ISRCTN11671196 https://doi.org/10.1186/ISRCTN11671196

Does having some ability to create insulin in type 1 diabetes help protect circulating cells that repair blood vessels and result in different immune responses, and does this work in combination with exercise?

Submission date
18/05/2022

Recruitment status
No longer recruiting

Registration date
06/06/2022

Overall study status
Completed

Last Edited
11/01/2024

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims

In type 1 diabetes (T1D), an individual's own immune system attacks the cells that create insulin, a hormone that controls blood sugar. Individuals with T1D have different types of autoimmune responses, with more severe responses quickly destroying all of the insulin producing cell. Up to 80% of people with T1D for >3 years do still release small amounts of insulin and C-peptide, a molecule involved in the creation of insulin, from the pancreas.

For people with T1D, exercise can be beneficial, potentially reducing the progression of diabetes-related complications. Creating insulin/C-peptide may also help protect against diabetes complications, although exactly how is currently unknown.

One possible way is through endothelial progenitor cells (EPCs), which circulate in the blood and repair blood vessels; with T1D is associated with having lower numbers of these important cells. We have discovered that individuals who no longer produce any insulin/C-peptide have lower resting count and are not able to increase the number of EPCs after exercise, compared to higher counts and exercise-induced increases for those who still produce insulin/C-peptide.

Exercise can also be beneficial for the immune system. Very limited research suggests that beneficial mobilisation of immune cells with exercise is blunted in people with T1D. However, it is not known whether having some ability to create insulin/C-peptide influences this. While different immune cell profiles at diagnosis can predict the rate of destruction, it is unknown whether the profiles differ between individuals with established diabetes and varying levels of insulin/C-peptide.

This study will explore how having some ability to still make insulin/C-peptide in T1D influences how well EPCs work in normal and high glucose conditions and whether this works in combination with exercise, as well as whether the immune response at rest and post-exercise is different between those who create no insulin/C-peptide and those who do.

Who can participate?
Patients aged 18-50 who have been diagnosed with type 1 diabetes for other 2 years, and non-diabetes healthy volunteers aged 18-50.

What does the study involve?
Participants with type 1 diabetes will undergo a urine test to measure how much insulin and C-peptide they may still create. All participants will do a resting blood sample. Some of the participants with type 1 diabetes and the non-diabetes controls will also undertake a graded exercise test on an indoor bike and a high intensity interval exercise bout on an indoor bike. A blood sample will be taken at rest and immediately post-exercise.

What are the possible benefits and risks of participating?
Participants will find out about their individual responses to exercise, receive feedback on fitness, and contribute to the care and management of those with type 1 diabetes. The risks of taking part include experiencing low blood sugar, injury, muscle soreness and pain from blood sample collection.

Where is the study run from?
The study is being run by Newcastle University and takes place in the clinical research facility in the Royal Victoria Infirmary (UK) and Newcastle University Sports Labs.

When is the study starting and how long is it expected to run for?
March 2022 to March 2023

Who is funding the study?
1. Diabetes Research and Wellness Foundation (UK)
2. Newcastle University (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
301646

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 301646, CPMS 52440

Study information

Scientific Title
Does residual β-cell function and exercise offer synergistic protection against hyperglycaemic induced circulating vasoprotective dysfunction and immune deficiency in type 1 diabetes?

Acronym
REBEL – CV

Study objectives
1. Serum from individuals with type 1 diabetes and high beta-cell function attenuates hyperglycaemia-induced apoptosis and dysfunction in endothelial progenitor cells (EPCs) more than serum from individuals with type 1 diabetes and undetectable beta-cell function, but less than serum from non-diabetes controls.
2. Individuals with established T1D and undetectable β-cell functions will have different immune profiles and have greater severity of immune reaction to pancreatic antigen stimulation than those with higher β-cell functions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/05/2022, Yorkshire & The Humber - South Yorkshire Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 2071048091; southyorks.rec@hra.nhs.uk), ref: 22/YH/0078

Study design
Single-centre observational exercise case control trial

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Other

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
Individuals with type 1 diabetes and varying levels of residual beta-cell function

Interventions
Ten participants with type 1 diabetes (T1D) and undetectable C-peptide (<0.001 nmol/mmol), 10 participants with T1D and micro C-peptide (0.001 – 0.030 nmol/mmol), 10 participants with T1D and low C-peptide (0.030 – 0.100 nmol/mmol), 10 participants with T1D and high C-peptide (>0. 100 nmol/mmol) , and 10 non-diabetes controls will be recruited. Type 1 diabetes participants will be identified using urinary C-peptide to Creatinine Ratio testing.

A resting venous blood sample will be taken from all participants. Samples will be analysed for leukocyte populations and responsivity to pancreatic proteins.

