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Investigating cardiac energy levels in people with lean-type type 2 diabetes

Submission date
27/01/2020

Recruitment status
No longer recruiting

Registration date
16/03/2020

Overall study status
Completed

Last Edited
19/02/2025

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
Type 2 diabetes is a common condition that causes the level of sugar (glucose) in the blood to become too high. It's caused by problems with a chemical in the body (hormone) called insulin. It's often linked to being overweight or inactive, or having a family history of type 2 diabetes.

The majority of people with type 2 diabetes (T2D) are overweight, and while weight gain is a major contributor to diabetes, a minority of patients with T2D are not overweight or obese. The reasons why lean or normal body weight individuals develop T2D (lean-T2D) are not yet understood. T2D occurs when the body does not produce enough insulin, or becomes less sensitive to its effects. Insulin acts like a key to allow sugar into cells and if someone is overweight that key works less well. Recent research suggests that T2D in lean people should be considered a different disease from the diabetes associated with obesity and the main problem in lean-T2D patients may be a reduced capacity of insulin secretion. However, some researchers argue that many seemingly thin people carry more fat than muscle, making them trim on the outside, but fat on the inside, and they are in fact not truly lean. This implies that just like overweight diabetics, lean diabetics also have high resistance to insulin. The main aim of our research is to better understand the main driver of T2D in lean individuals, as this will determine how best to treat these individuals.

There are many different types of drugs for treating T2D. Liraglutide improves insulin secretion capacity of the pancreas. Pioglitazone reduces resistance to insulin action. This study will compare the actions of these diabetes drugs on the blood supply and the heart's energy levels in lean-T2D and obese-T2D patients. This will allow the researchers to determine the ideal treatment strategies for improving cardiovascular health in lean-T2D patients, and better understand the role of impaired insulin secretory capacity, insulin resistance and excess fat deposition specifically in this group.

Who can participate?
Adults aged > 18 years with BMI between 18 – 25 kg/m² or with a BMI > 27 kg/m².

What does the study involve?
Participants will be randomly allocated to receive one drug for 16-weeks, after which they will

have 8-weeks break and then take the other drug for another 16-weeks. At the start and end of each drug taking period, participants will attend the clinic for a physical assessment.

What are the possible benefits and risks of participating?
While there are no direct benefits for participants, participation in this study will hopefully lead to better treatment strategies for patients with Type 2 Diabetes in the future.
The 2 drugs used in the study have known side effects. MRI scanning is safe and non-invasive, and routinely used clinically. Some people find the size limitation in the scanner uncomfortable. There is a low risk of side effects or reaction to the contrast agent used during the scan. The drug used to observe blood flow in the heart can cause some discomfort; however these effects subside within one to two minutes of stopping the drug.

Where is the study run from?
The Advanced Imaging Centre (AIC) at the Leeds General Infirmary (UK)

When is the study starting and how long is it expected to run for?
January 2020 to January 2021

Who is funding the study?
1. Diabetes UK
2. National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Kathryn Richards
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
265208

ClinicalTrials.gov (NCT)
NCT04657939

Protocol serial number
CPMS 44109, IRAS 265208

Study information

Scientific Title
Targeting beta-cell failure in lean patients with type 2 diabetes

Acronym
Lean-DM

Study objectives
Treatment with a GLP-1RA (Liraglutide) will promote beta-cell insulin secretion, restore coronary microvascular function, and modulate exercise metabolism in Ln-T2D patients compared to a peroxisome proliferator activated receptor gamma (PPAR-gamma) agonist (Pioglitazone), which targets peripheral insulin sensitivity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/01/2020, West Midlands - Black Country Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8284; nrescommittee.westmidlands-blackcountry@nhs.net), ref: 19/WM/0365

Study design
Interventional randomised cross over trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
This is a single centre, open-label, randomized, cross-over study. Participants will attend 4 visits in total over the course of approximately 40 weeks. Two cohorts of patients will be recruited: 28 lean-T2D patients and 28 obese-T2D patients.

Potential participants will be invited to the Advanced Imaging Centre (AIC) at the Leeds General Infirmary for a screening/ baseline visit (Visit 1). At this visit, they will be given the PIS to read through, and given the opportunity to ask questions. If they are interested in participating, their consent will be taken in written form. Each participant will then have a series of non-invasive tests. At this baseline visit, the following assessments will be done:

• Review of medical history and concomitant medications
• Review of history of diabetes and complications
• Review of inclusion/exclusion criteria
• Collection of demographic data
• Vital signs
• Physical examination
• Height and weight
• Blood pressure
• Urine pregnancy test in women of childbearing potential
• Venepuncture (fasting sample): 20mls
• Multiparametric MRI
• EndoPAT testing
• 6-minute walk test
• 12-lead ECG
• Randomization
• Dispense study medication and issue patient diary
• Urine sample collection

At this visit, participants will be randomized to receive either liraglutide or pioglitazone first. Participants that are already taking certain classes of glucose-lowering medications may be excluded from the study (see exclusion criteria for more detail). Participants will continue to take their previously prescribed medications throughout the study.

After 16 weeks of treatment (Visit 2), participants will return to the AIC and have the following assessments:
• Vital signs
• Physical examination
• Blood pressure
• Weight
• Venepuncture (fasting sample): 20mls
• 12-lead ECG
• Multiparametric MRI
• EndoPAT testing
• 6-minute walk test
• Check current medication list and patient clinical status
• Check study medication compliance (diary review); and
• Urine sample collection.

