

# Dishabituation as a treatment for impaired awareness of hypoglycaemia in type 1 diabetes

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| <b>Submission date</b><br>24/10/2017   | <b>Recruitment status</b><br>No longer recruiting              | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol |
| <b>Registration date</b><br>25/10/2017 | <b>Overall study status</b><br>Completed                       | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results            |
| <b>Last Edited</b><br>17/08/2022       | <b>Condition category</b><br>Nutritional, Metabolic, Endocrine | <input type="checkbox"/> Individual participant data   |

## Plain English summary of protocol

### Background and study aims

Reduced awareness of low blood glucose (hypoglycaemia) affects about 25-30% of all people with type 1 diabetes. It puts that person at a much greater risk of severe hypoglycaemia with loss of consciousness or coma and it remains one of the major concerns of people with type 1 diabetes. There are currently no treatments for this condition other than structured education and sometimes pancreas transplantation when problems become extreme. This study is based on the new idea that repeated mild to moderate episodes of low glucose build up a memory in your brain which then learns to adapt to it. The brain has to adapt because each time it experiences low glucose the cells in the body become very stressed and this is damaging in the long term. This type of memory is called 'habituation' and this raises the possibility that by introducing a new stress, 'dishabituation', it might be possible to restore hypoglycaemia awareness. This study uses short bursts of high intensity exercise as a dishabituating stimulus to see if this will improve a person's awareness of low blood glucose.

### Who can participate?

Patients aged 18 to 55 with type 1 diabetes who have an impaired awareness of hypoglycaemia

### What does the study involve?

Participants are randomly allocated to either a period of rest or a high intensity exercise program on an exercise bike. The following day they undergo a hypoglycaemic clamp study where their blood glucose level is reduced in a controlled manner and their response is monitored using blood tests and questionnaires. Participants cross over two weeks later to undergo the opposite intervention and again undergo a hypoglycaemic clamp study. There are 5-7 visits to the Clinical Research Centre, and the study lasts about 6 weeks in total.

### What are the possible benefits and risks of participating?

Exercise is recommended for all people with type 1 diabetes for a variety of health benefits. It is hoped that this type of exercise may help participants regain symptoms of low blood glucose, and also that they will feel the general benefits and improvement in well-being with exercise. In addition, participants see a diabetes doctor at every visit and are given guidelines and advice as to how to adjust their insulin so that they can exercise more confidently. The study may not immediately benefit participants, but if the results of the study are positive this may lead on to

further research in this area and change the practice of managing patients with diabetes who have lost the symptoms and warning signs of hypoglycaemia. If so, participants may gain eventually from our discovering a new treatment for their condition. Exercise can increase the risk of hypoglycaemia, both during the activity and afterward during the night. Participants are supervised and have their glucose monitored regularly throughout the exercise program via continuous glucose monitor and are given standard advice about insulin adjustments before and after exercise. In addition, all participants are fitted with a continuous glucose monitor before, during and after the study. During exercise participants are fitted with a heart rate monitor. The hypoglycaemic clamp technique is very safe and is accepted as the gold standard worldwide for the study of hypoglycaemia. The chief investigator and his laboratory have experience in its use and have published in this area. It is a well-established, safe research technique with no major reported side effects. Participants have their blood glucose monitored every 5 minutes, and heart rate and blood pressure are monitored throughout. Blood sampling may cause some mild brief pain and bruising. As always care is taken by the doctor to minimise distress. There is a maximum of 7 visits to the Clinical Research Centre during this study. The researchers have attempted to reduce this burden by making 2 visits optional by teaching participants how to fit the continuous glucose monitor so that they can do this themselves rather than attend the Clinical Research Centre. They provide transport (taxi) or car parking for all of these visits.

Where is the study run from?  
Ninewells Hospital (UK)

When is the study starting and how long is it expected to run for?  
August 2017 to August 2019

Who is funding the study?  
1. Juvenile Diabetes Research Foundation International  
2. Diabetes UK

Who is the main contact?  
Prof. Rory McCrimmon

## Contact information

**Type(s)**  
Scientific

**Contact name**  
Prof Rory McCrimmon

**Contact details**  
School of Medicine  
Ninewells Hospital and Medical School  
Ninewells Avenue  
Dundee  
United Kingdom  
DD2 9SY

## Additional identifiers

**EudraCT/CTIS number**

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**

2017DM15

## **Study information**

### **Scientific Title**

Dishabituation as a treatment for impaired awareness of hypoglycaemia in type 1 diabetes: a randomised cross over study

### **Study objectives**

People with type 1 diabetes 'habituate' to hypoglycaemia and this leads to the development of impaired awareness of hypoglycaemia. Therefore the counter regulatory response to hypoglycaemia and hypoglycaemia awareness in people with type 1 diabetes can be restored through the introduction of a novel strong dishabituating stimulus.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

East of Scotland Regional Research Ethics Committee - approval pending

### **Study design**

Randomised cross over study

### **Primary study design**

Interventional

### **Secondary study design**

Randomised cross over trial

### **Study setting(s)**

Hospital

### **Study type(s)**

Other

### **Participant information sheet**

Not available in web format, please use the contact details to request a patient information sheet

### **Health condition(s) or problem(s) studied**

Type 1 diabetes

### **Interventions**

Participants will be randomised to start with a period of rest or a high intensity exercise program on an exercise bike. The following day they will undergo a hypoglycaemic clamp study where their blood glucose level will be reduced in a controlled manner and their response monitored in the form of blood tests and questionnaires. Participants will cross over two weeks later to undergo the opposite intervention and again undergo a hypoglycaemic clamp study. There will be 5-7 visits to the Clinical Research Centre, the study will last approximately 6 weeks in total.

