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Aerobic exercise and hypoglycaemia (low blood sugar) after Roux-en-Y gastric bypass

Submission date
13/10/2021

Recruitment status
No longer recruiting

Registration date
29/10/2021

Overall study status
Completed

Last Edited
09/01/2024

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Weight-loss (bariatric) surgery is an effective method to help people living with severe obesity to achieve and maintain substantial weight loss and live longer. Exercise after bariatric surgery is an important factor which improves fitness, helps with weight maintenance, improves tasks of daily living and physical function (e.g. strength, endurance and flexibility), improves health-related quality of life and reduces the risk of underlying health conditions developing, returning or worsening.
There are no official exercise guidelines for individuals after bariatric surgery. However, European guidelines recommend that after bariatric surgery, patients should maintain a healthy lifestyle which includes 30 minutes of moderate-intensity exercise daily (e.g. walking, running, cycling).
Recent research suggests that exercise after bariatric surgery (in patients without type 2 diabetes) increases insulin sensitivity [the effectiveness of the body to use glucose (the sugar in the blood)]. Increased insulin sensitivity is considered an important risk factor for episodes of low blood glucose levels after a meal post-bariatric surgery. It is common that people who have undergone weight-loss surgery experience symptoms of low blood glucose levels during daily life which may contribute to a reduction in their quality of life and weight regain. Symptoms happen when food passes too quickly into the intestines (small bowel) due to changes in stomach structure after surgery. Glucose from food is absorbed quickly and too much insulin is released.
Due to the importance of exercise after surgery, the proposed study will investigate whether a single 30-minute bout of exercise increases the time spent with low blood glucose over the following 24 hours after bariatric surgery. If this is the case, then dietary changes may be needed to reduce the severity and frequency of having low blood glucose levels after moderate-intensity exercise.

Who can participate?
Persons aged 18 - 75 years who have had RYGB surgery in the past year.

What does the study involve?
There are a total of six study visits that will take place at the Leicester Diabetes Centre, Leicester General Hospital. The expected participation in the study is approximately one month.

Visit 0
• The energy requirement test, which is a test of expired air that measures your resting energy use.
• The walking test, you will be asked to walk on a treadmill whilst we look at your heart activity (Electrocardiogram [ECG]), blood pressure and breathing (collecting your expired air via a mouth nose mask).

If the results show that you are eligible to participate in the study, the following baseline measurements will be carried out:
• Height, weight, waist circumference, and will be measured using weighing scales and a tape measure.
• Blood pressure and resting heart rate will be measured using an upper arm monitor.
• Non-fasting blood sample to measure blood glucose (HbA1c), full blood count, renal function and liver function will be taken. Alternatively, your routine blood test results can be obtained from the hospital records, if these are available within the last 3 months.
• You will be asked to complete a self-reported physical activity questionnaire (IPAQ-SF)
• You will be given a glucose testing kit and training on how to check your blood glucose levels.
• Daily activity, you will also be asked to wear, continuously (24 hours/day), an activity monitor from this visit for the duration of the study (Visit 0 to Visit 5). This will involve wearing a waterproof wrist monitor similar to a watch. We would like you to keep a record of when you wake up, when you put on/take off your monitor, and when you go to sleep (we will give you an activity monitor log to record this information).
• Standardised meals, standardised meals will be provided to you to consume on-site and to take home as described in this information sheet. We will ask about your food preferences from a pre-determined menu.

Visit 1
Randomisation
You will be randomly allocated to perform one of two study protocol sequences. This is a bit like tossing a coin. You or the researcher cannot choose which sequence you undertake.

1. Sitting and walking at visit 2 followed by prolonged sitting at visit 4 OR 2. Prolonged sitting at visit 2 followed by sitting and walking at visit 4

Other procedures at visit 1:
You will be asked to wear a Continuous Glucose Monitor (CGM) called ‘Dexcom G6’ continuously from visit 1 to visit 5.
This will involve inserting a sensor into the skin on your tummy and then attaching a transmitter onto the sensor. You will be given a glucose monitoring diary.
We will also provide you with a standardised meal to consume the evening of visit 1 and a 3-day diet diary to document the time, type and amount of food eaten during the 3-day treatment period.

