Skeletal muscle glucose transport and mitochondrial function in type 1 diabetes

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1) Patients with type 1 diabetes display poorer mitochondrial function when compared to healthy controls matched for age-, sex- and physical activity. 2) Patients with type 1 diabetes display an altered reliance on skeletal muscle glucose uptake...

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23610

Source
NTR

Brief title
GRACE

Health condition

Type 1 diabetes

Sponsors and support

Primary sponsor: Vrije Universiteit Amsterdam
Source(s) of monetary or material Support: European Foundation for the Study of Diabetes

Intervention

Outcome measures

Primary outcome

Skeletal muscle glucose transport

Secondary outcome

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) Patients with type 1 diabetes display poorer mitochondrial function when compared to healthy controls matched for age-, sex- and physical activity. 2) Patients with type 1 diabetes display an altered reliance on skeletal muscle glucose uptake pathways such as the NOX2 pathway when compared to healthy controls matched for age-, sex- and physical activity. 3) Patients with type 1 diabetes display an altered myokine signalling profile following exercise when compared to healthy controls matched for age-, sex- and physical activity. 3) An increased reliance on the NOX2 pathway is associated with the extent of mitochondrial dysfunction in patients with type 1 diabetes 4) Exercise training will improve mitochondrial function, skeletal muscle glucose handling and myokine secretion in both patients with type 1 diabetes and healthy controls 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: 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. Study population: 16 otherwise healthy individuals with T1D (18-65

years) and 16 healthy controls without T1D) will be matched for age, body mass index, and physical activity levels. Intervention: Both groups will undertake a 4-week moderate-intensity exercise training intervention, wherein participants will perform 30-60 minutes of continuous moderate-intensity cycle exercise (at the steady-state heart rate associated with the gas exchange threshold, GET), 3 times per week. 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.

Study objective

1) Patients with type 1 diabetes display poorer mitochondrial function when compared to healthy controls matched for age-, sex- and physical activity. 2) Patients with type 1 diabetes display an altered reliance on skeletal muscle glucose uptake pathways such as the NOX2 pathway when compared to healthy controls matched for age-, sex- and physical activity. 3) Patients with type 1 diabetes display an altered myokine signalling profile following exercise when compared to healthy controls matched for age-, sex- and physical activity. 3) An increased reliance on the NOX2 pathway is associated with the extent of mitochondrial dysfunction in patients with type 1 diabetes 4) Exercise training will improve mitochondrial function, skeletal muscle glucose handling and myokine secretion in both patients with type 1 diabetes and healthy controls

Study design

Before and after exercise training

Intervention

Exercise training

Contacts

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Eligibility criteria

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:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-07-2021
Enrollment:	32
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
Participants' privacy will be protected, and personal data will be handled confidentially and in a coded way, and comply with the European General Data Protection Regulation (Algemene Verordening Gegevensbescherming or AVG). Participant identification will be coded for all study procedures. All obtained data (including the biopsies) will be coded by a unique code consisting of a combination of letters and numbers that is not reducible to the subject (e.g. no initials or date of birth). Only VUmc and VU researchers directly involved in the project are allowed to access the codes and participant data (including body tissue). Codes and participant data will be stored in password-protected files. After finishing the study, the key to the code will be safeguarded by the coordinating investigator. Research data will be stored by the Laboratory of Myology, Faculty of Behavioural and Movement Sciences, at the Vrije University for 15 years following completion of the project. Coded muscle biopsy samples will be stored in the Laboratory of Myology, Faculty of Behavioural and Movement Sciences, Vrije University according to its local protocol, until the investigation and analyses have been completed. All remaining tissue from this project will be destroyed once all relevant analyses have been completed. Both labs are located in the O|2 building at the VU campus. Professional secrecy and confidentiality will be maintained at all times. Participant information will not be disclosed to third parties. Data from the project will be shared with our research partners and collaborators, in the form of presentations and written scientific publications. In this case, data representative of the group mean responses will be shared, or data from individual participants deemed representative of the group responses. However, in no case will any data be linked with the identity of a given individual, and thus the privacy of each individual will be guaranteed.

Ethics review

Positive opinion

Date:	09-07-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52326
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9583
CCMO	NL76008.029.20
OMON	NL-OMON52326

Study results