Participants will then have an 8 week washout period, in which they will take no study drug. After these 8 weeks, they will return to the AIC (Visit 3) and have the same assessments as listed above for Visit 2. They will start taking the second study drug for 16 weeks.

After 16 weeks, participants will attend the AIC for a final time (Visit 4) and have the same assessments as listed above for Visit 2.

Collected blood will be tested for triglycerides, alanine aminotransferase, haemoglobin, haematocrit, creatinine, estimated glomerular filtration rate, N-terminal pro–B-type natriuretic peptide, insulin, free fatty acids, adiponectin, glucose and lipid profiles, glutamic acid decarboxylase antibodies, and Zinc transporter 8 antibodies. Urine will be spot-tested for albumin/ creatinine ratio.

Previous clinical studies have found an association between diabetes and impaired function of the endothelium of blood vessels. The EndoPAT 2000 is a machine that measures endothelium function via 2 thimble-sized sensors placed on the index fingers. This is a safe and non-invasive way of testing the condition of the participant's blood vessels, and testing takes about 5 minutes. The test is used in research studies at centres around the world. It is CE marked and we will be using it for its intended function. It is not used routinely clinically.

The 6-minute walk test is an exercise test that requires patients to walk along a long flat corridor for 6 minutes to see how far they can walk at their own pace. They will be able to stop and rest as they need. If they use walking aids they will be able to use these as normal.

Liraglutide will be administered at 0.6mg once weekly to start, then titrated up to 1.2mg after 2 weeks if the participant's glucose levels permit. Participants will be trained how to administer the injection themselves. Glucose assessments will be done after 2 weeks of treatment with Liraglutide. Pioglistazone is taken orally. Participants will be started on 15mg once daily; this will be titrated up to 30mg after 2 weeks, then to 45mg after another 2 weeks if glucose levels permit. Glucose assessments will be done 2 weeks after starting treatment, then 4 weeks after starting treatment.

These glucose assessments will be performed by the study team at the Leeds General Infirmary (LGI). Participants will be told to continue their usual schedule of glucose monitoring at home while on the study drugs (no additional monitoring at home will be necessary).

Before participants start liraglutide treatment, their blood will be collected to check their calcitonin levels. Before participants start Pioglitazone treatment, their blood will be collected to check their liver function tests and their urine checked for haematuria. These tests will be done at the visit in which the drugs are prescribed (visits 1 and 3).

Participants will be given diaries to complete while they are on both drugs. The diary for taking liraglutide should take 5 to 10 minutes a week to complete, as all is required is filling in the date and answering yes or no to if they took the drug that week. The diary for taking pioglitazone needs to be completed each day; this should take 1 to 2 minutes a day as all is required is filling in the date and answering yes or no to if they took the drug that day.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Liraglutide Pioglitazone

Primary outcome(s)
Myocardial perfusion measured by MRI at baseline and 16-weeks.

Key secondary outcome(s))
At baseline and 16-weeks:
1. Myocardial energetics (PCr/ATP ratio), measure by MRI spectroscopy.
2. Myocardial steatosis (myocardial triglyceride content), measured by MRI spectroscopy
3. Myocardial function, measured by MRI

4. Insulin resistance (HOMA-IR) measured by blood test
5. Physical performance, measure by 6 minute walk test
6. Hepatic triglyceride content, measured by blood test
7. Peripheral endothelial function, measure by the EndoPAT machine

Completion date
31/01/2023

Eligibility

Key inclusion criteria
Lean cohort:
1. Men and women >18 years of age
2. Normal body weight 18.5 ≤ BMI ≤25 kg/m²
3. T2D patients can be on treatment with oral glucose-lowering therapies, and if they are, they must have been on these treatments for at least 12 weeks prior to screening
4. 6.5 ≤ HBA1c ≤ 10% at screening
5. Agreement to maintain prior diet and exercise habits for the duration of the study

Overweight cohort:
1. Men and women >18 years of age
2. Increased body weight BMI >27 kg/m²
3. T2D patients can be on treatment with oral glucose-lowering therapies, and if they are, they must have been on these treatments for at least 12 weeks prior to screening
4. 6.5 ≤ HBA1c ≤ 10% at screening
5. Agreement to maintain prior diet and exercise habits for the duration of the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
41

Key exclusion criteria
All cohorts:
1. Any type of diabetes other than T2D
2. Past history of significant CAD
3. Known HF

4. Significant renal impairment (eGFR< 30ml/min/m²)
5. Participation in a clinical trial of an investigational medicinal product in the preceding 12 weeks
6. Known hypersensitivity to dobutamine or gadolinium or any other contra-indications to MRI
7. Participants with obesity where their girth exceeds the scanner bore
8. History of pancreatitis
9. Any history of liver disease
10. Patients with Multiple Endocrine Neoplasia syndrome type 2
11. Prior or current use of thiazolidinediones (aka PPAR-gamma agonists), fibrates, GLP-1RA or insulin
12. Patients with high serum calcitonin levels at baseline
13. Patients that are pregnant (female participants only)
14. Inflammatory bowel disease
15. Diabetic gastroparesis

Date of first enrolment
31/03/2020

Date of final enrolment
31/01/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

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

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/08/2024	19/02/2025	Yes	No
HRA research summary			28/06/2023	No	No
Other unpublished results			19/02/2025	No	No
Participant information sheet	Participant information sheet version v2.1	11/11/2025	11/11/2025	No	Yes
Protocol file		23/10/2019	01/04/2020	No	No