DAPAMAAST: A Double-blind, Randomized, Phase IV, Mechanistic, Placebo-controlled, Cross-over, Single-center Study to Evaluate the Effects of 5 Weeks Dapagliflozin Treatment on Insulin Sensitivity in Skeletal Muscle in Type 2 Diabetes Mellitus Patients

Published: 25-10-2017
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The aim of the study is to investigate effects of dapagliflozin on potential mechanisms explaining improved insulin sensitivity in skeletal muscles.

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

Summary

ID

NL-OMON46385

Source
ToetsingOnline

Brief title
DAPAMAAST

Condition

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

Synonym
diabetes, Type 2 diabetes mellitus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Dapagliflozin, Insulin sensitivity, Mitochondrial function, Type 2 diabetes mellitus

Outcome measures

Primary outcome

To investigate if dapagliflozin improves skeletal muscle insulin sensitivity expressed as cGDR between placebo and active treatment after 5-week double blind treatment. Insulin sensitivity will be determined using a 2-step EHC procedure.

Secondary outcome

This study has the following exploratory objectives:

To investigate if dapagliflozin changes Endogenous Glucose Production (EGP) in comparison with placebo after 5 weeks of double blind treatment

To investigate if dapagliflozin improves metabolic flexibility as compared to placebo, determined by the change in respiratory exchange ratio (RER) from fasted state to insulin stimulated state during EHC after 5-week double blind treatment

To investigate if dapagliflozin changes RER and energy expenditure as well as

plasma metabolites such as beta-hydroxybutyrate and glucose as compared to placebo, before and after meals in the metabolic chamber after 5-week double blind treatment

To investigate if dapagliflozin improves maximal capacity to form acetylcarnitine following exercise and CRAT activity in muscle biopsy, as compared to placebo after 5-week double blind treatment

To investigate if dapagliflozin improves in vivo mitochondrial function as measured by phosphocreatinine recovery following exercise, as compared to placebo after 5-week double blind treatment

To investigate if dapagliflozin improves ex vivo mitochondrial function in permeabilized muscle fibers using high resolution respirometry, as compared to placebo after 5-week double blind treatment

To investigate if dapagliflozin changes body composition, skeletal muscle and liver fat content, as compared to placebo after 5-week double blind treatment.

To investigate if dapagliflozin changes blood biomarkers such as glucagon, insulin and FGF21 in comparison with placebo after 5 weeks of double blind treatment

To investigate if dapagliflozin changes expression of mRNA and/or proteins

involved in metabolic regulation in muscle tissue in comparison with placebo

after 5-weeks of double blind treatment.

Study description

Background summary

Type 2 diabetes mellitus (T2DM) results from combined derangements of insulin sensitivity and beta-cell function. The main tissues contributing to reduced whole body insulin resistance (IR) are the liver, skeletal muscles and adipose tissues. One of the earliest changes in first degree relatives to T2DM patients is reduced skeletal muscle insulin sensitivity. The degree of IR in skeletal muscle is typically investigated using an euglycemic hyperinsulinemic clamp (EHC) technique and given as glucose disposal rate (GDR). The cause of the IR associated with T2DM has not yet been fully understood.

A decreased mitochondrial function has been associated with skeletal muscle IR in several studies. However, it has been unclear if reduced mitochondrial function is a cause or a consequence of IR. A possible causal relationship between mitochondrial function and skeletal muscle insulin sensitivity is the ability of the mitochondria to export excess acetyl-CoA as acetylcarnitine by the action of carnitine acetyltransferase (CRAT). A strong association between levels of acetylcarnitine in skeletal muscles and insulin sensitivity has been shown in subjects with various levels of insulin resistance, indicating that decreased mitochondrial formation of acetylcarnitine could explain skeletal muscle insulin resistance.

T2DM and IR are associated with metabolic inflexibility as first described by Kelly et al. Metabolic inflexibility is likely to be caused by nutrient overload resulting in substrate competition at the level of the mitochondria.

Dapagliflozin is a sodium glucose co-transporter-2 (SGLT2) inhibitor indicated for the treatment of T2DM. The SGLT2 inhibition results in a loss of glucose and its associated energy (about 50-70 g/day) via urine. This mechanism results in a reduction in Hemoglobin A1c (HbA1c) and body weight. In a 2-year study, it was shown that dapagliflozin reduces HbA1c by 0.3%, weight by 4.5 kg and fat mass by 2.8 kg. It has also been shown that the reduction in body weight is faster over the first few weeks, followed by a more gradual decline that plateaus between 24 and 50 weeks of therapy).

An effect on insulin sensitivity, measured as a 17.5% increase in cGDR, has been demonstrated after 12 weeks of treatment with 5 mg dapagliflozin. This finding was repeated in a study with a treatment period of about 2 weeks where

cGDR increased by 16% in the dapagliflozin group but remained unchanged in the placebo treated group ($p<0.05$ vs baseline and placebo). This study also showed that endogenous glucose production (EGP) increased as a result of dapagliflozin treatment. In summary, 3 studies have investigated the effect of 2-12 weeks of treatment with SGLT2 inhibitors on insulin sensitivity and found 16 24% net improvements in cGDR. Treatment with SGLT2 inhibitors increases glucose excretion via the urine, which results in energy losses. Increased glucagon/insulin ratio explains increased hepatic glucose production, while indirect mechanisms explaining improved skeletal muscle insulin sensitivity are not known.

Study objective

The aim of the study is to investigate effects of dapagliflozin on potential mechanisms explaining improved insulin sensitivity in skeletal muscles.

