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Reversing type 2 diabetes through a low calorie diet and supervised exercise

Submission date
15/06/2021

Recruitment status
No longer recruiting

Registration date
22/06/2021

Overall study status
Ongoing

Last Edited
24/07/2025

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Type 2 diabetes is a condition that causes the level of sugar (glucose) in the blood to become too high. It is becoming more common and adults are getting it at younger ages. Many young adults (aged between 18-40 years) are now being diagnosed with the disease. This is worrying because heart, kidney and physical function problems related to diabetes can therefore happen at an early age. Past studies have shown that low-energy diets lead to over half of people reversing their type 2 diabetes. This means that blood sugar levels return to normal. This is called 'reversing diabetes.' A low-energy diet means eating a lot less than normal for a short period of time. Once people have lost enough weight, they can start to eat regular food again. Structured exercise, such as walking and simple weight training activities, can also improve blood sugar levels as well as heart function. The effects of combining the two approaches - a low-energy diet and structured exercise - have not been studied together in terms of reversing diabetes. The main goal of this study is to see whether combining structured exercise and a low-calorie diet can reverse diabetes. The study will also look at whether heart health is improved over 24 weeks.

Who can participate?
Adults who have type 2 diabetes and are between 18 and 45 years old (inclusive)

What does the study involve?
Participants are randomly allocated to one of two groups. The control group will continue to receive standard care. The intervention group will be prescribed a low-energy diet with total meal replacement for the first 2 weeks, followed by partial meal replacement from weeks 3-12. This will be followed by individualised food reintroduction (weeks 13-24). During weeks 3-12, this will be combined with supervised aerobic and resistance exercise, and a transition to unsupervised home-based exercise will be introduced in weeks 13-24. The intervention group will be taken off their glucose-lowering medication and antihypertensive medication by a study physician at the start of the intervention. However, ACE inhibitors or angiotensin receptor blockers will not be discontinued in the context of albuminuria (where the protein albumin is abnormally present in the urine). Following the 24-week intervention period, the control group will be offered the meal replacement component of the low-energy diet complemented by a 4-week food reintroduction period with support from the study dietitians and physicians.

What are the possible benefits and risks of participating?
During the study participants will receive close monitoring of their diabetes. The study will also provide detailed results of their heart function, body fat and exercise levels. The researchers will be happy to review the results with them after the study is completed. The diet used in this study can completely reverse diabetes. This happens in many patients who manage to stick to it. Patients often feel much healthier and this tends to occur quickly. This is usually within the first week. Their medication is likely to be reduced or stopped altogether. However, not everyone reverses their diabetes. Whether they are able to maintain this after the study depends on how their body responds over the longer term and how well they are able to continue the new eating habits. Exercise training improves fitness. It also helps to control blood sugars. Exercise training also lowers blood pressure, the amount of harmful fat in the blood and may improve the blood supply to the heart. These changes may have long-term benefits in preventing heart disease. The study will hopefully improve the understanding of how to reverse diabetes. It will also show how diabetes affects the heart. The results could lead to improved medical treatments and programmes in the future.
In past studies, the low-energy diet has led to symptoms like constipation, dizziness, fatigue, thirst, and/or headache in some people taking part. These tend to get better with fibre-based laxatives and time. It is also important to drink as much water as needed when on the diet. With exercise, there are risks of injury to joints, bones, and muscles. The supervisor will work with the participants to exercise as safely as possible. Exercise may also lead to fatigue and dizziness in some cases. Again, over time these should improve. Stopping diabetes and blood pressure medications at the beginning of the diet and exercise programme may lead to blood sugars and blood pressure going up. The researchers will monitor this to see if they need to restart medications. Diet and exercise may lead to low blood sugar and low blood pressure, but this is unlikely when not taking medication.

Where is the study run from?
1. Leicester Diabetes Centre (UK)
2. Research Institute of the McGill University Health Centre-Centre for Outcomes Research and Evaluation (main coordinating site - Canada) and Alberta Diabetes Institute – University of Alberta (participating centre)

When is the study starting and how long is it expected to run for?
March 2021 to October 2025

Who is funding the study?
1. Medical Research Council (UK)
2. Canadian Institutes of Health Research (Canada)
3. JR McConnell Foundation (Canada)

Who is the main contact?
UK: Prof. Tom Yates, ty20@leicester.ac.uk
Canada: Prof. Kaberi Dasgupta, Kaberi.Dasgupta@mcgill.ca

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
286182

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 48343, IRAS 286182

Study information

Scientific Title
Remission of diabetes and improved diastolic function by combining structured exercise with meal replacement and food reintroduction: the RESET for Remission trial

Acronym
RESET for Remission

Study objectives
Combining structured exercise training with a low-calorie diet will lead to diabetes remission and improvements in overall health status compared to the standard care control arm.