Visit 2
We will ask you to sit and be comfortable before inserting a cannula to remain in your arm for the day to allow us to take multiple blood samples.
The cannula is a very small, flexible tube which is placed into one of your veins, usually in your arm.
We will use the cannula to take 11 different blood samples and you will be asked to complete some questions on hunger and fullness.
If you are allocated to prolonged sitting followed by exercise, after 2 hours and 15 minutes of

sitting down you will be asked to walk on a treadmill.
A snack will be eaten before undertaking 35 minutes of steady walking on a treadmill (30-minute walk and an extra 5 minutes is provided for a warm-up and cool-down).
After the walk you will remain rested and seated for the rest of the visit.
We will provide you with a standardised meal to consume the evening of visit 2 and a standardised breakfast and lunch the following day.

Visit 3
At this visit we will check how you are getting on and provide you with a recap on how to manage symptoms of low blood glucose levels.
We will also check your glucose monitor (CGM) and potentially change depending on battery life.

Visit 4
Identical to visit 2 and if you are allocated to the first sequence (Sitting and walking at visit 2 followed by prolonged sitting at visit 4) you will remain rested and seated throughout this visit.

Visit 5
We will remove the CGM device and collect diaries.

What are the possible benefits and risks of participating?
Benefits:
All participants will benefit from a health assessment, a walking assessment combined with heart monitoring and advice on how to manage and treat symptoms of low blood glucose levels. Throughout the duration of the study, your general health will be reviewed by the study doctor. You will also receive information on your general fitness levels. Whilst the tests in this study are not designed for clinical diagnosis, in the unlikely event that we find an abnormality this will be discussed directly with you. We will also pass this on to your GP and healthcare professionals, with the aim of organising appropriate care and treatment. Potential participants with low blood glucose levels may be identified during the study and will be provided with nutritional advice (after completion of the study).
You will also add to evidence-based lifestyle information that may improve the treatment and support for people 12 months after undergoing gastric bypass in the future. The results of this study may contribute to the design of a potential treatment option to prevent low blood glucose episodes in people who have had weight loss surgery. By taking part you are contributing to the scientific understanding of the effects of the intervention.

Expenses and payments:
We will reimburse participants for any study-related car parking charges and reasonable travel costs up to a value of £7 per visit (original receipts must be provided).

Risks:
During any exercise there is always an increased risk of a heart event or injury. The walking test is being performed before you start the study to ensure the risks to health are very low. These risks are also lowered because brief education is provided in the management and treatment of low blood glucose level symptoms. There will also be a trained researcher undertaking all aspects of the study. If there are any abnormalities you will not participate and we will inform your GP and other healthcare professionals as appropriate, e.g. cardiologist.
All clinic measurements are carried out by qualified members of the research team. Some people experience minor discomfort and slight bruising during blood tests. A fully qualified research team member will carry out the blood test to ensure any pain is kept to a minimum. If we find your blood results are not ‘normal’ we will inform your GP in order to investigate them further, if required.

You should also be aware that if you lose the ability to make decisions for yourself on matters relating to the study during the study, you will be withdrawn from any further study involvement. Any data collected up to that point will be retained for study analysis and will be destroyed five years after the end of the study.

Where is the study run from?
University of Leicester (UK)

When is the study starting and how long is it expected to run for?
April 2020 to October 2024

Who is funding the study?
1. Novo Nordisk UK Research Foundation
2. Leicester Diabetes Centre.

Who is the main contact?
Mamta Joshi, mamta.joshi@uhl-tr.nhs.uk, BariEX_Mailbox@uhl-tr.nhs.uk
Dr Dimitris Papamargaritis, Dp421@leicester.ac.uk
Dr Louisa Herring, Louisa.herring@uhl-tr.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Miss Mamta Joshi

Contact details
Leicester Diabetes Centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW
+44 (0)116 258 4214
mamta.joshi@uhl-tr.nhs.uk

Type(s)
Scientific

Contact name
Dr Dimitris Papamargaritis

Contact details
Leicester Diabetes Centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

-
Dp421@leicester.ac.uk

Type(s)
Scientific

Contact name
Dr Louisa Herring

Contact details
Leicester Diabetes Centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW
-
Louisa.herring@uhl-tr.nhs.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
286897

