ISRCTN15236211 https://doi.org/10.1186/ISRCTN15236211

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

Submission date
24/10/2017

Recruitment status
No longer recruiting

Registration date
25/10/2017

Overall study status
Completed

Last Edited
17/08/2022

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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 adapts 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

Protocol serial number
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

Study type(s)
Other

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(s)
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

Key secondary outcome(s))

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 ± 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 ± 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 ± 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 ± 10 minutes into hypoglycaemic clamp (insulin will only be measured during hypoglycaemic clamp study)

Completion date
02/08/2019

Eligibility

Key inclusion criteria
1. Adults ≥18 and ≤ 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 ≥4 or Modified Clark score≥4 or DAFNE hypoglycaemia awareness rating 2 or 3)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

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
United Kingdom

Scotland

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

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)
The British Diabetic Association, 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

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?
Results article	results	01/04/2020	04/09/2020	Yes	No

Protocol article		21/07/2020	17/08/2022	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes