Targeting the beta-2 adrenergic pathway to improve skeletal muscle glucose uptake in obese humans

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The primary objective is to assess whether the insulin-stimulated glucose uptake in quadriceps muscle can be improved through 4 weeks of supplementation of clenbuterol.

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

Summary

ID

NL-OMON51975

Source
ToetsingOnline

Brief title
Obese human beta-2 adrenergic stimulation and muscle glucose uptake

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Eurostars grant

Intervention

Keyword: Beta-2 adrenergic agonist, glucose homeostasis, obese human, skeletal muscle

Outcome measures

Primary outcome

Main study parameter is insulin-stimulated 18F-FDG uptake in quadriceps muscle

as assessed using radio-active labelled tracer in PET-MRI

Secondary outcome

The secondary outcome parameter is insulin-stimulated 18F-FDG uptake in BAT as

assessed using radio-active labelled tracer in PET-MRI.

Study description

Background summary

Skeletal muscle insulin resistance is a primary factor underlying an impaired postprandial glucose clearance and a major hallmark in the development of type 2 diabetes mellitus (T2DM). As such, stimulation of skeletal muscle glucose uptake independent of the insulin pathway could significantly contribute to a positive disease outcome. In this context, we have recently demonstrated in pre-clinical models that skeletal muscle glucose uptake can be mediated through an alternative novel pathway involving β2-adrenergic receptors, through activation of mTORC2. Thus, robust improvements in glucose homeostasis were observed in diabetic rodents upon treatment with the selective β2-agonist clenbuterol, also when administered at lower doses. Furthermore, we are currently finalizing a study in young, healthy individuals which indicates that a standard dose of clenbuterol (40 µg/day) is well-tolerated by adult humans. During the current study, we will therefore investigate the effect of clenbuterol supplementation on glucose homeostasis in obese subjects to identify if targeting the β2-adrenergic-mTORC2 pathway could alleviate insulin resistance in skeletal muscle and activate brown adipose tissue (BAT).

Study objective

The primary objective is to assess whether the insulin-stimulated glucose uptake in quadriceps muscle can be improved through 4 weeks of supplementation

of clenbuterol.

Study design

4-week randomized, double-blinded, placebo-controlled, cross-over design with a minimum wash-out period of 6-8 weeks.

Intervention

4-week oral supplementation with clenbuterol hydrochloride (40 ug/day) or placebo. Capsules (20 ug) will be consumed twice daily

Study burden and risks

This study will not induce any benefits for the subjects and the major burden will be the time investment and potential side effects of clenbuterol. In total, the subjects will visit the University of Maastricht on 8 occasions (excluding screening) for measurements. Performed measurements will be without risks, but hematomas or bruises could develop upon blood sampling or muscle biopsies taken. This risk will be minimized due to state-of-the-art techniques and sterility measures taken. Clenbuterol or placebo supplementation will be given for 28 days, in which subjects ingest 1 capsule (20 ug) twice daily (40 ug/day). Clenbuterol could induce adverse effects, e.g. headache, increased heart rate/blood pressure, tremors, dizziness. However, during this study we will use a standard dose of clenbuterol (40 ug/day), which has previously been demonstrated to be a safe dose for human application. Furthermore, we will apply a relatively short supplementation duration (4 weeks). To limit the number of subjects that need to be included we decided for a cross-over design in which every participant serves as his/her own control. Risks related to the clamp and PET-MRI measurements are low due to clear exclusion criteria and well-experienced researchers performing these tests. For the PET scan, a [18F]-FDG bolus will be infused in the subject, which is a radio-active tracer commonly used in standard medical practice. The total radiation burden in the study per subject is ~2.7 mSv (normal background radiation in the Netherlands is ~2.5 mSv). No contrast agents are used. MRI is a modern diagnostic tool, which does not imply significant risks (no ionizing radiation).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Male or (postmenopausal; defined as 1 year after the last cycle) female;
2. Age between 40-75 years;
3. BMI: 25-35 kg/m2;

Exclusion criteria

1. Not meeting all inclusion criteria
2. Cardiovascular disease (determined by means of questionnaires, heart rate/blood pressure measurements and an ECG)
3. Respiratory diseases (including asthma, bronchitis and COPD);
4. Unstable body weight (weight gain or loss > 5 kg in the last three months);
5. Intention to lose or gain body weight (e.g. with caloric restriction or physical activity)
6. Excessive alcohol and/or drug abuse;
7. Hypokalaemia;
8. Hyperthyroidism
9. Anaemia;
10. Epilepsy;
11. Smoking;
12. Renal and/or liver insufficiency;

13. Diagnosed with type 1 or type 2 diabetes mellitus;
14. Any contra-indications to MRI scanning. These contra-indications include patients with:
a. Electronic implants such as pacemakers, defibrillators or neurostimulators
b. Central nervous system aneurysm clip
c. Some hearing aids (such as cochlear implant) and artificial (heart) valves which are contraindicated for MRI/MRS
d. Iron containing corpora aliena in the eye or brains
e. Claustrophobia
15. Participation in another biomedical study within 1 month before the first study visit, possibly interfering with the study results;
16. Medication use known to hamper subject*s safety during the study procedures; *
17. Subjects who do not want to be informed about unexpected medical findings; *
18. Subjects who do not want that their treating physician to be informed;
19. Inability to participate and/or complete the required measurements;
20. Participation in organised or structured physical exercise;
21. Any condition, disease or abnormal laboratory test result that, in the opinion of the Investigator, would interfere with the study outcome, affect trial participation or put the subject at undue risk;

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-08-2022
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Clenbuterol hydrochloride
Generic name:	Spiropent

Ethics review

Approved WMO Date:	01-10-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-10-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-09-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-02-2023
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	EUCTR2021-000731-31-NL
ClinicalTrials.gov	NCT04921306
CCMO	NL76746.068.21