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High intensity exercise as a possible treatment for loss of symptoms of low blood sugar in people with type 1 diabetes

Submission date
18/12/2018

Recruitment status
No longer recruiting

Registration date
08/02/2019

Overall study status
Completed

Last Edited
04/03/2025

Condition category
Nutritional, Metabolic, Endocrine

[_] 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 (loss of consciousness or coma) and it remains one of the major concerns of people with type 1 diabetes. There is currently no treatments for this condition other than structured education and sometimes when extremely problematic, pancreas transplantation. This trial is based on the idea that repeated mild to moderate episodes of low glucose build up a memory in the 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 stressed and this is damaging in the long term. This type of memory is called 'habituation'. This concept raises the possibility that by introducing a new stress, 'dishabituation', we might be able to restore hypoglycaemia awareness. We have recently completed a study in 12 people with type 1 diabetes and impaired awareness of hypoglycaemia and have shown that a single episode of high intensity exercise (HIT) could be used as the dishabituating stimulus, and at least partially restore responses to subsequent hypoglycaemia (ISRCTN15236211). However, while we have demonstrated that a single episode of HIT can at least temporarily reverse the defect induced by recurrent hypoglycaemia, it remains possible that the effect is (a) not sustained or (b) individuals may over time adapt to the novel dishabituating stimulus. Therefore, before taking this novel and exciting physiological intervention into the clinic we need to perform a longer term pilot study to determine the impact of a 4-week HIT programme and hormone and symptom awareness of hypoglycaemia.

Who can participate?
Patients aged 18 to 60 with type 1 diabetes who have an impaired awareness of hypoglycaemia

What does the study involve?
Participants are randomly allocated to 4 weeks of continuous glucose monitoring (CGM) or CGM and HIT. There is a 4 week run-in period to optimise diabetes control. Following this all participants undergo a hypoglycaemic clamp study where we will reduce their blood glucose level in a controlled manner and monitor their response in the form of blood tests and questionnaires. There are then 4 weeks of CGM with or without high intensity exercise

(intervention period). At the end of the 4 weeks they again undergo a hypoglycaemic clamp study. There are eight study visits.

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 will 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 8 visits to the Clinical Research Centre during this study. The researchers have attempted to reduce this burden by making four visits flexible in time and location. They provide transport (taxi) or car parking for all of these visits.

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

When is the study starting and how long is it expected to run for?
October 2018 to April 2021

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

Clinical Research Centre
James Arrott Drive
Ninewells Hospital and Medical School
University of Dundee
Dundee
United Kingdom
DD1 9SY
+44 (0)1382383135
r.mccrimmon@dundee.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
1-021-18

Study information

Scientific Title
High Intensity Training as a novel treatment for impaired awareness of hypoglycaemia in type 1 diabetes

Acronym
HIT4HYPOS

Study objectives
This study tests the hypothesis that people with type 1 diabetes 'habituate' to recurrent episodes of 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 may be restored through the introduction of a novel strong dishabituating stimulus. The study will use high intensity exercise (HIT) as a dishabituating stimulus to find out whether HIT can be used as treatment for impaired awareness of hypoglycaemia and if the effect can be maintained over a 4 week period.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South East Scotland Research Ethics Committee 2, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, Tel: +44 (0)131 536 9000, Email: Joyce. Clearie@nhslothian.scot.nhs.uk (for enquiries), 17/12/2018, ref: 18/SS/0160

Study design
Randomized parallel group pilot study

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Type 1 diabetes

Interventions
Randomisation will be carried out by an independent individual, at the University of Dundee. Randomisation will be done in a GCP-compliant manner using http://www.randomization.com/. Randomisation will be carried out using a validated web-based block randomisation generator to ensure that an equal number of participants are assigned to each intervention at baseline. Once the randomisation has taken place the allocation list will be concealed from the CI and PI until the recruit has been consented. The PI will be informed of the intervention allocation and will inform the participant once they have consented to take part in the study.

