MAASFLEX: A Double-Blind, Randomized, Phase IV, Mechanistic, Placebo-Controlled, Cross-Over, Single-Center Study to Evaluate the Effects of 2 Weeks Dapagliflozin Treatment on Nocturnal Substrate Oxidation, Glucose Metabolism and Muscle Mitochondrial Function in Individuals with Impaired Glucose Homeostasis

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The primary objective is to examine the effects of dapagliflozin on nocturnal substrate oxidation in overweight or obese subjects with disrupted glucose homeostasis but without T2D.

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

Summary

ID

NL-OMON55824

Source
ToetsingOnline

Brief title
MAASFLEX

Condition

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

Synonym
Disrupted Glucose Homeostasis; prediabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Astra Zeneca,Astrazeneca AB

Intervention

Keyword: Dapagliflozin, Glucose metabolism, Impaired glucose homeostasis, Nocturnal substrate oxidation

Outcome measures

Primary outcome

To investigate if Dapagliflozin improves nightly substrate oxidation as

measured by respiratory quotient (VCO2/VO2) between placebo and active

treatment after 2 week double blind treatment. Nightly substrate oxidation will

be determined during the sleep-period.

Secondary outcome

This study has the following secundary objectives:

To investigate if Dapagliflozin changes hepatic glycogen content in the morning

and evening as compared to placebo after 2 week double blind treatment.

To investigate if Dapagliflozin changes muscle mitochondrial function as

compared to placebo after 2 week double blind treatment.

Study description

Background summary

Metabolic health is characterized by a good metabolic flexibility: the capacity to switch from fat oxidation in the overnight fasted state to glucose oxidation in the postprandial state when insulin levels are high. Patient with Type 2 Diabetes Mellitus (T2D), but also individuals with so-called pre-diabetes * healthy, but have a disrupted glucose homeostasis - have an impaired metabolic flexibility. Including higher rates of glucose oxidation in the fasted state, and reduced insulin-induced glucose oxidation rates. A continuous state of *over-nutrition* either due to high food intake and/or excessive substrate storage and turnover - including substrate storage in peripheral tissues such as muscle and liver - will contribute to this lack of substrate switch over the day. In fact, among the best strategies to prevent and/or treat T2D are exercise and calorie restrictions: both interventions result in a temporary energy deficit, even when 24h energy balance may not be affected by compensatory food intake. The beneficial health effects of calorie restriction and exercise do not seem to depend on weight loss.

Inhibition of sodium-glucose cotransporter 2 (SGLT2) by a pharmacological intervention results in excessive glucose drainage via the urine. SGLT2 inhibitors have been shown to have beneficial effects on glucose homeostasis and metabolic health in general in T2D patients. We here suggest that the glucosuria resulting from SGLT2 inhibition results in an energy deficit that may trigger exercise-like improvements in metabolic health. More specific, we hypothesize that especially urinary glucose loss during the night will result in a larger energy deficit during this period, resulting in a more pronounced fasting state. We propose that this may lead to a more pronounced decrease in insulin and increase in glucagon during the night and a pronounced switch to fatty acids oxidation. This restoration of a normal day-night pattern in substrate metabolism will also trigger energy and substrate turnover in peripheral tissues, resulting in larger intracellular glycogen depletion, leading to improvements in mitochondrial function and restoration of metabolic flexibility.

Study objective

The primary objective is to examine the effects of dapagliflozin on nocturnal substrate oxidation in overweight or obese subjects with disrupted glucose homeostasis but without T2D.

Study design

The study is a double-blind, randomized, phase IV, mechanistic, placebo-controlled, cross-over, single-center study

Intervention

This study has a cross-over design with two periods:
Period 1: Participants will receive either 10mg dapagliflozin or the matching placebo for a maximum of 14 days based on randomization sequence.

Period 2: Participants that received 10mg dapagliflozin in the first treatment period will receive the matching placebo in the second treatment period and patients who received the placebo in the first treatment period will receive 10 mg dapagliflozin in the second treatment period, for a maximum of 14 days.

Study burden and risks

The use of Dapagliflozin can have side effects, which are described in the IB.

The patient will have 5 visits, which will take about 103 hours in total. The burden and risks of the tests performed are described below.

Muscle biopsy (4 times): patients can experience a dull pain when the biopsy is taken, despite sedation. A small scar remains where the biopsy was taken. After the biopsy, subjects are not allowed to perform intense exercise and should not remove the bandage for 24 hours. In extreme circumstances subjects may have to take paracetamol.
DEXA (1 time): exposure to a very small dose of radiation (<0.01mSv)
MRS (MRI) (4 times): the subjects will enter the MRI scanner 4 times, during which 4 MRS scans are made. There is a chance that MRI/MRS reveals an unexpected medical condition, of which the subject and treating physician will be informed.
Venapunction (2 times): this procedure can cause temporary pain and a bruise. In exceptional cases, nerve damage can occur.
Overnight stay in the respiration chamber (2 times): the subjects will stay in the respiration chamber for 36 hours per visit, where they have access to a toilet, bed, computer and television set.

There are no direct benefits for the subject. Subjects will receive compensation for participating in the study. Subjects will receive 853 euros for completing all study test, and expenses regarding travel expenses and parking costs will be compensated.

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

1. Provision of signed and dated informed consent prior to any study specific procedures.
2. Males aged * 40 and * 75 years and post-menopausal women (defined as at least 1 year post cessation of menses) aged * 50 and * 75 years
3. Body mass index (BMI) * 27 and * 38 kg/m2.
4. Sedentary lifestyle (not more than 2 hours of vigorous exercise per week).
5. Stable dietary habits.
6. Disrupted glucose homeostasis based on one or a combination of the following criteria:
- Impaired Glucose Tolerance (IGT): plasma glucose values * 7.8 mmol/l and * 11.1 mmol/l 120 minutes after consumption of the glucose drink during the 2h, 3-point OGTT.

- Impaired Fasting Glucose (IFG): fasting plasma glucose * 6.1 mmol/l and * 6.9 mmol/l.
- Insulin Resistance: glucose clearance rate * 360 ml/kg/min, as calculated by Oral Glucose Insulin Sensitivity 120 (OGIS120) model based on the 2h, 3-point OGTT.
- HbA1c * 5.7% and * 6.4%.

Exclusion criteria

1. Clinical diagnosis of Type 1 or 2 Diabetes Mellitus.
2. Active cardiovascular disease
3. Weight gain or loss > 5 kg in the last 3 months, ongoing weight-loss diet (hypocaloric diet) or use of weight loss agents.
4. Regular smoking and other regular nicotine use.
5. Anaemia.
6. Uncontrolled hypertension.
7. Clinically significant abnormalities in clinical chemistry or hematology
8. Unstable or rapidly progressing renal disease or estimated Glomeral Filtration Rate (eGFR) <60 mL/min (Cockcroft-Gault formula).
9. Use of anti-coagulant treatment
10. Use of medication such as oral glucocorticoids, anti-estrogens or other medications that are known to markedly influence insulin sensitivity.
11. Use of loop diuretics.
12. Intake of dietary supplements except multi-vitamins and minerals.
13. Alcohol consumption of > 14 drinks per week for women and > 21 drinks per week for men.
14. Known hypersensitivity to dapagliflozin or any of the excipients of the product.
15. For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.
16. Any contraindication for MRI scanning.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-09-2019
Enrollment:	57
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Farxiga
Generic name:	Dapagliflozin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-12-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	13-03-2019
Application type:	First submission
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	EUCTR2018-003283-31-NL
ClinicalTrials.gov	NCT03721874
CCMO	NL67170.068.18