The effect of sitagliptin on brown adipose tissue and whole-body metabolism in overweight pre-diabetic men

Published: 15-10-2014
Last updated: 21-04-2024

To investigate whether STG enhances BAT activation, thereby increasing energy expenditure and combustion of TG-derived fatty acids, resulting in lowering of plasma TG levels and body weight.

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

Summary

ID

NL-OMON44534

Source
ToetsingOnline

Brief title
Sitagliptin and brown adipose tissue

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Type 2 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: De studie wordt gefinancierd door MSD

Intervention

Keyword: Brown adipose tissue, Energy expenditure, GLP-1, Glucose metabolism

Outcome measures

Primary outcome

To evaluate the effect of sitagliptin treatment on BAT activity (measured via

cold-induced 18F-FDG PET-CT scans)

Secondary outcome

To assess the effect of sitagliptin treatment on 1) resting energy expenditure,

2) muscle glucose metabolism, 3) fat mass, 4) glucose metabolism, and 5) plasma

lipid levels in overweight, pre-diabetic subjects.

Study description

Background summary

The obesity epidemic has resulted in an exponential increase in obesity-related disorders including type 2 diabetes, dyslipidemia and cardiovascular disease. The associated morbidity and mortality have major consequences both at an individual as well as on the socioeconomical level. Thus, the development of novel therapies aimed at reducing the development of obesity is highly warranted. Brown adipose tissue (BAT) recently emerged as a novel player in energy expenditure in humans as it combusts fatty acids towards heat. Interestingly, obese subjects have less BAT as compared to lean subjects and activation of BAT by means of intermittent cold exposure reduces fat mass. Therefore, BAT is considered a promising novel target to reduce obesity and associated disorders. As cold exposure is not the most desired therapeutic strategy for humans, current pre-clinical research focuses on pharmacological activation of BAT.
Interestingly, we have recently shown that central agonism of the receptor for the incretin hormone glucacon-like peptide-1 (GLP-1) results in activation of BAT in mice. Of note, enhancing GLP-1 availability is currently a therapeutic strategy to treat type 2 diabetes as it, amongst others, enhances insulin secretion. One of the currently used anti-diabetic drugs that enhances GLP-1 availability is Sitagliptin (STG). STG increases GLP-1 availability by inhibiting breakdown of dipeptidylpeptidase-4 (DPP-4), the enzyme that

hydrolyzes GLP-1 and hence normally results in only short availability (half-life approx. 1.5 min) of endogenous GLP-1. Interestingly, STG also reduces body weight and plasma triglyceride (TG) levels in type 2 diabetes mellitus (T2DM) patients. The mechanism underlying these beneficial metabolic effects is currently unknown.

Study objective

To investigate whether STG enhances BAT activation, thereby increasing energy expenditure and combustion of TG-derived fatty acids, resulting in lowering of plasma TG levels and body weight.

Study design

We will perform a randomized double-blinded placebo-controlled study in which 30 male Dutch Caucasian adults aged 35-55 years with moderate obesity and pre-diabetes are included. Subjects will be treated for 12 weeks with STG or placebo. Before and after treatment, we will determine BAT volume and total BAT activity via cold-induced 18F-FDG PET-CT scans, resting energy expenditure via indirect calorimetry using ventilated hoods, body weight, and body composition via DEXA scan. Furthermore, before and after treatment, blood samples will be taken to measure plasma lipids, glucose and insulin levels. After 4 and 8 weeks of treatment, the will be a check-up and resting energy expenditure will also be measured via indirect calorimetry.

Intervention

Sitagliptin (100 mg/day p.o.) for 12 weeks. The medication will be given to the subjects all at once.

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
- The most frequently reported side-effects of sitagliptin are upper respiratory infections and headache. In addition, hypoglycemia might occur but this is mostly the case when concomitant glucose-lowering drugs, especially sulfonylurea derivatives are used. This is not the case in our subjects. We will make sure that our subjects are aware what symptoms of hypoglycemia are and will provide them with a glucose meter.
- The effective dose of the PET/CT procedure and DXA-scan is 9.38 mSv, which is considered a low risk. Due to participation in this study, the subjects cannot participate in other research that involves radiation

Contacts

Public
Merck Sharp & Dohme (MSD)

Waarderweg 3 39
Haarlem 2003 PC
NL
Scientific
Merck Sharp & Dohme (MSD)

Waarderweg 3 39
Haarlem 2003 PC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male volunteers, 30 Caucasians, born in the Netherlands
- Age: 35-55 years
- BMI * 25 and * 35 kg/m2
- Plasma glucose levels 2 h after OGTT between 7.8 and 11 mM (e.g. impaired glucose tolerance) or fasted plasma glucose >5.6 mM

Exclusion criteria

- Diabetes mellitus (determined on basis of oral glucose tolerance test (OGTT) defined by ADA criteria
- BMI > 35 kg/m2 or < 25 kg/m2

- Plasma glucose levels 2 h after OGTT < 7.8 mM or > 11.1 mM
- Use of medication known to influence glucose and/or lipid metabolism or BAT activity (e.g. beta blockers)
- Any significant chronic disease
- Renal, hepatic or endocrine disease
- Smoking
- Participation in an intensive weight-loss program or vigorous exercise program during the last year before the start of the study
- Difficulties to insert an intravenous catheter
- Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-02-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Januvia
Generic name:	Sitagliptin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-10-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-11-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-02-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2014-003532-39-NL
CCMO	NL50531.058.14