Ethics approval required
Old ethics approval format

Ethics approval(s)

1. UK: Approved 12/03/2021, East Midlands - Nottingham Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8104; NRESCommittee.EastMidlands-Nottingham1@nhs.net), REC ref: 21/EM/0026
2. Canada:
2.1. Approved 08/06/2021, McGill University Health Centre - Centre for Applied Ethics (5100, boul. de Maisonneuve Ouest, 5th floor, Office 576, Montreal, Quebec, H4A 3T2, Canada; +1 (0) 514 934 1934 ext-34323; cae@muhc.mcgill.ca), ref: 2021-7148
2.2. Approved 23/08/2021, University of Alberta - Health Research Ethics Board - Biomedical Panel (Suite #2-01 Power Plant North 11312 - 89 Ave NW, Edmonton, AB T6G 2N2, Canada; +1 (0) 780 492 2615; reoffice@ualberta.ca), ref: Pro00101088

Study design
Prospective randomized two-arm open-label blinded-endpoint (PROBE) multinational trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

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 2 diabetes mellitus (T2DM)

Interventions
This trial is a 24-week randomised control trial with two arms. Randomisation (at the individual level, stratified by country) will occur once all baseline measures are completed and individuals are confirmed to be eligible. Individuals deemed ineligible following baseline evaluation will not be randomised. A permuted block randomisation will be performed and an independent statistician will develop a computer-assisted random sequence within the block. When the investigator is not blinded, and the block size is fixed, the allocation is predictable. To preserve allocation concealment, the block size will be varied (e.g., 2, 4).

1. The control group - participants randomly allocated to this group will continue to receive standard care.

2. The intervention group will be prescribed a low energy diet with total meal replacement for the first 2 weeks, followed by partial meal replacement from weeks 3-12. This will be followed by individualised food reintroduction (weeks 13-24). During weeks 3-12, this will be combined with supervised aerobic and resistance exercise, and a transition to unsupervised home-based exercise will be introduced in weeks 13-24. Individuals randomly assigned to the intervention group will be taken off their glucose-lowering medication and antihypertensive medication by a

study physician at the onset of the intervention. However, ACE inhibitors or angiotensin receptor blockers will not be discontinued in the context of albuminuria.

Following the 24-week intervention period, participants enrolled into the control group will be offered the meal replacement component of the low energy diet complemented by a 4-week food reintroduction period with support from the study dietitians and physicians.

Participants will receive the same level of clinical and dietetic management as the intervention arm, but captured data will not form part of the study outcomes.

Intervention Type
Behavioural

Primary outcome measure
Current primary outcome measures as of 26/08/2022:
Diabetes remission measured through HbA1c collected by venous blood sampling at Week 24. HbA1c below 6.5% without glucose-lowering medication during the prior 12 weeks will be defined as remission.

Previous primary outcome measures:
Diabetes remission defined as HbA1c <6.5% (48 mmol/mol) without prescribed glucose-lowering medications between 12 and 24 weeks of the study period. HbA1c will be obtained through a venous blood sample.

Secondary outcome measures
Current secondary outcome measures as of 26/08/2022:

Measured at baseline, week 12 and week 24 unless specified otherwise:

1. Other remission, glycemic, and insulin resistance measures:
1.1. Diabetes remission measured through venous blood sampling at Week 12
1.2. Fasting glucose and insulin, Homeostatic Model Assessment for Insulin Resistance measured through venous blood sampling
2. Main cardiovascular magnetic resonance imaging (CMR) measures:
2.1. Left ventricular peak early diastolic strain rate (circumferential and longitudinal) measured through an MRI scan at Baseline and Week 24 only
2.2. End-diastolic mass to volume ratio measured through MRI scan at Baseline and Week 24 only
3. Main fitness measure:
3.1. VO_2 peak measured through a graded treadmill exercise test
4. Main fat and lean mass measures:
4.1. Total fat and lean soft tissue mass measured by dual-energy X-ray absorptiometry (DXA) scan
4.2. Weight (measured on scales) and body mass index (BMI)
5. Cardiometabolic indicators:
5.1. Hypertension remission, systolic and diastolic blood pressure, heart rate measured using a standardised blood pressure cuff procedure
5.2. Total cholesterol, HDL, LDL, and triglycerides measured through venous blood sampling.