### **Intervention Type**

Behavioural

### **Primary outcome measure**

The difference in the adrenaline response to hypoglycaemia following the HIT and no exercise protocols, measured at baseline, immediately post HIT intervention and -30, 0, 30, 60 and 90 minutes into hypoglycaemic clamp

### **Secondary outcome measures**

1. Changes in awareness of hypoglycaemia and symptom scores (Edinburgh Hypoglycaemia Score), measured at baseline, immediately post intervention and -30, 0, 30, 60 and 90 minutes  $\pm$  10 minutes into hypoglycaemic clamp
2. Changes in cognitive function (Digital Symbol Substitution Test, 4-Choice Reaction Time), measured at baseline, immediately post intervention and -30, 0, 30, 60 and 90 minutes  $\pm$  10 minutes into hypoglycaemic clamp
3. Changes in mood (standard validated psychometric measures of mood state), measured at baseline, immediately post intervention and -30, 0, 30, 60 and 90 minutes  $\pm$  10 minutes into hypoglycaemic clamp
4. Changes in other counter regulatory hormones (glucagon, noradrenaline, lactate, cortisol, growth hormone, insulin, cytokine panel and brain derived neurotrophic factor), measured at baseline both interventions, immediately post HIT intervention and -30, 0, 30, 60 and 90 minutes  $\pm$  10 minutes into hypoglycaemic clamp (insulin will only be measured during hypoglycaemic clamp study)

### **Overall study start date**

02/08/2017

### **Completion date**

02/08/2019

## **Eligibility**

### **Key inclusion criteria**

1. Adults  $\geq 18$  and  $\leq 55$  years
2. Type 1 diabetes
3.  $> 5$  years disease duration
4. HbA1c  $< 75$  mmol/l
5. On intensive insulin therapy (CSII or MDI)
6. Impaired awareness of hypoglycaemia (Gold score  $\geq 4$  or Modified Clark score  $\geq 4$  or DAFNE hypoglycaemia awareness rating 2 or 3)

### **Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

12

**Total final enrolment**

12

**Key exclusion criteria**

1. Competitive sportsman/woman
2. History of significant heart disease
3. Treatment with beta blockers
4. Renal impairment (eGFR<60)
5. History of significant lung disease – that limits exercise
6. History of significant neurological disease – including seizures second to hypoglycaemia
7. High risk foot disease
8. Previous amputation of toes/foot/leg
9. Pregnant women or breast feeding mothers
10. Participation in HIT or equivalent in past 6 months
11. Physical ability that may limit exercise
12. Inability to give consent

**Date of first enrolment**

08/01/2018

**Date of final enrolment**

01/08/2018

**Locations****Countries of recruitment**

Scotland

United Kingdom

**Study participating centre**

**Clinical Research Centre Ninewells Hospital University of Dundee**

James Arnott Drive

Ninewells Hospital and Medical School

Dundee

United Kingdom

DD2 1GZ

# Sponsor information

## Organisation

University of Dundee/NHS Tayside

## Sponsor details

Tayside Medical Sciences Centre (TASC)  
Level 3, George Pirie Way  
Ninewells Hospital  
Dundee  
United Kingdom  
DD2 9SY

## Sponsor type

Other

## ROR

<https://ror.org/03h2bxq36>

# Funder(s)

## Funder type

Charity

## Funder Name

Juvenile Diabetes Research Foundation International

## Alternative Name(s)

Juvenile Diabetes Research Foundation, International, JDRF

## Funding Body Type

Private sector organisation

## Funding Body Subtype

Trusts, charities, foundations (both public and private)

## Location

United States of America

## Funder Name

Diabetes UK

**Alternative Name(s)**

DIABETES UK LIMITED, British Diabetic Association

**Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Trusts, charities, foundations (both public and private)

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

As this is a non-CTIMP single intervention a detailed protocol will be published with the final manuscript. The trialists will publish the results of this study in a medical journal as well as to present at national and international conferences. In addition, they will also disseminate the results through meetings with various stakeholder groups as well as communicate through other media options.

**Intention to publish date**

01/08/2020

**Individual participant data (IPD) sharing plan**

The data will be available in anonymised form for 5 years from end of study definition, because after this the study files and data will be destroyed. The contact will be Prof. Rory J. McCrimmon (r.mccrimmon@dundee.ac.uk).

**IPD sharing plan summary**

Available on request

**Study outputs**

| Output type                      | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|----------------------------------|---------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a>  | results | 01/04/2020   | 04/09/2020 | Yes            | No              |
| <a href="#">Protocol article</a> |         | 21/07/2020   | 17/08/2022 | Yes            | No              |