The effect of Exenatide on brown adipose tissue activity and energy expenditure in healthy young men

Published: 28-07-2016
Last updated: 20-04-2024

Primary objective- To evaluate the effect of Exenatide treatment on brown adipose tissue activity and energy expenditure in healthy young Dutch male subjects of South Asian and white Caucasian descent. Secondary objective- To validate the MRI scan...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46200

Source
ToetsingOnline

Brief title
Effect of Exenatide on brown adipose tissue

Condition

- Other condition

Synonym
Metabolic disease, obesity

Health condition

Nutritional and Metabolic Diseases

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,Het onderzoek wordt gefinancierd door Astra Zeneca.

Intervention

Keyword: Adipose Tissue, Brown, Glucagon-like peptide 1 receptor agonist, Magnetic Resonance Imaging, South Asians

Outcome measures

Primary outcome

- The effect of Exenatide on brown adipose tissue activity (measured by 18F-FDG

PET-CT scan and MRI scan) and validation of the MRI scan as a novel technique

for measuring brown adipose tissue activity

- The effect of Exenatide on energy expenditure (measured by indirect

calorimetry)

Secondary outcome

- The effect of Exenatide on glucose- and lipid metabolism (measured in the

blood)

- The effect of Exenatide on fat mass (measured by bio-impedance analysis)

Study description

Background summary

The obesity epidemic has led to a enormous increase in the prevalence of type 2 diabetes mellitus (T2D), dyslipidemia and cardiovascular events. Particularly South Asians, who comprise 1/5 of the world population, are at increased risk of developing a disadvantageous metabolic phenotype and these diseases. Moreover, T2D occurs at a younger age and at a lower BMI when compared to white Caucasians. Recent research has shown that South Asians not only have a lower energy expenditure than their white Caucasian counterparts, but also less

active brown adipose tissue (BAT).

For some time, it has been known that adult humans have active BAT. This metabolic tissue produces heat by combusting triglycerides, in contrast to white adipose tissue, which stores this form of energy. It has been shown that activation of BAT has a positive effect on whole body metabolism, via increasing energy expenditure and improving glucose- and lipid metabolism. For this matter, BAT has been proposed as a major key player in energy homeostasis, which may be implemented in the current combat against the obesity epidemic.

Aside from cold exposure, more research focuses on pharmacological activation of BAT. Glucagon-like peptide 1 (GLP-1) is an incretin hormone which is produced by intestinal L-cells and upon food intake stimulates insulin secretion by pancreatic beta cells. The GLP-1 analogue Exenatide is a currently much used antidiabetic drug to reduce hyperglycemia via this aforementioned mechanism. Beyond its blood glucose-improving effects, Exenatide has also shown to lower body weight and improve dyslipidemia in T2D patients. Elucidation of the underlying mechanism of these beneficial effects is highly relevant.

Recent preclinical research in our group has shown that central activation of the GLP-1 receptor through Exenatide increases BAT activity and thereby contributes to weight loss and improvement of dyslipidemia. The aim of this research project is to investigate whether Exenatide is also able to activate BAT and increase resting energy expenditure, thereby improving glucose- and lipid metabolism and reducing fat mass and body weight in humans. Moreover, we aim to validate the MRI scan as a novel way to measure BAT activity. We hope that these forthcoming findings lead to the discovery of new treatment strategies against obesity.

Study objective

Primary objective
- To evaluate the effect of Exenatide treatment on brown adipose tissue activity and energy expenditure in healthy young Dutch male subjects of South Asian and white Caucasian descent.

Secondary objective
- To validate the MRI scan as a novel technique for measuring brown adipose tissue activity

Study design

Open-label single arm prospective study with 24 healthy young lean males (BMI * 18 and *27 kg/m2), of whom 12 Dutch South Asians and 12 Dutch Caucasians. After a screening, included subjects will receive 12 weeks of treatment with the GLP-1 analogue Exenatide (Bydureon; 2 mg s.c. 1x/wk). Study subjects will visit

the LUMC weekly during the first 4 weeks, where the injection will be administered under the supervision of the researcher, to maximize compliance and monitor the injection technique. If the researcher is confident that subjects are able to administer the injections themselves without supervision, subjects can administer the medication at home for the final 8 weeks and will be called weekly to monitor possible side effects and compliance. Before and after treatment there will be a study day, in which brown adipose tissue activity (by means of 18F-FDG PET-CT scan and MRI scan), resting energy expenditure (thermoneutral and after being exposed to mild cold, measured by indirect calorimetry) and fat mass (by bio-impedance analysis) will be measured. Per study day, two blood draws will take place in order to investigate the effects of Exenatide on lipid- and glucose metabolism.