Other secondary outcomes:
6. Renal function measures:
6.1. Creatinine and estimated glomerular filtration rate measured through venous blood sampling

6.2. Urine albumin to creatinine ratio measured through urine sampling
7. Hepatic function measures:
7.1. Aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and bilirubin measured through venous blood sampling
8. Depression, anxiety, and distress measured using the Hospital Anxiety and Depression Scale and Diabetes Distress Scale
9. Indirect calorimetry:
9.1. Resting metabolic rate measured through indirect calorimetry (ventilated hood system)
10. Additional cardiac and aortic MRI-based measures:
10.1. Longitudinal and circumferential measures of systolic strain, end-systolic volume, ejection fraction, and mean T1 time measured through MRI scan at Baseline and Week 24 only
10.2. Cross-sectional areas and distensibility of ascending and descending aortae measured through MRI scan at Baseline and Week 24 only
11. Additional measures of muscle mass and adiposity
11.1. Neck, hip, and waist circumference measured via tape measure
11.2. Visceral adipose tissue, pancreatic and liver fat percentages, subcutaneous adipose tissue, and muscle mass measured through MRI at Baseline and Week 24
12. Dietary variables:
12.1. Total energy and macronutrient intake (protein, carbohydrates, lipids) assessed through a 4-day food diary
12.2. Selected carbohydrate types (total sugars, starch, fibre), selected lipid types (saturated, monounsaturated, polyunsaturated, cholesterol), and alcohol assessed through a 4-day food diary
13. Accelerometer-based physical activity measures and sleep (daily average):
13.1. Steps, overall acceleration, and intensity gradient metric measured objectively through a wrist-worn accelerometer device
13.2. Minutes for each of sedentary, light, and moderate to vigorous physical activity measured objectively through a wrist-worn accelerometer device
13.3. Sleep time, duration of night, and sleep efficiency (sleep time/duration of night) measured objectively through a wrist-worn accelerometer device
14. Other exercise stress test measures:
14.1. VCO_2 peak and the maximum gradient achieved measured through a graded treadmill exercise test

Tertiary outcomes:
15. Bone measures:
15.1. Total bone mineral density and bone mineral content measured by DXA scan
16. Physical function:
16.1. Handgrip strength measured using a hand dynamometer device
16.2. Physical function assessed using the Short Physical Performance Battery
16.3. Impact of breathlessness on daily activities measured using the Dyspnoea scale
17. Overall health state measured using:
17.1. EQ-5D-5L score (EuroQuol group 5-dimensional 5-level questionnaire)
17.2. WHO Disability Assessment Schedule 2.0
18. Process evaluation
18.1. Acceptability, feasibility, facilitators, barriers and adherence to the intervention determined through interviews at Week 24 only

Previous secondary outcome measures:
Measured at baseline, 12 weeks and 24 weeks (unless stated otherwise):
1. Indices of cardiac function and structure, including the variables listed beneath, assessed using magnetic resonance imaging at baseline and 24 weeks only: left ventricular (LV) end-

