The effect of L-arginine on brown adipose tissue metabolism in South Asian and white Caucasian subjects

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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-OMON41875

Source
ToetsingOnline

Brief title
The effect of L-arginine on brown adipose tissue activity

Condition

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

Synonym
overweight

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Rubicon post-doc beurs;toegekend aan

Mariëtte Boon ,Hankintatukku OY

Intervention

Keyword: Brown adipose tissue, L-arginine, South Asians

Outcome measures

Primary outcome

1) glucose uptake by brown adipose tissue

2) energy expenditure

3) fat mass

Secondary outcome

1) Thermoregulation (skin temperature, core temperature, skin perfusion and

endothelium-dependent and -independent vasodilation) and endothelial function

2) Plasma lipids and glucose tolerance

3) Systemic inflammation and adipose tissue inflammation

4) Insulin signaling in muscle

Study description

Background summary

Within the academic hospital Maastricht and Maastricht University, the departments of endocrinology, surgery, and human biology together with the department of endocrinology at the Leiden University Medical Center study metabolic diseases. Overweight and obesity are metabolic diseases that become

increasingly prevalent and can lead to the development of type 2 diabetes, which may lead to several complications including cardiovascular disease. Since 2009, it has been known that brown adipose tissue (BAT) is important for energy expenditure. BAT is a small organ which is mainly located along the great vessels and is capable of rapidly burning fat towards heat. The more BAT a subject has, the faster the metabolism is. People that are overweight have been shown to have only little BAT. Perhaps the stimulation of BAT may be a novel treatment to combat ovewreight and obesity. Interestingly, we have also shown recently that not only people that are overweight, but also people from South Asian descent have little BAT. The South Asian population has an increased risk to develop overweight and type 2 diabetes as compared to white Caucasians and the presence of little BAT from a young age on may contribute to their increased risk. Mouse studies have shown that nitric oxide is important for the formation of BAT. Interestingly, both white Caucasians with overweight and healthy South Asian adolescents have been shown to have reduced release of nitric oxide.

In this study, we will investigate the effect of increasing bioavailability of nitric oxide in the body on BAT activity and metabolism and investigate whether the efficacy of this strategy differs between South Asian and white Caucasian subjects. We will study this by investigating the effect of suppletion of the amino acid L-arginine, the precursor of nitric oxide.

Study objective

In this study, we will investigate the influence of the amino acid L-arginine, which enhances release of nitric oxide in the body, on BAT activity and metabolism in healthy subjects with overweight. This will increase understanding on the effect of L-arginine and nitric oxide on overweight and BAT and hopefully, we will be more capable to treat overweight and obesity in the future.

Study design

The study is a randomized, double blind placebo-controlled study with cross-over design. Subjects will be randomized to receive first L-arginine/placebo for 6 weeks, followed by a wash-out period of 4 weeks, and then again 6 weeks of treatment with L-arginine/placebo. As the study is double blind, the subject nor the investigator will know when the subject receives which treatment.
At the end of both interventions, 2 study days will take place. On the first day, the subject will arrive at 10.00 pm after a small breakfast at the University and a cold-induced brown fat scan (PET-CT scan) will be made. This study day will take approximately 5 hours. It is facultative to also undergo a PET-MRI scan after the PET-CT scan. This takes approximately 45 min. In that case, the first study day takes 6 hours. On the morning of day 2, the subject

will again arrive sober at the University and a muscle- and white fat biopsy will be taken. The muscle biopsy will be taken from the big muscle in the upper thy, and the fat biopsy from the subcutaneous abdomen. After the muscle and fat biopsy, a glucose tolerance test will be performed. This second day will take approximately 4.5 hours.

Intervention

L-arginine (9 gram/day) and placebo. The study has a cross-over design and is furthermore double blind. That means that the subject will first receive one of these interventions for 6 weeks, followed by a 4-week 'wash-out' period and then again 6 weeks of the other intervention. The subject does not know when he receives L-arginine or placebo.

Study burden and risks

- There is a risk for the participant of getting a haematoma after the muscle biopsy if the biopsy has not been executed well
- There is a risk for the participant of getting a heamatoma after placing the catheter
- We do not expect that administration of L-arginine will be harmful to the subjects in this study. The L-arginine is given in a physiological dose and this dose has been given in previously published studies without reporting of side effects by the subjects (36)
-Unexpected medical findings can potentially be detected
- We do not expect that administration of L-arginine will be harmful to the subjects in this study. However, possible side effects may include: 1) enhanced risk of bleeding (especially in people with bleeding disorders); 2) hypoglycaemia (especially in people with type 2 diabetes or people that take drugs, herbs or supplements that affect blood glucose); 3) hyperkalemia (especially in people with liver or kidney function disorders); 4) hypotension (especially in people that use anti-hypertensives) 5) bloating; diarrhea; hematuria; increased inflammatory response (in people with asthma); leg restlessness, lower back pain; nausea, night sweats and flushing (with arginine withdrawal); rash; reduction in hematocrit; stomach and intestine discomfort; systemic acidosis.
- The effective dose of the PET/CT procedure and DXA-scan is 5.8 mSv, which is considered a low risk. Due to participation in this study, the subjects cannot participate in other research that involves radiation
- The PET-MRI scan is not associated with extra risk or radiation

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Caucasians and South Asians ethnicity
- Age: 35-50 years
- Gender: male
- BMI: 25-30 kg/m2
- Plasma glucose levels 2 h after OGTT between 7.8 and 11 mM (e.g. impaired glucose tolerance) or Fasting plasma glucose > 5.5 mM
- Good general health

Exclusion criteria

- Type 2 diabetes (determined on basis of oral glucose tolerance test (OGTT))
- BMI > 30 kg/m2
- Plasma glucose levels 2 h after OGTT < 7.8 mM or Fasting plasma glucose < 5.5 mM
- Use of beta-blockers (these inhibit BAT activity) < 1 month before start of study or during

study
- Participation in an intensive weight-loss program or vigorous exercise program during the last year before the start of the study
- Abuse of drugs and/or alcohol
- Hyperthyroidism or hypothyroidism
- Creatinine (enzymatic method) < 45 or > 100 *mol/L
- Participation in earlier research or medical examinations that included PET-CT scanning
- Psychologically unstable subjects (as judged by the treating medical specialist)
- Subjects with mental retardation (as judged by the treating medical specialist)
- Subjects with severe behavior disorders (as judged by the treating medical specialist)
- Contra-indications MRI (facultative): presence of metallic objects in which the magnetic field can disrupt its function, including pacemaker, insulin pump, neurostimulator, vascular clips, interior hearing device and artificial cardiac valves. Additionally, we will exclude subjects with metallic residues in the eye (posttraumatic), large tattoos and orthopaedic protheses in the field of the camera.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-10-2015
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Argimax

Generic name:	L-arginine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-09-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-10-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-05-2015
Application type:	Amendment
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
EudraCT	EUCTR2014-001733-86-NL
CCMO	NL49173.068.14

Study results

Date completed: 25-10-2015

Actual enrolment: 22

Summary results
Trial ended prematurely