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 49407, IRAS 286897

Study information

Scientific Title
The effect of acute aerobic exercise on the time spent in hypoglycaemia after Roux-en-Y gastric bypass

Acronym
BariEX

Study objectives
A single bout of moderate intensity aerobic exercise (in accordance with the European Guidelines for post-bariatric surgery management) in people without diabetes after Roux-en-Y gastric bypass will increase the time spent in hypoglycaemia over the 24-h period after aerobic exercise.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/06/2021, London - Bromley Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT; +44 (0)2071048211; bromley.rec@hra.nhs.uk), ref: 21/LO/0404

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Quality of life

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
The effect of exercise on recovery from gastric bypass surgery

Interventions
This is a single centre, randomised, two-period, crossover study with the following experimental period sequences:
AEX intervention: prolonged sitting for ≈6 hours (h) 15 minutes (min) punctuated by 30min AEX performed at 60% VO2 peak
Control: prolonged sitting for ≈6h 45min
Group 1) Control at visit 2 and then followed by the intervention at visit 4
or
Group 2) Intervention at visit 2 and then followed by the control at visit 4

A crossover design has been selected as it reduces the influence of confounding covariates as each crossover patient serves as their own control. The randomised nature ensures that there is no bias with regards to the sequence at which the intervention is performed.
The expected study duration is approximately one month with participants attending six visits in total.

Visit 0 - This visit comprises consent, screening (including indirect calorimetry and a maximal exercising test (with ECG and blood pressure monitoring), in addition, blood samples will be obtained for HbA1c, full blood count (FBC), renal function and liver function. Alternatively routine blood test results (<3 months) can be obtained from the hospital records (including electronic systems for blood tests). A urine pregnancy test will also take place for all female participants of child bearing potential. In addition demographic information, past medical /surgical history, concomitant medication and medication history will also be collected at this

visit. A general physical examination will be performed by a trained delegated clinician. The provision of monitors (blood glucose meter and accelerometer), monitor paper diaries/logs and the necessary training for hypoglycemia treatment (for safety purposes).
The accelerometer will be worn for the duration of the study (Visit 0 to visit 5).
Food preferences will be obtained from a pre-determined menu to guide standardised meals to be provided.

Following the screening visit, the study will consist of two treatment arms over three consecutive days with a three day minimum washout period between them (maximum of 28 days).
Each treatment arm will consist of three days, comprising five visits in total. All food and drink during participation in the 3 day treatment arms will be standardised and recorded in a 3-day diet diary.

Those who successfully complete screening and the maximal exercise test will be randomised (1:1) to either experimental period sequence one or two (as described above) at Visit 1.

Visit 1 & 3 - A blinded CGM device will be fitted to participants on this visit and asked to wear these monitors from visit 1 to visit 5. Training in capillary blood glucose (CBG) testing and HYPO treatment will be provided. A glucose diary will be provided to record HYPO symptoms, glucose levels and the treatment received. A food and drink diary will also be provided for completion.
If the CMG device does not need to be re-inserted at visit 3 (if <10 days between insertion of CGM device and end of treatment period 2 and participant will continue wearing the CGM), visit 3 becomes optional to attend. Also if the window between visit 1 and visit 5 is less than 10 days then visit 3 can occur remotely. Visit 3 can be carried out over the phone or video call as per participant's preference.

All participants will be provided with a standardised meal to consume on the evening before Visits 2 and 4 (day 2 of each treatment period), no later than 10 hours before their study visit. Participants will be allowed to consume caffeinated drinks on the day before each of visits 2 and 4, but will be asked to record and replicate these as per any other food or drink item in both treatment periods, and not drink these after consumption of their standardised meal.

Visits 2 & 4 - The experimental period (≈6h 45min duration) will take place on day 2 of each treatment period and will include the intervention (30 min AEX bout or sitting in a chair) as well as a standardised lunch [mixed meal tolerance test (MMTT)] with frequent blood sampling. Participants will be provided with a standarised breakfast.
The impact of each intervention (30 min AEX bout or sitting in a chair) on the time spent in HYPO over the next 24-h will be assessed through CGM under standardise dietary, but otherwise free living conditions. The two treatment periods will be identical; the only difference will be the intervention (30 min AEX bout or sitting).
Participants will be asked to refrain from moderate-to-vigorous physical activity and alcohol for 24h prior to intervention visits. They will also be asked to standardise all food and drink during each of the 3-days treatment periods and to refrain from any food or drink, other than water after consumption of evening standardised meal.
All participants will be provided with a standardised meal to consume on day 3. Meals consumed at Visit 2 will be replicated at Visit 4.