diastolic volume; LV end-systolic volume; LV ejection fraction; LV stroke; volume; LV cardiac output; LV diastolic myocardial mass; LV peak diastolic filling rate; LV systolic global longitudinal strain; LV systolic global circumferential strain; LV longitudinal peak early diastolic strain rate and LV circumferential peak early diastolic strain rate.
2. Cardiometabolic risk factors, such as lipid profile (including total cholesterol, HDL, LDL and triglycerides) and systolic and diastolic blood pressure. Among those not requiring angiotensin-converting enzyme inhibitors (ACE I) inhibitors or angiotensive receptor blockers (ARB) specifically for micro/macroalbuminuria, the researchers will examine hypertension remission. Urea and electrolytes [U&Es], creatinine (for estimated glomerular filtration rate [eGFR]) and liver function tests [LFTs]) will be obtained through venous blood sampling.
3. Aerobic capacity (peak oxygen uptake; VO_2peak) (to include absolute VO_2peak (L•min-1) and VO_2peak relative to lean body mass (LBM) (i.e., ml•kg LBM-1•min-1) and relative to overall body mass (ml•kg BW-1•min-1)), measured through gas analysis during maximal CardioPulmonary Exercise Testing (CPET)
4. Physical function measured using the Short Physical Performance Battery (SPPB) and handgrip dynamometry
5. Anthropometry and body composition (to include total body weight, BMI, lean body mass, fat mass [FM]):
5.1. Body composition measured through bioelectrical impedance testing and Dual Energy X-Ray Absorptiometry (DEXA)
5.2. Anthropometrics such as height and waist circumference measured using standardised tape measure procedures
6. Intra- and inter-organ adiposity (to include subcutaneous abdominal adipose tissue (SAT), visceral adipose tissue (VAT), intrahepatic and pancreatic fat, liver fat, mid-thigh fat and muscle area, assessed through magnetic resonance imaging at baseline and 24 weeks only)
7. Resting metabolic rate (RMR) assessed via indirect calorimetry
8. Sleep, sedentary time and physical activity measured using a wrist-worn device
9. Urine albumin to creatinine ratio (ACR) measured with a urine sample
10. Mental wellbeing (to include anxiety, depression and diabetes distress) assessed through the Hospital Anxiety and Depression scale (HADS)
11. Quality of life assessed through the EQ-5D-5L questionnaire
12. Health resource usage assessed through medical notes and a health resource questionnaire
13. Acceptability, feasibility, facilitators, barriers, adherence to the intervention as assessed through process evaluations
14. Dietary micro-macro nutrient compositions captured through validated nutritional analysis software
15. Average glucose, glucose variability (standard deviation and coefficient of variation) and percent time in range (3.9 to 10 mmol/l) measured using continuous glucose monitoring starting at baseline and during weeks 2, 4, 11 and 23 within a sub-sample of the intervention group

Overall study start date
12/03/2021

Completion date
31/10/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/08/2022:
1. Age 18 to 45 years, inclusive

2. Type 2 diabetes: physician diagnosis more than 3 months and less than 6 years previously
3. Hemoglobin A1c 6.5% to 10%, inclusive if not taking glucose-lowering medication; 6.0% to 10% if taking glucose-lowering medication
4. Body mass index 30 kg/m² to 45 kg/m², inclusive if White or Indigenous[1], 27 kg/m² to 45 kg/m², inclusive if other background, including mixed
5. Weight stability: weight changes of less than 5 kg over the prior 6 months
6. Walking ability: able to walk without assists and to participate in structured exercise training requiring the lower limbs
7. Capacity: able to understand written and spoken English and/or French
8. Able to provide informed consent
9. Willing to be randomized and able to participate
10. Willing to attend supervised exercise sessions, if so randomized
11. Willing to adopt low energy diet, including abstinence from alcohol, if so randomized
12. Willing to self-monitor glucose and blood pressure at the required frequency, if randomized to the low energy diet plus supervised exercise arm

[1]Term for the original peoples of North America and their descendants; includes First Nations, Inuit, and Métis peoples
[2]An exception is made for women who are on insulin therapy in case of pregnancy occurrence because of insulin's established safety profile in pregnancy, rather than because of inability to control glycemia on oral agents alone. If these women are willing and able to use a reliable form of contraception, they may be enrolled.

Previous inclusion criteria:
1. Age 18 to 40 years, inclusive
2. A clinically coded diagnosis of T2DM between 3 months and 6 years previously
3. HbA1c 6.5% (48 mmol/mol) to 10% (86 mmol/mol), inclusive, within the last 12 months
4. BMI ≥30 kg/m² and ≤45 kg/m² (≥ 27.0 kg/m² if BAME (self-identified)), within the last 12 months
5. Self-reported stable weight over the previous 6 months (<+/- 5 kg)
6. Treatment stable; no significant change to glucose-lowering regimen in the preceding 3 months, as determined by a study investigator
7. Able to provide informed consent
8. Able to understand written and spoken English
9. Able to take part in structured exercise training requiring the lower limbs (e.g., able to walk without assists or impairment)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
45 Years

