Investigating disturbances in glucose and glycogen dynamics in prediabetes

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

Summary

ID

NL-OMON53214

Source
ToetsingOnline

Brief title
Glucose and glycogen dynamics in prediabetes

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Prediabetes, prestage of type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Diabetes fonds en EFSD

Intervention

Keyword: acipimox, gluconeogenesis, glycogen, prediabetes

Outcome measures

Primary outcome

- Liver and muscle glycogen (13C-MRS)

- Whole body gluconeogenesis (fractional gluconeogenesis determined by deuterated water x EGP determined by 6,6D2-glucose)

- Postprandial glucose uptake measured by [18F]-FDG-PET

Secondary outcome

Secundary:

- Whole body gluconeogenesis (fractional gluconeogenesis determined by deuterated water x EGP determined by 6,6D2-glucose), upon Acipimox treatment

- Glucose tolerance determined by OGTT, upon Acipimox treatment

- Liver glycogen (13C-MRS), upon Acipimox treatment

Other:

- Hepatic acetylcarnitine determined by 1H-MRS as a measure for hepatic gluconeogenesis

- Substrate oxidation (fat and carbohydrate oxidation overnight)

- Plasma metabolites related to energy metabolism

- Body composition (fat mass/fat free mass)

- Dynamic measurements of postprandial changes in water relaxation times (1H-MRS)

Study description

Background summary

Type 2 diabetes mellitus (T2D) prevalence has increased drastically, making it a major public health problem globally. The disease is preceded by a state of prediabetes that is characterized by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). While disturbances in glucose metabolism are implicated in T2D pathogenesis, little is known about whether glucose metabolism is differentially affected in IGT and IFG, especially during postprandial and nocturnal states. This knowledge will help to develop more targeted, individualized therapies that delay or even prevent the progression of prediabetes into overt T2D.

Study objective

The aim is to investigate changes in nocturnal and postprandial glucose and glycogen metabolism in individuals with IFG and IGT when compared to healthy, non-diabetic, overweight participants. In addition, it will be investigated if reducing gluconeogenesis in people with prediabetes can increase glucose tolerance and fat oxidation by increased reliance on hepatic glycogen (through a 4-day acipimox intervention).

Study design

This is an observational study in healthy overweight participants and prediabetic participants with IFG or IGT, with an additional intervention of a 4- day Acipimox treatment in a subset of the prediabetic participant groups (10 IFG and 10 IGT). Volunteers will visit the university for a screening visit and a visit with overnight stay for measurements of gluconeogenesis, glycogen, glucose uptake, glucose tolerance and substrate oxidation. Ten participants with IGT and 10 with IFG will follow a 4-day treatment with acipimox, followed by a second overnight visit
(with measurements of gluconeogenesis, glycogen, glucose tolerance and substrate oxidation).

Intervention

A subset of prediabetes individuals (first 10 IFG and 10 IGT subjects enrolled) will receive a 4-day Acipimox treatment: 3x 250mg capsules for three days (one with breakfast, one with lunch and one with evening snack) and 1x 250mg in the morning of the last day.

Study burden and risks

Participants will not directly benefit from this study, but the obtained results will provide insights in disturbances in nocturnal and postprandial glucose and glycogen dynamics in prediabetes individuals which will help to find new targets for the improvement of glucose tolerance and disturbed energy metabolism in prediabetes. The burden predominantly consists of time investment, the blood draws, and taking Acipimox medication for 4 days. In addition, [18F]-FDG-PET and MRI measurements are performed, participants stay in the respiration chamber overnight, and participants are asked to remain fasted several times. In previous studies within our research group in which [18F]-FDG-PET, MRI measurements, nights in the respiration chamber, blood sampling and being fasted were a part of the study, the study was not experienced as very burdening by participants. For the PET measurements, participants will receive a bolus of [18F]-FDG of 4MBq/kg =0.072mSv/kg), which is acceptable for research conducted in healthy adults. In this study, participants are allowed to go out of the scanner, go to the toilet and drink some water in between MRI scans, thereby limiting the burden of the MRI scans. To limit the burden of the MRI protocol, participants are allowed to go out of the scanner, go to the toilet and drink some water in between MRI scans. The current study takes relatively little time. The risks, and its impact, of participating in this study are limited.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

General for all groups:
-Participants are able to provide signed and dated written informed consent prior to any study specific procedures
- Participants should have suitable veins for cannulation or repeated venipuncture
- Women are post-menopausal (defined as at least 1 year post cessation of menses)
- Aged >= 45 and <= 75 years
- Body mass index (BMI) 27 - 38 kg/m2
- Stable dietary habits (no weight loss or gain >5kg in the past 3 months)
- Sedentary lifestyle (not more than 2 hours of sports per week)

Prediabetic groups specifically:
IFG: fasting blood glucose between 6.1 and 6.9 mmol/L and 2-h plasma glucose after ingestion of 75g oral glucose load below 7.8 mmol/L
IGT: fasting blood glucose below 6.1 mmol/L and 2-h plasma glucose after ingestion of 75g oral glucose load between 7.8 and 11.1 mmol/L

Exclusion criteria

General for all groups:
- Previous enrolment in a clinical study with an investigational product during the last 3 months or as judged by the Investigator
- Previously diagnosed with type 2 diabetes
- Patients with congestive heart failure and/or severe renal (eGFR <50mL/min) and or liver insufficiency or another condition that may interfere with outcomes measured in this study.
- Any contra-indication MRI scanning
- Alcohol consumption of >2 servings per day for men and >1 servings per day for woman
- Smoking in the past 6 months
- Medication use that may influence main outcome parameters, specifically the following types of medication: Type 2 diabetes medication, corticosteroids, thyroid medication.
- Participation in research or medical examination that included PET scanning

in the last 3 months

Healthy overweight specifically:
- Any of the criteria mentioned above to define prediabetes

Prediabetic groups who will undergo acipimox treatment:
- Gout
- Hypersensitivity to acipimox or to any of the excipients in the tablet
- Peptic ulcer/dyspepsia
- Medication use that interfere with Acipimox (statins, fibrates).

A medical doctor will judge participation eligibility based on the medical history questionnaire, medication use and fasting blood parameters. If the medical doctor advises that a volunteer cannot participate, the volunteer will be excluded from enrollment.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-02-2024
Enrollment:	106
Type:	Actual

Ethics review

Approved WMO

Date:	22-08-2023
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
CCMO	NL84574.068.23