Visit 5 - On day 3 of the final treatment arm participants will arrive at least 24-hours after completion of the intervention (after midday) for accelerometer, and CGM removal. All diaries and logs will be collected. If the participant would prefer to post the monitors and diaries/logs back this will be an available option.

Participants will also be encouraged, but this will not be obligatory, to continue completing study diaries and logs during the washout period of the study (between the 1st and 2nd treatment period), as they will continue to wear an accelerometer and the continuous glucose monitoring device (until at least the end of sensor's life for the CGM device).

Intervention Type
Behavioural

Primary outcome measure
% time in hypoglycaemia (defined as interstitial glucose levels <3.0mmol/l) in continuous glucose monitoring after RYGB during the 24-h period after completion of the intervention.

Secondary outcome measures
1. Difference in Area Under the Curve (AUC)(0-180), pre-meal, peak and nadir glucose levels after mixed meal tolerance test (3-h MMTT) between the two interventions (AEX vs control) after RYGB.
2. Difference in AUC(0-180) insulin, pre-meal and peak insulin levels during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.
3. Difference in the ratio AUC(0-180) insulin/AUC(0-180) glucose during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.
4. Difference in the ratio AUC(0-30) insulin/AUC(0-30) glucose during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.
5. Difference in the ratio AUC(60-180) insulin/AUC(60-180) glucose during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.
6. Difference in the ratio of maximum/minimum plasma glucose during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.
7. Difference at the number of mixed meal tests required to be stopped due to symptomatic HYPO with blood glucose/capillary glucose levels <3.0 mmol/l during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.
8. Difference in %time in interstitial glucose levels <3.9 mmol/l in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
9. Difference in %time in interstitial glucose levels <3.3 mmol/l in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
10. Difference in % time in interstitial glucose levels <2.2 mmol/l in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
11. Difference in % time in range (definition 1, defined as interstitial glucose levels between 3.9 – 7.8 mmol/l) in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
12. Difference in % time in range (definition 2, defined as interstitial glucose levels between 3.0 – 7.8 mmol/l) in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
13. Difference in % time in interstitial glucose levels between 3.9 – 10 mmol/l in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
14. Difference in % time in interstitial glucose levels between 3.0 – 10 mmol/l in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
15. Difference in % time interstitial glucose >7.8 mmol/l in CGM between the two interventions

(AEX vs control) after RYGB during the 24-h period after completion of the intervention.
16. Difference in % time interstitial glucose >10 mmol/l in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
17. Difference in the mean interstitial glucose in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
18. Difference in the standard deviation (SD) of the mean interstitial glucose between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
19. Difference in the coefficient of variation (CV) (CV=SD/mean interstitial glucose) between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
20. Difference in the frequency and intensity of symptoms suggestive of postprandial hypoglycaemia reported by the patients during CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
21. Difference in the number of hypoglycaemic events/day (defined as interstitial glucose levels <3.0 mmol/l) in CGM between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
22. Difference in the number of hypoglycaemic events/day (defined as interstitial glucose levels <3.0 mmol/l) in CGM with symptoms suggestive of hypoglycaemia required treatment between the two interventions (AEX vs control) after RYGB during the 24-h period after completion of the intervention.
23. Difference in risk of hyperglycaemia between the two interventions (AEX vs control) after RYGB calculated as the high blood glucose index (HBGI) for the 24-h period after completion of the intervention using the EasyGV workbook (www.phc.ox.ac.uk/research/technology-outputs/easygv).
24. Difference in risk of hypoglycaemia between the two interventions (AEX vs control) after RYGB calculated as the low blood glucose index (LBGI) for the 24-h period after completion of the intervention using the EasyGV workbook (www.phc.ox.ac.uk/research/technology-outputs/easygv).
25. Difference in AUC(0-180) satiety and hunger Visual Analogue Scale levels during the 3-h MMTT between the two interventions (AEX vs control) after RYGB.