Study design

This is a randomized, double-blind, cross-over, placebo controlled, single-center phase 4 study

Intervention

This study has a cross-over design with two periods:
Period 1: Patients will receive either dapagliflozin 10 mg or matching placebo for a maximum of 40 days based on randomization sequence.
Period 2: Patients that received 10 mg dapagliflozin in the first treatment period will receive matching placebo in the second treatment period and patients who received placebo in the first treatment will receive 10 mg dapagliflozin in the second treatment period, for a maximum of 40 days.

Study burden and risks

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

The study will last a maximum of 134 days in total. The patient will have 9 visits during this period. The burden and risks of the tests performed are described below.

Muscle biopsy (2 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, patients are not allowed to perform intense exercise and should not remove the bandage for 24 hours. In extreme circumstances patients may have to take paracetamol.
DEXA (2 times): exposure to a very small dose of radiation (0.001 mSv).

MRs (MRI) (6 times): the patiens will enter the MRI scanner 6 times, during which 8 MRS scans are made. There is a chance that the MRS may reveal an unexpected medical condition, of which the patient and the treating physician will be informed.
VO2 max and knee-extension test (6 times all together): can cause muscle ache and discomfort
Euglycemic hyperinsulinemic clamp (2 times): in extreme circumstances symptoms of hypoglycemia can occur. Furthermore, placing a catheter can be painful and can cause a bruise and discomfort.
Venapunction (3 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 patients will stay in the respiration chamber for 36 hours per visit, where they have access to a toilet, bed, computer and television set.

All together, approximately 625 mL of blood will be taken during the course of the study.

The benefits of participating in the study for the patient is that dapagliflozin could reduce blood sugar levels. Furthermore, dapagliflozin can reduce body weight, HbA1c and can increase insulin sensitivity. Patients will receive compensation for participating in the study. Patients will receive 1000 euros for completing all study tests. If patients make expenses regarding parking costs, travel expenses and/or hotel stays (hotel stays are optional for visits 4 and 7) they 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. Patients are able to provide signed and dated written informed consent prior to any study specific procedures.
2. Women are post-menopausal (defined as at least 1 year post cessation of menses) and aged >= 45 and <= 70 years. Males are aged >= 40 years and <= 70 years. Patients should have suitable veins for cannulation or repeated venipuncture.
3. Patients are diagnosed with T2DM for at least the last 6 months, based on American Diabetes Association 2016 standards
4. Patients are on no anti-diabetic drug treatment or on stable metformin treatment for at least the last 3 months: maximum 3000 mg metformin daily dose.
5. HbA1c levels >=6.0% (=42 mmol/mol) and <=9.0% (75 mmol/mol).
6. Have a body mass index (BMI) <= 38 kg/m2.

Exclusion criteria

1. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff and staff at third party vendor or at the investigational sites).
2. Previous enrolment in the present study or participation in another clinical study with an investigational product during the last 3 months or as judged by the Investigator.
3. History of or presence of any clinically significant disease or disorder including a recent (< 3 months) cardiovascular event which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study or influence the results or the patient*s ability to participate in the study.
4. Clinical diagnosis of Type 1 diabetes, maturity onset diabetes of the young, secondary diabetes or diabetes insipidus.
5. Unstable/rapidly progressing renal disease or estimated Glomerular Filtration Rate < 60 mL/min (Cockcroft-Gault formula).
Males:

Creatinine clearance (mL/min) = Weight (kg) X (140-Age) X 1.23
Serum creatinine (µmol/l)
Females:
Creatinine clearance (mL/min) = Weight (kg) X (140-Age) X 1.04
Serum creatinine (µmol/l)
6. Clinically significant out of range values of serum levels of either alanine aminotransferase (ALT), aspartate aminotransferase (AST) or alkaline phosphatase (ALP) in the Investigator*s opinion.
7. Contraindications to dapagliflozin according to the local label.
8. Use of antidiabetic drugs other than metformin within 3 months prior to screening.
9. Weight gain or loss > 5 kg in the last 3 months, ongoing weight-loss diet (hypocaloric diet) or use of weight loss agents.
10. History of drug abuse or alcohol abuse in the past 12 months. Alcohol abuse is defined as > 14 drinks per week for women and > 21 drinks per week for men (1 drink = 35 cl beer, 14 cl wine or 4 cl hard liquor) or as judged by the Investigator.
11. Any clinically significant abnormalities in clinical chemistry, hematology or urinalysis or other condition the Investigator believes would interfere with the patient*s ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the patient at undue risk.
12. Plasma donation within one month of screening or any blood donation/ blood loss > 500 mL within 3 months prior to screening or during the study.
13. Anemia defined as Hemoglobin (Hb) < 115 g/L (7.1 mM) in women and < 120 g/L (7.5 mM) in men.
14. Use of anti-coagulant treatment such as heparin, warfarin, platelet inhibitors, thrombin and factor X inhibitors.
15. Use of medication such as oral glucocorticoids, anti-estrogens or other medications that are known to markedly influence insulin sensitivity.
16. Use of loop diuretics.
17. Regular smoking and other regular nicotine use.
18. Any contra-indication to magnetic resonance imaging scanning. These contra indications include patients with following devices:
- Central nervous system aneurysm clip
- Implanted neural stimulator
- Implanted cardiac pacemaker of defibrillator
- Cochlear implant
- Metal containing corpora aliena in the eye or brain.
19. Patients, who do not want to be informed about unexpected medical findings, or do not wish that their physician be informed about coincidental findings, cannot participate in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2018
Enrollment:	60
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:	25-10-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	27-12-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	26-02-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-07-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-09-2019
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	EUCTR2016-003991-27-NL
ClinicalTrials.gov	NCT03338855
CCMO	NL63333.068.17