent about its processing of your personal data and the participant information sheet should provide a clear explanation of how your data will be collected, processed, stored, and destroyed.

If you have any queries about the University of Exeter's processing of your personal data that cannot be resolved by the research team, further information can be obtained from the University's Data Protection Officer at: https://www.exeter.ac.uk/aboutoursite/dataprotection/dpo/ . If you have any concerns about how the data is controlled and managed for this study, then please contact the Sponsor Representative, Dr Antony Walsh, Head of Research Governance, Ethics and Compliance, University of Exeter, Tel: 01392 726621 or Email: res-sponsor@exeter.ac.uk .

Who is organising and funding this research?

The research will be managed through the NIHR Exeter Clinical Research Facility (Exeter CRF), which is funded by the National Institute for Health and Care Research, a part of the NHS, and a collaboration with the University of Exeter. Funding for the project has been provided by The Leona M. and Harry B. Helmsley Charitable Trust.

What will happen at the end of the study?

The research findings will be published in a peer-reviewed journal(s) and abstracts will be submitted to national/ international conferences. We will share the study results with you via a newsletter and the study website. Data sharing with other researchers is important to ensure that research is open to peer scrutiny, to optimise the use of good quality research data and to support policy and other decision-making. Therefore, your anonymised research data will be included in the final dataset and stored in an approved data repository. Additionally, if you decide to gift your surplus samples and data for use in future research, we will transfer them to the Peninsula Research Bank (PRB) once the study is completed. You can find out more about the PRB here: https://exetercrfnihr.org/about/exeter-10000-prb/ and our research team can explain more about it at your visits. Should you not choose to gift your surplus samples or be re-contacted for future research, your samples and/or identifiable data will be destroyed securely at the end of study.

Where can I find out more?

For further information about the project, please contact Lynsey Beall, Senior Research Nurse or a member of the study research team, on: **01392 408181**
Additional information can be found on the study website:

https://www.diabetesgenes.org/current-research/muggle

The Health Research Authority (HRA) provides information on their website about how health researchers use participant's information in research studies: Patient Data and Research leaflet - Health Research Authority (hra.nhs.uk)

Who has reviewed this study?

This project has been reviewed and approved by the London - Hampstead Research Ethics Committee and the Health Research Authority (HRA).

What if there is a problem?

Should you have a problem, please contact the research team. However, if you have concerns or complaints arising from your experience of participating in this study which you do not wish to discuss with the research team directly, the RD&E Patient Engagement/Patient Advice & Liaison Service (PALS) team (01392 402093) will provide independent advice. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation against The University of Exeter or Royal Devon University Healthcare NHS Foundation Trust but you may have to pay your legal costs. The University of Exeter has no fault compensation/cover in place and negligence does not have to be proved to be awarded compensation.

Thank you for reading this leaflet, which is yours to keep.

If you wish to participate in this study, you will be asked **to sign a consent form in the presence of a member of the research team,** a copy of which you will be given to keep.

The consent form you will be asked to complete will include the following statements:

CONSENT STATEMENTS

I have been given the study information leaflet. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

I agree, for the duration of the study, to:

- allow the research team to contact my clinicians/GP to verify details about my health/treatment, advise my study participation, and to provide them with clinical results relevant to my care.
- allow the research team to obtain information about my health that is relevant to the study, via my hospital medical records and/or my clinician/GP.
- provide blood samples for analysis, including genetic studies using DNA. Samples will be stored for the duration of the study.

I understand that:

- my participation is voluntary and that I may withdraw at any time without giving any reason, without my medical care or legal rights being affected.
- individuals from the study team, University of Exeter, regulatory authorities, or the UK NHS Trust, will have access to relevant sections of my medical notes and data collected during the study for research, monitoring and audit purposes. I give permission for these individuals, with training in data protection, to have access to my records for the duration of the study.
- the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers after the end of the study, via a sponsor and funder-approved data repository.

I agree to take part in this study.

Optional Consent Statements:

- I agree to gift my samples and anonymised data from the project to the Peninsula Research Bank (PRB), managed by the NIHR Exeter Clinical Research Facility, to be used for future research.
- I am happy to be contacted by the Peninsula Research Bank (PRB) about participating in other future studies, requiring my contact details to be kept on a secure database managed by the PRB indefinitely or until I ask for them to be deleted.
- I agree that information held by the Exeter Molecular Genetics Laboratory and in my medical records may be used to follow up on my future health status for 15 years after the end of the study.