Combined effects of SGLT2 inhibition and GLP-1 receptor agonism on food intake, body weight and central satiety and reward circuits in obese T2DM patients

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Primary objective:To investigate the separate and combined actions of the SGLT2 inhibitor dapagliflozin and GLP-1 receptor agonist exenatide on activity in central reward and satiety circuits in response to food related stimuli in obese patients...

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

Summary

ID

NL-OMON48777

Source
ToetsingOnline

Brief title
DECREASE

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)
- Central nervous system vascular disorders

Synonym
'diabetes', 'Obesity', 'overweight', 'Type 2 Diabetes Mellitus'

Health condition

obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Astra Zeneca,industrie

Intervention

Keyword: brain, GLP1 RA, SGLTi, weight

Outcome measures

Primary outcome

Differences in neuronal activity in the central reward and satiety circuits in response food related stimuli by BOLD fMRI signal compared to baseline and 16 weeks of treatment between the exenatide+dapagliflozine, exenatide + placebo, dapagliflozin+placebo and double placebo groups

Secondary outcome

* Differences in neuronal activity in the central reward and satiety circuits in response food related stimuli by BOLD fMRI signal compared to baseline and 1.5 weeks of treatment and 1.5 and 16 weeks of treatment between the exenatide+dapagliflozine, exenatide + placebo, dapagliflozin+placebo and double placebo groups

* feeding behaviour, measured by quantitative and qualitative changes in food choice, during an ad libitum lunch buffet compared between the groups (at baseline and 1,5 week , baseline and 16 weeks and 1.5 and 16weeks)

* difference in self reported hunger, satiety and ful;ness by visual analogue scale

*difference in resting energy expenditure measured by indirect calorimetry

measurements between the groups (at baseline and 1,5 week , baseline and 16 weeks and 1.5 and 16weeks)

* Change in bodyweight (kg) and body mass index (kg/m2) between the groups (at baseline and 1,5 week , baseline and 16 weeks and 1.5 and 16weeks)

* Difference in bodycomposition measured by bio electrical impedance analysis and other body measurments such as waist and hip circumference between the 4 groups (at baseline and 1,5 week , baseline and 16 weeks and 1.5 and 16weeks)

*difference in resting brain activity by fMRI; resting state measurements

* effect on cardiovasculair autonomic balance by cardiovasculair reflex tests with finger plethysmography (Nexfin) (bloodpressure, hartfrequency, ECG).

* arterial stiffness: Pulse Wave Analysis (PWA) will be assessed using the SphygmoCor® System (Atcor Medical, West Ryde, Australia), a non-invasive system using applanation tonometry

* renal measurements by 24 urine ; glucose excretion (0-1,5, 0-16, 1,5-16), creatinine clearance (0-1,5, 0-16, 1,5-16 weeks), tubulair function ; sodium excretion and urinary pH (0-1,5, 0-16, 1,5-16 weeks), renal damage markers albumin/creatinin ratio (0-1,5, 0-16, 1,5-16weeks)

* Change in the plasma/serum biomarkers of metabolism, liver function, estimated renal function (eGFR), electrolytes and haematocrit (0-1,5, 0-8, 0-16, 1,5-16 weeks)

Safety outcomes:

The following safety variables will be collected during the study:

* Occurrence of adverse events (as reported by the patient) starting at the

informed consent and trough 30 days after administration of the last dose of study medication

* Vital signs (pulse rate, blood pressure, body temperature)

* Different end-point assessments that also serve as safety measurements: glucose, HbA1c, cholesterol, LDL and HDL cholesterol, sodium, creatinine, Ht, electrocardiograms.

Exploratory objectives:

* Cerebral perfusion assesed by Arterial Spin Labeling

* Blood will be collected to have the opportunity to perform measurements of hormones, such as leptin, cortisol and ghrelin.