Intervention

Study subjects will receive Exenatide treatment during 12 weeks, via a weekly 2 mg subcutaneous injection. During both study days, subjects will be exposed to 2,5 hours of very mild cold.

Study burden and risks

Each subject will undergo a medical screening (including a medical history questionnaire, physical examination, anthropometric measurements and a basal blood sample by means of a venapunction), followed by one study day before and one after 12 weeks of treatment with Exenatide via a subcutaneous injection of 2 mg once a week. During the first 4 weeks, subjects will visit the LUMC weekly and the Exenatide injection will be performed under supervision of the researcher. If the researcher is convinced that subjects are able to perform the injection adequately, the last 8 injections can be performed by the subjects themselves at home. In that case, the researcher will contact the subject weekly by telephone and ask for compliance and possible side-effects. One week after ending of the study, a follow-up phone call will take place.

Per study day, the following measurements will take place:
- Noninvasive antropometric measurements (blood pressure, body weight)
- One bio-impedance analysis measurement (noninvasive method to measure fat mass)
- Two times indirect calorimetry measurement (noninvasive method of measuring energy expenditure by means of placing a transparent light-weighted plastic hood over the subject's head)
- Measurement of tissueoxygenation via PortaMon (noninvasive method via near infrared spectroscopy)
- Two blood draws. There is a risk of developing a hematoma at the place of the intravenous catheter.
- Exposure to two and a half hours of mild cold (by laying in a bed between two water-perfused mattresses)

- One MRI scan to measure BAT activity and liver fat. For this purpose, one time a MRI questionnaire will be taken beforehand.
- One 18F-FDG-PET-CT scan to measure BAT volume and activity, which for both study days together accounts for a total radiation burden of 8.0 mSv and is considered a low risk according to the current ICRP guideline of the European Committee (category IIb, risk due to radiation burden of maximally five in ten thousand). In line with this, our research concerns acquisition of knowledge, aimed at prevention or cure of a disease and serves a collective purpose for the community.

Between the study days, participants will fill in a food diary 4 times for 1 day and 4 times a hunger and satiety questionnaire.

The most common side effects of Exenatide are gastrointestinal complaints. At site of the injection, an itchy rash and/or erythema may appear. If these potential side-effects occur, they are expected to disappear within a few weeks. A rare side effect of Exenatide is acute pancreatitis. Patients are informed on possible symptoms and the researchers will ask for these during the weekly contact. There is also the risk of hypoglycemia, which is not to be expected however, since this is mostly the case when using concomitant glucose-lowering drugs (especially sulphonylurea derivates), and this is not the case in the study subjects. All subjects will be made aware of possible symptoms and will be provided with a glucose meter and instructions. The researchers will also ask for these symptoms and check for compliance during the weekly contact.

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

- Dutch South Asian or white Caucasian male, 20-36 years of age
- BMI * 18 and * 27 kg/m2
- Good general health

Exclusion criteria

- BMI > 27 kg/m2 or < 18 kg/m2
- Use of medication known to influence glucose and/or lipid metabolism or brown fat 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
- Participation in > 4 research projects within the last year, participation in multiple medicinal research projects at the same time'
- Contraindications for undergoing an MRI scan:
- Presence of non-MR safe metal implants or objects in the body.
- Pacemaker, neurostimulator, hydrocephalus pump, drug pump, non-removable hearing aid, large recent tattoos.
- Claustrophobia
- Tinnitus or hyperacusis

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-09-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bydureon
Generic name:	Exenatide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-07-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-08-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-10-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	16-11-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-05-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-01-2018
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	EUCTR2016-000238-23-NL
CCMO	NL56537.058.16