ISRCTN15177113 https://doi.org/10.1186/ISRCTN15177113

Reversal of type 2 diabetes by weight loss then maintenance of a steady weight in non-obese people

Submission date
12/11/2018

Recruitment status
No longer recruiting

Registration date
03/12/2018

Overall study status
Completed

Last Edited
06/02/2023

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
Over the past 10 years research has demonstrated that type 2 diabetes is caused by less than one gram of excess fat in the pancreas, with loss of specialized function of the insulin-producing cells. Individuals differ very much in their personal susceptibility to diabetes. The Personal Fat Threshold hypothesis potentially explains the major reasons why this should be. Individuals can reverse to normal glucose control by decreasing their BMI by about 4 units, and this is so whether the person is obese or merely overweight. In the UK, only 50% of people newly diagnosed with type 2 diabetes are obese, just under 40% are overweight and 11% are 'normal' as defined by BMI. Type 2 diabetes in non-obese individuals is frequently regarded as having a different cause from that affecting obese people. However, experimental evidence does not support this, and the concept of a personal level of tolerance of total body fat could explain the phenomenon. The aims of this study are to test the Personal Fat Threshold hypothesis and to identify blood markers which may be of assistance in the management of individuals.

Who can participate?
Patients with type 2 diabetes classified by BMI as normal or marginally overweight

What does the study involve?
After an overnight fast, weight, height, waist circumference and body fat are measured, followed by an MRI scan. This involves about 30 minutes lying in the scanner, and is entirely free of any discomfort. Following this test, a small plastic tube is sited in an arm vein to permit painless blood sampling. Tests include those for fat tissue inflammation as well as insulin, glucose and fats. A standard breakfast is then be provided, and blood sampling continues for 150 minutes. A convenient period to start the low calorie diet is chosen by the participant. On Day 1, all tablets to control blood sugar are stopped and the low calorie diet starts. Fasting blood sugar falls rapidly and is normal in most people by day 7. Also on Day 1, any blood pressure medication is stopped. The low calorie diet consists of 600 kcal/day from a liquid formula product, plus 240g of non-starchy vegetables. This is used to achieve a 5% decrease in body weight over about 2 weeks. This is supervised by the research dietitian by telephone contact. Participants monitor fasting and blood glucose levels after meals twice weekly. After

the first weight loss period, participants gradually return to an isocaloric (moderate) diet of normal foods over 2 weeks. The nature of the diet is chosen by the participant in discussion with the research dietitian using the prototype version of the Diet Decision Aid. After a total of 8 weeks since the start of the weight loss, the MRI and meal tests are repeated together with measurement of weight, waist circumference and body fat. The cycle of weight loss, weight maintenance then tests is repeated twice to achieve a 15% decrease in body weight. If an individual achieves normalization of both fasting blood glucose and HbA1c after the second cycle, then the third cycle is not undertaken.
The results of all tests are discussed with the participant as soon as available. At the end of each person's involvement, a full plan for future wellbeing is drawn up in discussion between the research dietitian and the participant. With the individuals consent, this is also sent to their GP.
In order to be able to interpret the special test results in relation to what is genuinely normal, a control group of participants with normal blood glucose control needs to be studied. No data are available for any of the special measurements in respect of normal range for people of BMI between 19 and 27m/kg2. To be able to establish without doubt that each control person has normal glucose tolerance, a glucose tolerance test is carried out as part of the initial determination of suitability to participate. The possibility of an abnormal result is discussed in advance, and any such result would be fed back to the individuals' GPs, with their consent.

What are the possible benefits and risks of participating?
The benefit for participants is primarily the possibility of reversing type 2 diabetes back to normal such that they can stop all diabetes medication and be re-classified as not having diabetes. Even if diabetes does not go away, the weight loss itself confers major health benefits in terms of everyday well-being and decreased risks of heart disease. There are no significant risks associated with the study.