* A blood sample will be collected for the study of genetic variation, for example. FTO gene variant

Study description

Background summary

SGLT2 inhibitors promote the renal excretion of glucose and lower elevated blood glucose levels in patients with type 2 diabetes (T2DM), independent of insulin action. Furthermore, SGLT2 inhibitors are associated with a decrease in body weight, caused by the chronic urinary calorie loss. However, the observed weight loss has been consistently less than expected from the amount of urinary glucose excretion. Recently, it has been shown that there is a mean weight loss of 3 kg during treatment with a SGLT2 inhibitor, whereas the observed calorie loss through glycosuria was predicted to result in a weight loss of 11 kg. As studies have shown that acute or chronic treatment with an SGLT-2 inhibitor does not alter energy expenditure, the discrepancy between observed and expected weight loss implies that patients increased their energy intake. These findings are supported by studies in animals that show compensatory hyperphagia

in response to SGLT2 inhibition.
It is important to understand the mechanisms whereby glycosuria may influence appetite regulation and food intake. In addition, it is of interest to investigate whether the effects of SGLT2 inhibitors on weight could be improved by combining SGLT2 inhibitors with interventions aimed at reductions in appetite and food intake.
It has been hypothesized that excessive eating due to changes in CNS satiety and reward responses to the consumption of food is fundamental in the development of obesity and T2DM. We and others have demonstrated altered responses within CNS satiety and reward circuits (including striatum, amygdala, orbitofrontal cortex, anterior cingulate cortex, insula, hypothalamus) in obese and T2DM relative to non-obese individuals, and these responses were shown to predict future weight gain. SGLT2 inhibitors may influence appetite and food intake through direct or indirect effects on the CNS, but the effects of SGLT2 inhibitors on these reward and satiety centers have not been investigated. Interestingly, GLP-1 receptor agonists have been shown to decrease appetite, food intake and body weight through effects on central reward and satiety circuits. Preliminary data show that when SGLT-2 inhibitors are combined with GLP-1 receptor agonists, the increased food intake during treatment with SGLT-2 inhibitors may be prevented. However, the effects of combined administration of SGLT2 inhibitors and a GLP-1 receptor agonist on central reward and satiety circuits, food intake and body weight have not been investigated.

Hypothesis: treatment with SGLT2 inhibitors is associated with alterations in central reward and satiety circuits in response to food related stimuli, leading to increased appetite and food intake. In addition, we hypothesize that adding a GLP-1 receptor agonist to treatment with an SGLT2 inhibitor may increase weight loss and prevent the increased food intake during treatment with SGLT2 inhibitors due to effects on neuronal activity of central satiety and reward circuits in response to food-related stimuli in obese patients with T2DM

Study objective

Primary objective:
To investigate the separate and combined actions of the SGLT2 inhibitor dapagliflozin and GLP-1 receptor agonist exenatide on activity in central reward and satiety circuits in response to food related stimuli in obese patients with T2DM

Secondary objective:
To investigate the separate and combined actions of the SGLT2 inhibitor dapagliflozin and GLP-1 receptor agonist exenatide on quantitative and qualitative aspects of food intake, energy expenditure, body measurements, resting state brain activity networks, cardiovascular autonomic nervous function, renal function and plasma/serum biomarkers

Safety objectives:
To evaluate the safety and tolerability of the separate and combined actions of the SGLT2 inhibitor dapagliflozin and GLP-1 receptor agonist exenatide

Exploratory objectives:
-to study the possible influence of concomitant changes in several important hormones and novel hormone measurements that may become available in the near future.
-to allow the study of the effects of human genetic variation on the endpoints in the future
- drug effects on microbiome
- changes in overall food intake, measured by a fooddiary

Study design

Double blind placebo-controlled randomized trial

Intervention

Subjects will be randomized in one of the following arms:

1) SGLT2 inhibitor dapagliflozin 10 mg/day in combination with placebo GLP-1 receptor agonist exenatide twice daily,
2) GLP-1 receptor agonist exenatide twice daily in combination with placebo dapagliflozin,
3) combination of dapagliflozin 10 mg/day and exenatide twice daily, or
4) placebo dapagliflozin and placebo exenatide twice daily