Sex
Both

Target number of participants
100

Key exclusion criteria
Current exclusion criteria as of 24/08/2022:
1. Other diabetes types:
1.1. Type 1 diabetes
1.2. Gestational diabetes
1.3. Monogenic diabetes
2. Poorly controlled blood pressure: resting systolic blood pressure greater than 150 mmHg or resting diastolic blood pressure greater than 90 mmHg diastolic
3. Weight loss interventions: currently participating in a weight reduction program in addition to routine care
4. Previous bariatric surgery
5. Medications:
5.1. Insulin therapy[2]
5.2. Use of licensed weight loss medications
5.3. Significant changes in glucose-lowering medications in the prior 3 months, as judged by study physicians
5.4. Steroids by mouth or injection
6. Allergies: self-reported allergies or intolerances to components of the meal replacement products (e.g., milk protein allergy)
7. Dietary practices that prohibit the use of meal replacement products
8. Pregnancy, lactation or planning to become pregnant in the next 8 months
9. Eating disorder: self-reported or diagnosed
10. Substance abuse: alcohol, drugs
11. Estimated glomerular filtration rate: less than 60 ml.min-1 per 1.73m²
12. Retinopathy: receiving or requiring active treatment for retinopathy
13. Clinically manifest vascular disease:
13.1. Myocardial infarction
13.2. Stroke
13.3. Peripheral vascular disease
14. Other cardiac disease:
14.1. Heart failure
14.2. Atrial fibrillation
14.3. Pacemaker
14.4. Implantable cardioverter defibrillator (ICD)
15. Other conditions that could impact weight and/or safety: active malignancy or other chronic disease
16. Run-in phase:
16.1. Failure to complete at least 5 or requested 7 days of accelerometer wear
16.2. Failure to complete a food diary for three weekdays and one weekend day

Previous exclusion criteria:
1. Individuals with type 1, gestational or monogenic diabetes mellitus
2. On insulin therapy (An exception may be made for women who are on insulin therapy in case of pregnancy occurrence because of insulin’s established safety profile in pregnancy, rather than because of inability to control glycaemia on oral agents alone. If these women are willing and able to use a reliable form of contraception, they may be enrolled.)
3. eGFR <60 ml.min-1 per 1.73m²
4. Currently participating in a weight reduction program in addition to routine care

5. Previous bariatric surgery
6. Currently on injected steroids
7. Currently on weight loss medications (not including glucose-lowering medication)
8. Conditions that could impact weight (i.e., active malignancy/treatment in past year, pregnancy, lactation, planning to become pregnant in next 8 months)
9. Individuals with a self-reported or diagnosed eating disorder
10. Self-reported milk protein allergy or other allergy or dietary practice that prohibits the use of meal replacement products
11. Previous myocardial infarction, stroke, amputation secondary to T2DM/peripheral vascular disease, or other evidence of clinically manifest vascular disease
12. Previous clinically diagnosed atrial fibrillation
13. Previous clinically diagnosed heart failure
14. Pacemaker or implantable cardioverter-defibrillator (ICD)
15. Substance abuse. The requirement for alcohol abstinence during the initial 12 weeks will make it unlikely that individuals with alcohol dependence will enrol. Substance abuse will be queried.
16. Average resting blood pressure >150 mmHg systolic and/or >90 mmHg diastolic. In the case of borderline hypertension, individuals will be offered the opportunity to repeat the test at a later date.
17. Currently receiving or requiring active treatment for retinopathy.
18. Current participation in another research study with investigational medical product

Date of first enrolment
24/09/2021

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
Canada

England

United Kingdom

Study participating centre
Leicester Diabetes Centre
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Study participating centre

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Website
http://www.le.ac.uk/research/regi/sponsorship

ROR
https://ror.org/04h699437

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Sponsor type
Research organisation

Website
https://rimuhc.ca/

ROR
https://ror.org/04cpxjv19

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Canadian Institutes of Health Research

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR, IRSC

Funding Body Type

Government organisation

Funding Body Subtype
National government

Location
Canada

Funder Name
John R McConnell Foundation

Results and Publications

Publication and dissemination plan
A protocol paper (detailing all aspects of the protocol, including the statistical analyses) will be submitted for publication as soon as possible. The researchers aim to publish the findings from this investigation within a year of the overall trial end date. The results of this trial will be published in peer-reviewed journals and through educational and conference presentations.

Updated 04/06/2024:
A protocol paper detailing all aspects of the protocol (including the statistical analyses) has been published in BMJ Open, please see the following link: https://pubmed.ncbi.nlm.nih.gov/36130753/

Intention to publish date
31/03/2026

Individual participant data (IPD) sharing plan
Following the publication of the primary papers and all ancillary analyses by the research team, datasets will be available from the principal investigators (UK: Prof. Tom Yates - ty20@leicester.ac.uk) or (Canada: Prof. Kaberi Dasgupta - kaberi.dasgupta@mcgill.ca), contingent on the agreement of both Principal investigators and the associated Research Ethics Boards, on reasonable request. Any publications stemming from these data will be reported on group-level only so that individual participant anonymity is maintained.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		21/09/2022	22/09/2022	Yes	No
HRA research summary			28/06/2023	No	No
Statistical Analysis Plan	version 1.0	18/07/2025	24/07/2025	No	No