Glucose transport and mitochondrial function in type 1 diabetes mellitus

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Primary Aim: We aim to determine markers for NOX2-mediated insulin-independent glucose uptake signalling pathways, mitochondrial function, myokine secretion both at rest and after a bout of acute exercise in individuals with T1DM and healthy...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON52326

Source
ToetsingOnline

Brief title
GRACE

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit
Source(s) of monetary or material Support: European Foundation for the Study of Diabetes/Boehringer Ingelheim European Research Programme on "Multi-System Challenges in Diabetes"

Intervention

Keyword: diabetes, exercise, metabolism, muscle

Outcome measures

Primary outcome

Main study parameters: The differences in markers of insulin-independent glucose uptake, parameters of mitochondrial function and exercise tolerance between T1DM and control groups both before and after the exercise training intervention.

Secondary outcome

Secondary Study Parameters: The differences in exercise tolerance and aerobic function parameters between T1DM and control groups before and after the exercise training intervention, and their relationships with markers of mitochondrial function.

Study description

Background summary

Rationale: Type 1 diabetes mellitus (T1DM) is caused by immune-mediated destruction of the insulin-producing pancreatic β-cells, resulting in lifelong reliance on exogenous insulin (via multiple daily injections or insulin pump). During exercise, glucose disposal increases via insulin-independent means in healthy people and those living with T1DM. Some remnants of these cellular features (such as increased NOX2 signalling) have also been described in animal models of T1DM, but never for humans with T1DM. This insulin-independent glucose signalling likely comes at a price of an impaired skeletal muscle mitochondrial function. The observation that mitochondrial dysfunction and exercise intolerance also occur in young, physically active, and otherwise healthy individuals with T1DM confirms this suggestion. Since the cause of this mitochondrial dysfunction in individuals with T1DM is unknown, this limits preventive measures and effective treatment. Not only will we study the intracellular metabolism in T1DM, we also expect that myokine secretion levels

are altered in T1DM, affecting inter-organ communication and whole-body glucose and fat metabolism. In this project, we hypothesise that:
1) Individuals with T1DM will have larger NOX2-dependent cytosolic alterations in metabolism in vastus lateralis biopsies compared to the individuals without T1DM, and that these differences are exacerbated during exercise.
2) These alterations in insulin-independent glucose signalling contribute to mitochondrial dysfunction, altered myokine secretion, and impaired exercise tolerance in individuals with T1DM.
3) Aerobic exercise training will improve skeletal muscle glucose handling, mitochondrial function and myokine secretion in T1DM.

Study objective

Primary Aim: We aim to determine markers for NOX2-mediated insulin-independent glucose uptake signalling pathways, mitochondrial function, myokine secretion both at rest and after a bout of acute exercise in individuals with T1DM and healthy controls, and secondly, to determine each of these variables both before and after an exercise training intervention. The secondary objective of this study is to obtain insight into the determinants of exercise intolerance in T1DM by assessing the relationships between the measures obtained from muscle biopsies (i.e. mitochondrial function) and whole-body exercise tolerance, both before and after an exercise training intervention.

Study design

Study design: An exercise training intervention study in individuals with T1DM and healthy controls will be performed to assess insulin-independent glucose metabolism, mitochondrial function, and exercise tolerance by invasive as well as non-invasive measurements.

Intervention

4 weeks of moderate-intensity cycle exercise training on a cycle ergometer in the laboratory. Sessions will consist of 3 x 30 minutes exercise in week 1, 3 x 40 minutes exercise in week 2, 3 x 50 minutes exercise in week 3, and 3 x 60 minutes in week 4.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participants in this study will be asked to perform physical exercise tests, give muscle biopsies (4 samples), blood samples (4 x 10-15 ml), and complete a 4-week exercise training intervention. There is some extent of burden and risk associated with harvesting muscle biopsies and blood samples, however this will be mitigated by the fact that these procedures will only be carried out by highly trained physicians.

Moreover, the scientific gain from obtaining intracellular information outweighs these relatively quick procedures with minimal discomfort afterwards. The risks of the physical exercise measurements are negligible. The main risk for the individuals with T1DM is the occurrence of hypoglycaemia during exercise, which will be circumvented by observing strict pre-exercise regulations for glucose concentrations: exercise will only commence if blood glucose concentration is between 7-12 mmol.L-1.
There is a significant time investment on behalf of the participants, since participants are required to visit the laboratory on 16 occasions for approximately one-to-two hours per session. Although it cannot be guaranteed, it is likely that participants in both groups will benefit from the exercise training with regards to their physical fitness and overall health. Moreover, participants will receive reimbursement for the biopsies. The outcome of the research project is expected to provide insight in the critical physiological determinants of exercise intolerance, insulin-independent glucose handling, and mitochondrial dysfunction in T1DM. This will enable targeted interventions (e.g. exercise training programmes, new drugs) aimed at ameliorating these deleterious consequences of T1DM to be studied in future research.

Contacts

Public
Vrije Universiteit

De Boelelaan 1108
Amsterdam 1081HZ
NL
Scientific
Vrije Universiteit

De Boelelaan 1108
Amsterdam 1081HZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, participants with T1DM must meet all of the following criteria:
• Individuals with T1DM with a diagnosed disease duration of 1 - 45 years
• Male or female
• Aged between 18-65 years

In order to be eligible to participate in this study, healthy control participants must meet all of the following criteria:

• No chronic health conditions and between the ages of 18-65

Exclusion criteria

• History of asthma, stroke, chronic obstructive pulmonary disease, congestive heart failure, heart surgery, or congenital heart diseases
• Current treatment with drugs known to interfere with metabolism e.g. systemic corticosteroids, statins, SGLT2 inhibitors, GLP1 receptor agonists
• Are current smokers or have been a regular smoker within the last 12 months
• Insulin pump therapy
• Symptomatic autonomic or distal neuropathy
• BMI >30 due to adiposity, since this is known to cause difficulties in obtaining muscle biopsies.
• Pregnancy
• Recent acute myocardial infarction (<6 months)
• Uncontrolled arrhythmia/severe conduction disorder (atrial fibrillation or second/third degree AV block) causing hemodynamic compromise
• Implantable pacemaker or other cardiac device with complete ventricular pacing
• Uncontrolled heart failure with hemodynamic compromise
• Uncontrolled hypertension (Systolic Blood Pressure >150 mmHg and Diastolic Blood Pressure > 100 mmHg on repeated measurements)
• Active infection, anaemia, severe renal dysfunction (estimated Glomerular filtration rate <30 ml/min/1,73m2) likely to significantly impact on exercise performance
• Chronic illness (including orthopaedic, endocrinological, haematological, malignant, gastrointestinal, neurological, muscle or inflammatory disorders) likely to significantly impact on exercise performance

• > 6 alcohol units per day or >14 alcohol units per week
• Use of anticoagulants or anti platelet therapy

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-04-2021
Enrollment:	41
Type:	Actual

Ethics review

Approved WMO Date:	31-03-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 23610
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL76008.029.20
OMON	NL-OMON23610