The role of muscular periarteriolar adipose tissue on vasoreactivity

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1. Does mPAT directly impair vasoreactivity to insulin and acetylcholine ex vivo in arterioles obtained from muscle biopsy in lean and obese individuals?2. Is obesity in humans associated with the accumulation of mPAT and an inflammatory mPAT...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON37944

Source
ToetsingOnline

Brief title
The role of mPAT on vasoreactivity

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Vascular hypertensive disorders

Synonym
Insulin-resistance, microvascular dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Nederlandse Hartstichting project 2009B098

Intervention

Keyword: insulin, mPAT, obesity, vasoreactivity

Outcome measures

Primary outcome

The first main study parameter is the rate of muscle microvascular recruitment on insulin infusion, as measured by change of signal strength during contrast enhanced ultrasonography.

The second main outcome is the amount of mPAT in muscle biopsies obtained from lean and obese subjects, quantified by confocal microscopy.

The third main outcome is the microvascular vasoreactivity of human muscle arterioles as measured in pressure myography ex vivo.

The fourth main outcome is the effects of mPAT on the insulin signalling cascade, as measured by Western blotting of mPAT and comparing results of Western blots from subjects with a normal vasoreactivity and those of subjects with perturbed vasoreactivity.

Secondary outcome

N/A

Study description

Background summary

Obesity is associated with impairment of insulin-mediated glucose uptake, hypertension and endothelial dysfunction, contributing to cardiovascular risk. Microvascular dysfunction, characterized by impaired endothelium-dependent vasodilatation and impaired effects of insulin on microvascular function, plays an important role in the pathogenesis of the metabolic syndrome.
Insulin-mediated glucose uptake occurs primarily in muscle, and depends not

only on the rate of uptake by myocytes, but also on the rate of delivery of glucose and insulin via the microcirculation. Under physiological conditions, an increase in insulin has both vasodilator (via NO synthesis) and vasoconstrictor (via endothelin-I synthesis) effects on muscle resistance arteries, with a net result of increased microvascular perfusion. In obesity, however, the vasodilator effects have been shown to be impaired, thereby limiting the ability of insulin to increase substrate access to muscle. The causes of this impaired insulin-mediated blood flow in obesity are, however, not clear. Insulin*s effects in (vascular) cells are mediated via a complex signalling cascade (figure), and impaired activation of this cascade in vascular cells has been demonstrated and likely contributes to the perturbation of insulin*s effects on vasoreactivity.
Expression of TNF-α is increased in the adipose tissue of obese humans and animals. Insulin induces vasoconstriction of skeletal muscle resistance arterioles in the presence of TNF-α by inhibition of the vasodilator pathway at the level of Akt. However, levels of TNF-α are primarily higher in adipose tissue than in the systemic circulation, suggesting local production of TNF-α is necessary in order to influence vasoreactivity.
A previously undiscovered type of fat was described recently. This adipose tissue is called muscle periarteriolar adipose tissue (mPAT), and is located around the origin of the arteriole. We hypothesize that mPAT may be able to influence vasoreactivity of the arteriole, thereby affecting delivery of nutrients and other substances to the vascular tree. mPAT may exert these effects by influencing the insulin signalling-cascade through the production of adipokines, such as TNF-α.

This study aims to determine whether obesity and/or other metabolic syndrome markers are associated with accumulation of mPAT with an inflammatory phenotype, whether the mPAT phenotype differs from subcutaneous and visceral adipose tissue, and whether this mPAT disturbs insulin-mediated vasoreactivity. We further hypothesize that mPAT produces adipokines that inhibit insulin-mediated vasodilatation.

This project should be performed, because mPAT is a previously unstudied type of adipose tissue. The role of mPAT in the pathophysiology of insulin resistance is potentially important.

Study objective

1. Does mPAT directly impair vasoreactivity to insulin and acetylcholine ex vivo in arterioles obtained from muscle biopsy in lean and obese individuals?
2. Is obesity in humans associated with the accumulation of mPAT and an inflammatory mPAT phenotype?
3. Is this human mPAT quantitatively and/or qualitatively associated with an impaired muscle blood flow response to hyperinsulinemia, as assessed by Contrast Enhanced UltraSonography (CEUS)?

Study design

This study is conducted as a case control study. The setting is outpatient based, with three visits to the clinical research unit at the VUmc. The first visit will take approximately one-and-a-half hours, the second visit 5 hours and the third will take approximately 1 hour.

Study burden and risks

Subjects will visit the clinical research unit three times after an overnight fast, the first time to undergo a detailed medical history, physical examination and blood sampling, the second time to undergo hyperinsulinemic euglycemic clamping, and contrast enhanced ultrasonography, as well as iontophoresis and laser Doppler, and the third time a biopsy of the quadriceps muscle will be performed under local anaesthesia. Risks associated with participation consist of (not necessarily) myalgia and bleeding after biopsy, as well as small risks of hypoglycaemia or hyperglycaemia during hyperinsulinemic euglycemic clamping, and headache, flushing and back pain during contrast enhanced ultrasonography. Bruising and local pain in the antecubital fold may be experienced during and after placement of venous catheters and/or during blood sampling.
Subjects will receive ¤250 after completion of the protocol.
The groups are chosen because of their high likelihood to express different amounts and phenotypes of mPAT.

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

-Age 18-55 years
-BMI >30 AND a waist-circumference of >94 cm in males, >80 cm in females, or BMI <25 AND a waist-circumference of <94 cm in males, <80 cm in females.

Exclusion criteria

-Diabetes or impaired glucose tolerance (FPG > 6.1 mmol/l)
-Hypertension or other cardiovascular disease (stroke, coronary artery disease, peripheral vascular disease, heart failure) in medical history
-Use of medication for hypertension or diabetes, as well as use of medication known to disturb endothelial function or glucose metabolism
-Physical exercise (sporting) more than two times a week
-Pregnancy or intention to become pregnant during the study period
-Smoking

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:	Will not start
Start date (anticipated):	01-04-2010
Enrollment:	50
Type:	Anticipated

Ethics review

Approved WMO Date:	06-05-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2012
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

No registrations found.

In other registers

Register	ID
CCMO	NL25172.029.09