Participants with T1D and undetectable C-peptide, participants with T1D and high C-peptide, and non-diabetes controls will also complete a cardiopulmonary exercise test (CPET) to exhaustion, performed on a cycle ergometer. They will also complete high intensity interval exercise bout on a cycle ergometer, completing 4×30 second cycle sprints at 150% of maximum wattage achieved during the CPET, interspersed with 2 minutes of recovery at 40% of maximum wattage. Blood samples will be taken at rest and post-exercise. Samples will be analysed for leukocyte populations and responsivity to pancreatic proteins. Serum will be added to endothelial progenitor cells cultured in hyperglycaemic (25mmol/L) or normoglycaemic (5mmol /L) environments, and the apoptosis and function measured.

Intervention Type
Other

Primary outcome measure
Measured at a single time point:
1. Apoptosis (measured by flow cytometry) of EPCs grown in high glucose condition.
2. Count of leucocyte cells (measured by flow cytometry) within the peripheral blood.

Secondary outcome measures
Measured at a single time point:
1. Function of EPCs (measured by scratch and proliferation assays) grown in high glucose.
2. Responsivity to stimulus (pancreatic proteins) of white blood cell populations as measured by ELISpot.

Overall study start date

01/03/2022

Completion date
15/12/2023

Eligibility

Key inclusion criteria
Individuals with T1D:
1. Willing and able to provide informed consent
2. Aged 18 to 50 years old
3. Clinical diagnosis and classic presentation of T1D (primary osmotic symptoms, weight loss, hyperglycemia, ketosis, insulin initiation at diagnosis)
4. T1D diagnosis for ≥2 years

Non-diabetes controls:
1. Willing and able to provide informed consent
2. Aged 18 to 50 years old
3. No history of any chronic disease

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Both

Target number of participants
50

Key exclusion criteria
Individuals with T1D:
1. Participation in another research study
2. Aged >50 years or <18 years
3. Resting hypertension (≥160 mmHg systolic and/or ≥90 mmHg diastolic)
4. Respiratory disease with peak respiratory flow <300 l/min
5. Previous stroke
6. Pregnancy
7. Irregular period
8. Hormonal treatment for menopause
9. Unable to read and understand the instructions provided in English
10. Contraindication to venous blood sampling

11. Unwilling to undertake exercise
12. Smoker
13. Unwilling to undertake and send a home urine sampling kit
14. Current diagnosis of diabetes complications, including nephropathy, retinopathy (apart from non-proliferative diabetic retinopathy) and neuropathy.
15. Current or previous diagnosis of other autoimmune or chronic diseases, including cardiovascular disease, renal disease and cancer.
16. HbA1c >70 mmol/mol

Non-diabetes controls:
1. Participation in another research study
2. Aged >50 years or <18 years
3. Any sign/symptom of cardiovascular, metabolic or renal disease
4. Previous or current diagnosis of a chronic disease, including but not limited to, cardiovascular disease (myocardial infarction or stroke), diabetes and cancer
5. Fasting blood glucose ≥5.5 mmol/L
6. Resting hypertension (≥160 mmHg systolic and/or ≥90 mmHg diastolic)
7. Respiratory disease with peak respiratory flow <300 l/min
8. Previous stroke
9. Pregnancy
10. Irregular period
11. Hormonal treatment for menopause
12. Currently on any medication that may influence angiogenic cells or leukocytes, including Statins, NSAID, Opioids, Antihypertensives and Antibiotics
13. Unable to read and understand the instructions provided in English
14. Contraindication to venous blood sampling
15. Unwilling to undertake exercise
16. Smoker

Date of first enrolment
15/06/2022

Date of final enrolment
01/10/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
NIHR Newcastle Clinical Research Facility
Level 6, Leazes Wing
Royal Victoria Infirmary
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United Kingdom
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Sponsor information

Organisation
Newcastle University

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Sponsor type
University/education

Website
http://www.ncl.ac.uk/

ROR
https://ror.org/01kj2bm70

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
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Level 1, Regent Point
Regent Farm Road
Gosforth
Newcastle upon Tyne
England
United Kingdom
NE3 3HD
+44 191 282 4519
nuth.nuthsponsorship@nhs.net

Sponsor type

Hospital/treatment centre

Website
https://newcastlejro.com/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Diabetes Research and Wellness Foundation

Alternative Name(s)
Diabetes Research & Wellness Foundation, Diabetes Research and Wellness Foundation UK, DRWF

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Funder Name
Newcastle University

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal and presented at academic conferences.

Intention to publish date
01/04/2024

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 3	18/05/2022	19/05/2022	No	No
HRA research summary			28/06/2023	No	No