# Is microvascular dysfunction an early phenomenon in the development of skeletal muscle insulin resistance? A dietary intervention study in healthy men

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Primary objective: To assess the effects of hypercaloric overfeeding in humans on vascular and metabolic insulin sensitivity and moreover, to establish whether insulin resistance develops in the vasculature before it occurs in peripheral tissue...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Glucose metabolism disorders (incl diabetes mellitus) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON44864

**Source**
ToetsingOnline

**Brief title**
DESIRE study

### Condition

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

**Synonym**
Obesity, overweight/fatness

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W,Aanvragen bij diabetes fonds en hartstichting lopen nog,Astra Zeneca

## Intervention

**Keyword:** Humans, Hypercaloric diet, Insulin resistance, Microvascular dysfunction

## Outcome measures

### Primary outcome

1. Metabolic insulin sensitivity: rate of disappaerance (Rd) en endogenous

glucose production (EGP)

2. Vascular insuline senitivityt: changes in microvascular blood volume (MBV)

### Secondary outcome

1. Microvascular vasoreactivity in vitro with and without PVAT (myograph

technique)

2. Insulin mediated protein expression and activation in microvessels, adipose

and skeletal muscle tissue

3. Gen expression of insulin signaling genes in endothelial cells

4. PVAT morphology/characteristics, including adipocyte size, celltypes and

expression of adipokines

5. Plasma insulin, glucose, lipid spectrum, inflammatory parameters

6. Physical activity (by means of accelerometry)

7. Gut microbiota composition (fecal analysis)

# Study description

## Background summary

Excessive caloric intake causes overweight, obesity, insulin resistance and ultimately type 2 diabetes and cardiovascular diseases (CVD). In rodents with obesity-associated insulin resistance induced by high-fat diet, insulin resistance develops in the vasculature well before these responses are detected in skeletal muscle, liver or adipose tissue. Insulin signaling in vascular endothelium, therefore, seems more susceptible than other tissues to the deleterious effects of nutrient overload. Furthermore, insulin signaling in vascular endothelium has been proposed to regulate its own delivery to skeletal muscle, by increasing blood flow and recruiting perfused capillaries and thus may be an important therapeutic target to improve insulin resistance in skeletal muscle. In humans, the early adaptation of the microvasculature during the initial phase of overfeeding and weight gain has not been studied yet. Therefore, it remains unclear whether insulin resistance in endothelial cells precede insulin resistance in skeletal muscle and if improving endothelial insulin signaling/microvascular function may thus serve as a preventive/therapeutic strategy for ameliorating peripheral insulin resistance.

## Study objective

Primary objective:
To assess the effects of hypercaloric overfeeding in humans on vascular and metabolic insulin sensitivity and moreover, to establish whether insulin resistance develops in the vasculature before it occurs in peripheral tissue during hypercaloric overfeeding.

Secondary objectives:
To assess whether the effects on hepatic, skeletal muscle tissue, adipose tissue and microvascular insulin sensitivity induced by caloric overfeeding are reversible during a subsequent hypocaloric diet.
To determine if hypercaloric overfeeding in humans influences insulin-mediated recruitment in skeletal muscle and adipose tissue differently.
To determine if direct pharmacological stimulation of capillary recruitment by a stable prostacyclin (PGI2) analogue can overcome diet-induced resistance to glucose disposal in skeletal muscle?
To determine if hypercaloric overfeeding in humans influences adipocyte size, cell types and paracrine effects of PVAT surrounding skeletal muscle arterioles.
To determine if hypercaloric overfeeding in humans influences insulin-signaling in subcutaneous adipose fat tissue.
To determine if hypercaloric overfeeding affects gen expression in endotheial cells.

## Study design

This is an expiremental dietary intervention study: 30 days hypercaloric diet and a subsequent hypocaloric diet.
Measurements will take place at baseline, 7 days after the start of the hypercaloric diet, at the end of the hypercaloric diet and at the end of the hypocaloric diet. These measurements will include a 2-step hyperinsulinaemic-euglymic clamp, contrast enhanced ultrasounds (CEUS) to determine metabolic and vascular insulin sensitivity. Furthermore, we will take 1 muscle and adipose tissue biopsy per person, either at the end of the hypercaloric or hypocaloric phase.

**Intervention**

The intervention consists of a hypercaloric (60% caloric excess) diet, during a period of approximately 30 days, followed by a hypocaloric phase (1.0 x resting energy expenditure), until subjects return to their baseline weight. The surplus of engery will be provided asunhealthy foods, such as sugared bevarages and patato chips.

**Study burden and risks**

After inclusion, participants will be randomized to either study group (n=24) or control group (n=10). The control group will undergo all measurmenets without any dietary interventions. The study group participants will enter a diet intervention during a total of 60 days, starting with a high caloric diet, followed by a subsequent low caloric diet. The hypocaloric diet will be continued until participants return to baseline body weight. We expect that all effects caused by the hypercaloric diet are reversible. During the whole diet intervention participants will visit the medical centre a total of five times. The first visit is a screening day, which will include anamnesis, physical examination and obtaining blood samples for analysis. The other four visits will consist of a two step hyperinsulinaemic-euglymic clamp and two contrast-enhanced ultrasounds. During the end of the hypercaloric diet, half of the participants will receive an iloprost infusion during the clamp. Furthermore, to compare muscle microvessels between the hypercaloric and hypocaloric phase we will take a muscle biopsy. To minimize the discomfort we will randomly divide all subjects into two groups and take only one biopsy per subject.

Risks associated with hyperinsulinaemic-euglymic clamps are hypo- or hyperglycemia, which we will prevent by adjusting pump levels. Iloprost infusion is known to have some side effects, but non are severe at a low dose. Muscle biopsies require a local anaesthesia, which can give some discomfort to the participants. Also, after the biopsy participants can expect some muscle ache. We expect no severe or serious events during our study.

There is no health benefit for the participants. As a compensation for their

time and effort, as well as the burden/discomfort of the invasive procedures, subjects will receive 1000 euros after completion of the investigation.

## Contacts

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NL
**Scientific**
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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. Age 18*30 years
2. Male gender
3. Caucasian
4. BMI 20*25 kg/m2
5. Normal insulin sensitivity
6. Normoglycemia at time of screening
7. Normal diet pattern

8. Stable body weight during 6 months before enrolment in the study (<3% shifts)

### Exclusion criteria

1. Presence of any relevant disease
2. Use of any relevant medication
3. First-degree relative with type 2 diabetes
4. Smoking
5. Shift work
6. A history of chronic glucocorticoids use or GC use < 3months
7. Excessive sport activities

## Study design

### Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Basic science |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 29-01-2015 |
| Enrollment: | 15 |
| Type: | Actual |

## Ethics review

Approved WMO

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|---|---|
| Date: | 18-12-2014 |
| Application type: | First submission |

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|---|---|
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 18-03-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 16-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 21-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 02-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 02-02-2017 |
| 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 | NL49320.029.14 |