Participants will be randomised to 4 weeks of continuous glucose monitoring (CGM) or CGM and HIT. There will be a 4 week run-in period to optimise diabetes control. Following this all participants will undergo a baseline hypoglycaemic clamp study where we will reduce their blood glucose level in a controlled manner and monitor their response in the form of blood tests and questionnaires. There will then be 4 weeks of CGM +/- high intensity exercise (intervention period).

Arm 1: High Intensity Exercise: 30 second sprints on cycle ergometer followed by 2 minutes rest, repeated 4 times. This will be carried out 3 times a week for a month. During this period they will use a continuous glucose monitor.
Arm 2: This group will solely use continuous glucose monitor.

At the end of the 4 weeks they will again undergo a hypoglycaemic clamp study. There will be 8 study visits.

Intervention Type
Behavioural

Primary outcome measure
Adrenaline response to hypoglycaemia,measured at baseline and 30, 60 and 90 minutes into each hypoglycaemic clamp study

Secondary outcome measures

Measured at baseline and 30, 60 and 90 minutes into each hypoglycaemic clamp study:
1. Awareness of hypoglycaemia (Gold score, modified clark score, DAFNE awareness of hypoglycaemia score) and symptom scores (Edinburgh Hypoglycaemia Score)
2. Cognitive function (4-Choice Reaction Time test, Digit Symbol Substitution Test)
3. Well-being (The World Health Organisation- Five Well-Being Index (WHO-5))
4. Counter regulatory hormone levels (to include glucagon, Noradrenaline (NA), lactate, Cortisol, Growth hormone (GH), insulin, cytokine panel)

Overall study start date
01/10/2018

Completion date
26/04/2021

Eligibility

Key inclusion criteria
1. Adults ≥18 and ≤60 years
2. Type 1 diabetes:
2.1. >5 years disease duration
2.2. HbA1c <80 mmol/l
3. On intensive insulin therapy (continuous subcutaneous insulin infusion [CSII] or multiple daily injections [MDI])
4. Impaired awareness of hypoglycaemia (Gold score ≥4 or Modified Clark score≥4 or DAFNE hypoglycaemia awareness rating 2 or 3) and/or evidence of recurrent hypoglycaemia (on CGM or flash glucose monitoring)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Both

Target number of participants
32

Total final enrolment
22

Key exclusion criteria

1. Competitive sportsman/woman
2. History of significant heart disease: ischaemic heart disease, congestive cardiac failure or cardiac surgery
3. Treatment with beta-blockers
4. Treatment with oral steroids within the last 6 months
5. Anaemia (Hb <120 g/L for women, Hb <130 g/L for men)
6. Renal impairment (eGFR<60)
7. History of significant lung disease – that limits exercise
8. History of significant neurological disease – those with a history of seizures second to hypoglycaemia must be seizure free for 12 months prior to consent.
9. High-risk foot disease or previous amputation of toes/foot/leg
10. Pregnant women or breastfeeding mothers
11. Participation in HIT or equivalent in pthe ast 6 months
12. Physical ability that may limit exercise
13. Inability to give consent

Date of first enrolment
01/02/2019

Date of final enrolment
21/12/2020

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Clinical Research Centre, Ninewells Hospital, University of Dundee
James Arrott Drive
Dundee
United Kingdom
DD1 9SY

Sponsor information

Organisation
University of Dundee/NHS Tayside

Sponsor details
Tayside Medical Sciences Centre (TASC)
Level 3
George Pirie Way

Ninewells Hospital
Dundee
Scotland
United Kingdom
DD1 9SY

Sponsor type
University/education

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
31/12/2023

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	21/07/2020	08/02/2021	Yes	No
Other publications		20/08/2020	28/10/2022	Yes	No
HRA research summary			28/06/2023	No	No
Results article		27/11/2023	28/11/2023	Yes	No
Abstract results		03/08/2022	04/03/2025	No	No
Abstract results		25/08/2020	04/03/2025	No	No
Other publications	Post hoc analysis	23/09/2024	04/03/2025	Yes	No