Study burden and risks

We are aware of the possible demand that may be imposed on the participants in this study. After the screening visit participants will travel 4 times to the study location. The total duration of the 3 test visits is aproximately 4 hours, the screeningvisit will take aproximately 2hours, the safety control visit aproximately 1 hour and the telephone consultations 15 min. The total amount of blood will be 150 ml in the total study (4 months). The risks associated with participation are the risks of venous blood drawing.
The fMRI, calorimetry, cardiac autonomous nervous system function test are considered to be safe. No invasive procedures are involved. Participants could experience discomfort while being in a supine position while testing.
Both study medications haven been approved for blood glucose lowering treatment in type 2 diabetes patients and based on currently available data are considered to be safe. Side effects of exenatide including hypoglycaemia (in combination with SU), nausea, vomiting and diarrhea are usually mild and transient. Side effects of dapagliflozine including genital (fungal) infections and hypoglycaemia (in combination with SU) are usually mild and transient.

Three of the four intevention groups will have benefit from treatment, possibly weight reduction and better glucose regulation. The placebo group will not have a benefit from treatment in this study.
We have built in different ways to alleviate the burden for participants, including clear, repeated communication, frequent contacting, 24-hour availability of the research staff and study, travel reimbursement and during test-days we provide meals.

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

For all 4 study groups:
- Age 18-75 years
- BMI 25*40 kg/m2

- Stable bodyweight (<5% reported change during the previous 3 months).
- Diagnosed with T2DM > 3 months prior to screening
- Treatment with metformin and/or sulphonylurea at a stable dose for at least 3 months.
- HbA1C 7.0*10% for patients treated with metformin
- HbA1C 7.5*10% for patients treated with metformin and/or sulphonylurea
- Both genders; for women: post menopausal (excluding possible menstruation cycle effects)

Exclusion criteria

For all 4 study groups:
- GLP-1 based therapies, dipeptidyl peptidase (DPP)-4, thiazolidinediones or insulin within 3 months before screening
- Weight-lowering agents within 3 months before screening.
- Congestive heart failure (NYHA II-IV)
- Estimated Glomerular Filtration Rate (eGFR) < 45 mL/min/1.73m2 (per Modification of Diet in Renal Disease (MDRD))
- Liver disease
- History of gastrointestinal disorders (including gastroparese, pancreatitis and cholelithiasis)
- Patients with MEN2 syndrome or history or family history of medullary thyroid carcinoma
- Neurological illness
- Malignancy (except for basal cell carcinoma)
- History of major heart disease
- History of major renal disease
- Pregnancy or breast feeding
- Implantable devices
- Substance abuse
- Addiction
- Alcohol abuse (defined as: for men > 21 units/week, for women >14 units/week)
- Smoking/ nicotine abuse (defined as: daily smoking / a daily use of nicotine)
- Contra-indication for MRI, such as claustrophobia or pacemaker
- psychiatric illnesses; mood disorders, eating disorders, anxiety disorders, schizophrenia and other psychotic disorders, dissociative disorders, somatoform disorders, delirium, dementia and other cognitive disorders
- Chronic use of centrally acting agents or glucocorticoids within 2 weeks immediately prior to screening.
- Use of cytostatic or immune modulatory agents
- History of allergy for exenatide or other GLP-1 RA
- Participation in other studies
- Individuals who have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry
- Individuals who are investigator site personnel, directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- Individuals who have previously completed or withdrawn from this study or any other study investigating GLP-1 receptor agonist or dipeptidyl peptidase (DPP)-4 within 6 months

- Visual disability, not correctable with glasses or contact lens
- Individuals who, in the opinion of the investigator, are unsuitable in any other way to participate in this study
- Poor commandment of the Dutch language or any (mental) disorder that precludes full understanding the purpose, instruction and hence participation in the study

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-08-2017
Enrollment:	64
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Byetta
Generic name:	exenatide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Forxiga
Generic name:	dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-000841-28-NL
CCMO	NL62025.029.17