Where is the study run from?
Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2018 to February 2022

Who is funding the study?
Diabetes UK

Who is the main contact?
Alison Barnes
Alison.Barnes@newcastle.ac.uk

Contact information

Type(s)
Scientific

Contact name
Miss Alison Barnes

Contact details
Magnetic Resonance Centre,
Campus for Ageing and Vitality
Newcastle upon Tyne

United Kingdom
NE4 5PL
+44 (0)1912081172
Alison.Barnes@newcastle.ac.uk

Additional identifiers

Integrated Research Application System (IRAS)
234620

Central Portfolio Management System (CPMS)
36289

Protocol serial number
Diabetes UK No. 17/0005645

Study information

Scientific Title
Reversal of type 2 diabetes upon normalisation of energy intake in non-obese people (ReTUNE)

Acronym
ReTUNE

Study objectives
That the cause of common type 2 diabetes is the same in people with BMI under 27 as those over 27, and also that the personal fat threshold for an individual at which type 2 diabetes occurs can be detected by markers in blood.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/12/2017, North East – Newcastle and North Tyneside 1 Research Ethics Committee, (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)2071048139, (0)2071048255; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 17/NE/0384

Primary study design
Interventional

Study design
Non-randomised interventional study

Study type(s)
Other

Health condition(s) or problem(s) studied
Type 2 diabetes mellitus

Interventions

Participants will be invited via newspaper advertisement (n=24). After a full explanation of the study, written consent will be requested.

Tests will be carried out at baseline, during any prescribed tablet treatment. After an overnight fast, measurements of weight, height, waist circumference and % body fat by impedence meter will be made. Then each person will have magnetic resonance scans. This will involve approximately 30 minutes lying in the scanner, and this is entirely free of any discomfort. Music of choice can be listened to, and auditory contact with the research radiographer is maintained throughout. Following this test, a small plastic tube will be sited in an arm vein to permit painless blood sampling. This will be done in the clinical room adjacent to the scanner room. Tests include those for fat tissue inflammation as well as insulin, glucose and fats. A standard breakfast will then be provided, and blood sampling will be continued for 150 minutes.

A convenient period to commence the low calorie diet will be chosen by the participant. On Day 1, all tablets to control blood sugar will be stopped and the low calorie diet will be commenced. Fasting blood sugar falls rapidly and is normal in most people by day 7. Also on Day 1, any blood pressure medication is stopped. The diet causes a rapid normalisation of blood pressure, and the experience of our previous studies shows that stopping the tablets safely prevents any dizziness on standing.

The low calorie diet consists of 600 kcal/day from a liquid formula product, plus 240g of non-starchy vegetables. This will then be used to achieve a 5% decrease in body weight over approximately 2 weeks. This intervention will be supervised by the research dietitian via telephone contact. Participants will monitor fasting and post-prandial blood glucose levels twice weekly.

After the first weight loss period, a stepped return to an isocaloric diet of normal foodstuffs over 2 weeks will be then be undertaken. The nature of the diet will be chosen by the participant in discussion with the research dietitian using the prototype version of the Diet Decision Aid.

After a total of 8 weeks since the start of the weight loss, the magnetic resonance and meal tests will be repeated together with measurement of weight, waist circumference and % body fat.

The cycle of weight loss, weight maintenance then tests will be repeated twice. This will achieve approximately 15% decrease in body weight. If an individual achieves normalization of both fasting plasma glucose and HbA1c after the second cycle, then these tests will constitute the final end point for the individual and the third cycle will not be undertaken.

The results of all tests will be discussed with the participant as soon as available. At the end of each person's involvement, a full plan for future wellbeing will be drawn up in discussion between the research dietitian and the participant. With the individuals consent, this will also be send to their GP.

In order to be able to interpret the special test results in relation to what is genuinely normal, a control group of participants with normal blood glucose control needs to be studied (n=20). No data are available for any of the special measurements in respect of normal range for people of BMI between 19 and 27m/kg2. To be able to establish without doubt that each control person has normal glucose tolerance, a glucose tolerance test will be carried out as part of the initial determination of suitability to participate. The possibility of an abnormal result will be discussed in advance, and any such result would be fed back to the individuals' GPs, with their consent.

Once the whole ReTUNE study data are available, participants will be invited back to the MR Centre for the usual evening feedback session. This allows discussion of the results and what they really mean. A copy of the results will be provided to each person. Additionally, the session allows the investigators to hear from participants about their experiences. The overall design of this study reflects participant feedback sessions from all previous studies.

