Determination of the effect of perivascular adipose tissue on insulin-stimulated skeletal muscle glucose uptake in prediabetes by PET-CT

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The primary aim of this study is to determine the causal relationship between the accumulation and inflammation of perivascular adipose tissue (PVAT) and insulin-stimulated glucose uptake in skeletal muscle, measured using dynamic PET-CTA, in…

Ethical review	Approved WMO
Status	Pending
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON57348

Source
ToetsingOnline

Brief title
PVAT and skeletal muscle insulin sensitivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht

Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: glucose homeostasis, insulin sensitivity, Perivascular adipose tissue, PET-imaging, prediabetes, skeletal muscle

Outcome measures

Primary outcome

Primary outcome parameter is insulin-stimulated 18F-FDG uptake in quadriceps

muscle (expressed as Ki) as measured by means of [18F]-FDG PET and PVAT

quantity and inflammation measured by CT angiography.

Secondary outcome

Secondary study parameters are:

- Skeletal muscle blood flow measured by contrast enhanced ultrasonography

(CEUS);

- Hepatic, myocardial, and whole-body glucose uptake rate (Ki) measured with

PET-CT;

- Skeletal muscle mitochondrial function measured by means of Oroboros in

skeletal muscle biopsies;

- Skeletal muscle intracellular insulin signalling pathways measured by Western

blot in muscle biopsies.

Study description

Background summary

Insulin resistance, defined as insulin-stimulated glucose uptake in the body, is primary factor underlying postprandial glucose clearance and a major hallmark in the development of type 2 diabetes mellitus (T2DM). In this

context, approximately 70-80 percent of glucose uptake takes place in skeletal muscle, which is therefore an important determinant of T2DM risk. As such, the muscles microcirculation contributes to skeletal muscle glucose uptake by hitherto unclarified mechanisms. A recently identified part of this microvascular bed is so-called perivascular adipose tissue (PVAT), and this tissue has been shown in mice and isolated human muscle arterioles to regulate muscle blood flow and glucose uptake.

Recent methodological developments allow us to visualize and quantify glucose uptake in any given tissue using dynamic Positron Emission Tomography (PET) with 18Fluorinated glucose tracer (FDG) during insulin stimulation. Furthermore, quantity and inflammation of PVAT can be determined in man using CT angiography. During the current study, we will therefore evaluate whether PVAT properties differ between prediabetic and healthy individuals and relate to the effects of insulin on skeletal muscle glucose uptake and blood flow.

For this purpose, PVAT properties will be compared between fifteen individuals with prediabetes and fifteen healthy controls matched for age and sex and related to skeletal muscle glucose uptake and blood flow. All subjects will then undergo the optimized dynamic PET protocol to assess insulin-stimulated skeletal muscle glucose together with whole-body glucose uptake measures. A one-step hyperinsulinemic, euglycemic clamp will be performed to measure whole-body insulin sensitivity. Detailed characterization of PVAT in prediabetes can provide a new target for preventing T2DM and provide a basis for modeling prediabetes in vitro.

Study objective

The primary aim of this study is to determine the causal relationship between the accumulation and inflammation of perivascular adipose tissue (PVAT) and insulin-stimulated glucose uptake in skeletal muscle, measured using dynamic PET-CTA, in healthy and prediabetic men and (postmenopausal) women.

Study design

Observational cross-sectional study design.

Study burden and risks

This study will not provide direct benefits to the participants, and the main burden will be the time investment. In total, participants will visit Maastricht University twice (including the screening) for measurements. To minimize the required number of participants, we will conduct an observational cross-sectional study involving 32 individuals: 16 healthy controls (with an allowance for dropouts) and 16 individuals with prediabetes (with an allowance for dropouts). The study requires at least 30 participants to complete the

study.

The measurements performed are low-risk, though bruising may occur from blood draws or muscle biopsies. These risks are minimized through state-of-the-art techniques and sterilization of the equipment. The contrast used during ultrasonography carries minimal risk. Risks associated with the clamp and PET-CT are low due to the clear exclusion criteria and the experience of the researchers conducting the tests. For the PET scan, an 18F-FDG bolus will be injected into the participants. This is a radioactive glucose tracer commonly used in current medical practice. The total radiation exposure is approximately 5.94 mSv per participant (PET-CT= ~ 5.64 mSv + CTA= ~ 0.29 mSv = 5.94 mSv, compared to the normal background radiation in the Netherlands of about 2.9 mSv per year). Additionally, a contrast fluid used during the CT scan also has a low risk.

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

1. Caucasian (people will be excluded when having a >=50% racial African/Asian background);
2. Male or (postmenopausal; defined as 1 year after the last cycle) female;
3. Age between 40-75 years;
4. BMI: 25-35 kg/m2;
5. Pre-diabetes in one the following criteria:
a. Impaired glucose tolerance: plasma glucose values >= 7.8 mmol/l and <= 11.1 mmol/l, 120 minutes after glucose drink consumption during OGTT in screening;
b. Impaired fasting glucose: Fasting plasma glucose >= 6.1 mmol/l and <= 6.9 mmol/l;
c. Insulin resistance: glucose clearance rate <= 360 ml/kg/min, as determined using OGIS120;
d. HbA1c of 5.7-6.4%;
6. Stable dietary habits (no weight loss or gain >3kg in the past 3 months);
7. Sedentary lifestyle (not more than 2 hours of vigorous exercise per week).

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Not meeting all inclusion criteria;
2. Type 2 diabetes (fasted blood glucose > 7 mmol/L or non-fasted > 11mmol/L);
3. Any condition, disease or abnormal laboratory test result that, in the opinion of the Investigator, would interfere with the study outcome, affect trial participation or put the subject at undue risk.
4. Alcohol consumption of >2 servings per day;
5. Currently smoking, or having quit recently or a longer time ago;
6. Low Hb (men: <8.6 mmol/L; women <7.4 mmol/L);
7. Subjects using anticoagulant medication (antiplatelet agents can be used, but other medications should be excluded);
8. Subjects who have participated in another biomedical study within the last 3 months that could interfere with the study results;
9. Subjects were involved in previous research that included PET/CT scanning;
10. Participants who do not want to be informed about unexpected medical findings; *
11. Participants who do not want that their treating physician to be informed;
12. Inability to participate and/or complete the required measurements;
13. Participation in organised or structured physical exercise (>2h per week);
14. Allergic or hypersensitive to iodine-containing contrast medium.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-03-2025
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	18-03-2025
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	NL87584.068.24