Overall study start date
15/04/2020

Completion date
31/10/2024

Eligibility

Key inclusion criteria
1. Aged >=18 years but less than 75 years
2. Subjects >=1 year after gastric bypass (RYGB)
3. Able to understand written and spoken English
4. Able to provide informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 18; UK Sample Size: 18

Key exclusion criteria
Current exclusion criteria as of 19/01/2023:
1. A current diagnosis of type 2 diabetes (defined as HbA1C ≥6.5% at screening blood tests or HbA1C <6.5% at screening bloods but on glucose-lowering medications over last 3 months)
2. An eGFR value of <=30 ml/min over the last 6 months
3. History of revisional bariatric surgery, except of previous gastric banding which has been removed
4. Any other bariatric operation which is not RYGB (single anastomosis bypass patients will be excluded)
5. On any medications that affect glucose levels (e.g. glucose-lowering medications or steroids)
6. Any contraindications/limitations to AEX self-reported or identified in the maximal exercise test (e.g orthopaedic limitations, severe cardiovascular/pulmonary disease, chair bound)
7. An established diagnosis of PHH
8. Systolic blood pressure > = 160mmHg or Diastolic blood pressure > = 100mmHg at screening
9. Individuals which are taking part in regular structured exercise
10. Being on acarbose, diazoxide, octreotide or other treatment for postprandial hypoglycaemia
11. History of epilepsy
12. HbA1C >=6.5% or >=48 mmol/l at screening blood tests
13. Haemoglobin (Hb) <100 g/L at screening blood tests
14. Currently pregnant or breastfeeding
15. Recent active infection (over the last 10 days)
16. Adrenal insufficiency and/or substitution with glucocorticoids
17. >180 kg at screening due to the maximum weight capacity of the treadmill
18. Participating in another research study involving intervention within 3 months of screening

Previous exclusion criteria:
1. A history of diabetes mellitus (type 1 or type 2 diabetes mellitus)
2. An eGFR value of <=30 ml/min over the last 6 months
3. History of revisional bariatric surgery, except of previous gastric banding which has been removed
4. Any other bariatric operation which is not RYGB (single anastomosis bypass patients will be excluded)
5. On any medications that affect glucose levels (e.g. glucose-lowering medications or steroids)
6. Any contraindications/limitations to AEX self-reported or identified in the maximal exercise test (e.g orthopaedic limitations, severe cardiovascular/pulmonary disease, chair bound)
7. An established diagnosis of PHH
8. Systolic blood pressure > = 160mmHg or Diastolic blood pressure > = 100mmHg at screening
9. Individuals which are taking part in regular structured exercise
10. Being on acarbose, diazoxide, octreotide or other treatment for postprandial hypoglycaemia
11. History of epilepsy
12. HbA1C >=6.5% or >=48 mmol/l at screening blood tests

13. Haemoglobin (Hb) <100 g/L at screening blood tests
14. Currently pregnant or breastfeeding
15. Recent active infection (over the last 10 days)
16. Adrenal insufficiency and/or substitution with glucocorticoids
17. >180 kg at screening due to the maximum weight capacity of the treadmill
18. Participating in another research study involving intervention within 3 months of screening

Date of first enrolment
21/02/2022

Date of final enrolment
31/07/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leicester General Hospital
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

Sponsor information

Organisation
University of Leicester

Sponsor details
University Road
Leicester
England
United Kingdom
LE1 7RH
+44 (0)1162 584099
rgosponsor@le.ac.uk

Sponsor type
University/education

Website

http://www.le.ac.uk/

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Research organisation

Funder Name
Novo Nordisk UK Research Foundation

Alternative Name(s)
The Novo Nordisk UK Research Foundation, ovo Nordisk Research Foundation UK, NNUKRF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Leicester Diabetes Centre, Leicester General Hospital

Results and Publications

Publication and dissemination plan
Any original findings will be published as conference abstracts or as papers in reputable refereed journals. Authorship will include those listed as investigators In the research protocol. These individuals will take personal responsibility for their identified area of expertise and will identify their contributions to the research process in any publication. Collaborators, other contributors, funding bodies, the sponsor and the authorising REC will be acknowledged. We aim to disseminate within 6 months of completing study analysis.

Intention to publish date
31/03/2025

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No