Intervention Type
Behavioural

Primary outcome(s)
HbA1c and plasma glucose at baseline, 8 weeks, 16 weeks, and 52 weeks will be measured using HPLC (Tosoh Bioscience, UK) and oxidase method (Yellow Springs Inc., USA), by the Clinical Pathology Accreditation Laboratory (Newcastle upon Tyne Hospital NHS Foundation Trust, UK). An HbA1c under 48mmol/l is used to establish remission of type 2 diabetes.

Key secondary outcome(s)
1. Markers of adipose tissue overexpansion as potential guides to defining a Personal Fat Threshold during the weight loss phase. This includes:
1.1. Blood total lipid profile: (fasting plasma and taken up to 3h after standard meal test) are measured at baseline, after each weight loss phase (at 8 weeks, 16 weeks, and at 24 weeks if a 3rd weight loss cycle is required) and at 52 weeks by Clinical Pathology Accreditation Laboratory (Newcastle upon Tyne Hospital NHS Foundation Trust, UK)
1.2. Blood lipoprotein profile: Chylomicrons, VLDL1, VLDL2, and LDL will be separated from plasma at the same timepoints as above using is MX 150+ ultracentrifuge and S140-AT rotor (Thermo Scientific, Germany). Triglyceride level will be measured for each lipoprotein fraction using standard method (Roche Diagnostics, UK).
1.3. Inflammation markers and hormones: plasminogen activator inhibitor-1, C-reactive protein, TNFα, interleukin 6), adiponectin and leptin will be measured in house using commercially available kits (ELISA) at the baseline of the study and following each cycle of weight loss.
2. Pancreatic fat content and morphology during the weight loss phase, measured by magnetic resonance using in house developed methods (MR-opsy). This will be performed at baseline, 8 weeks, 16 weeks and 52 weeks. If a 3rd cycle of weight loss is required then a further scan will be done at 24 weeks. For normal glucose tolerance group, this will be carried out at one timepoint only. Pancreas volume will be measured using volume rendering technique of the acquired magnetic resonance images following the same time course.
3. Fatty acid composition of fasting plasma and lipoprotein fraction determined using standard FAME analysis by GC-MS (Thermo Scientific, Waltham, MA) at baseline, during and after restriction of food energy
4. Achievement and maintenance of weight loss target, choice of dietary strategy and number of times this is changed during the intervention, evaluation of dietary intake by 24 hour recall x3 using Intake 24 (an online 24 hour recall survey) preceding baseline visit, week 8 visit, week 16 visit and final visit at week 52. Where a 3rd cycle of weight loss is required dietary intake will also be assessed in the same way leading up to week 24 visit/scan.

Completion date
20/02/2022

Eligibility

Key inclusion criteria

1. Documented type 2 diabetes of duration less than 6 years (same as DiRECT)
2. All ethinicities
3. BMI of 21-27 kg/m2 for people of Caucasian ethnicity and 19-27 kg/m2 for people of other ethnicity due to documented differing metabolic risks per BMI unit

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Current insulin use
2. HbA1c > = 12%
3. Substance abuse
4. Known cancer
5. Myocardial infarction within previous 6 months
6. Learning difficulties
7. Diagnosed eating disorder or purging
8. Pregnant or considering pregnancy
9. Previous hospitalisation for depression
10. Presence of metal implants preventing magnetic resonance scanning
11. Claustrophobia likely to cause discomfort in the MR scanner

Date of first enrolment
25/04/2018

Date of final enrolment
20/08/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust
United Kingdom
NE4 5PL

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Diabetes UK; Grant Codes: 17/0005645

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 datasets generated during and/or analysed during the current study are/will be available upon request from Prof. Roy Taylor (roy.taylor@newcastle.ac.uk). Metabolic and MR data will become available on completion of the study but after publication for 5 years, available to scientifically qualified people. This data sharing is included in participant consent. No personal data will be released, only group data; all data will be handled in an anonymised fashion.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results		03/08/2022	18/01/2023	No	No

Abstract results		01/09/2021	18/01/2023	No	No
HRA research summary			26/07/2023	No	No
Protocol file	version v1.3	07/11/2017	03/12/2018	No	No