A phase 4, monocenter, prospective, randomized, placebo-controlled, double-blind, cross-over, mechanistic intervention trial to assess effect of 4-week Ertugliflozin (SGLT-2 inhibitor) therapy on renal (cortical and medullary) oxygenation as determined by BOLD-MRI and renal (cortical and medullary) oxygen consumption as determined by positron emission tomography (PET) using ^{11}C-acetate in patients with type 2 diabetes mellitus and healthy controls.

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Despite multifactorial treatment approaches residual risk for the development and progression of DKD remains high and novel therapies to halt renal burden in T2DM are urgently needed. SGLT-2 inhibitors are a relatively recent additions to the...

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

Summary

ID

NL-OMON55355

Source
ToetsingOnline

Brief title
Renal Oxygenation and Consumption, hemodynamic Kinetics, dIabetES

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Nephropathies
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Adult-onset diabetes, Type 2 Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Industrie,Merck Sharp & Dohme (MSD)

Intervention

Keyword: BOLD-MRI, Diabetes, Renoprotection, SGLT2

Outcome measures

Primary outcome

To investigate the effect of 4-week treatment with SGLT-2 inhibitor

ertugliflozin 15mg QD on renal (separated as cortical and medullar) oxygenation

measured by BOLD-MRI (R2*)

Secondary outcome

The most important secondary efficacy parameters include the effect of

ertugliflozin on:

• Renal oxygen consumption as determined by positron emission tomography (PET)

^{11}C-acetate (compartment model parameter k2).

• Renal hemodynamic (GFR en ERPF); measured by the gold standard iohexol and

PAH-clearance method

• Calculated filtration fraction (FF) and local filtration fraction as measured by dynamic contrast enhanced MRI (DCE-MRI)

• Renal efficiency measured as sodium reabsorption (TNa) divided by oxygen consumption

• Cortical blood flow measured by contrast-enhanced ultrasound (CEUS)

• Renal arterial blood flow measured by arterial spin labelling (ASL) and DCE-MRI

• 24-hour sodium and glucose excretion after 2 days (acute response) and 4 weeks (chronic response)

• Renal tubular function

o Iohexol-corrected fractional sodium excretion

o Urine osmolality

o Urinary pH

• Renal damage markers, measured as:

o Urinary albumin excretion in 24-hour urine samples

• Change in inflammatory profile assessed by flow cytometry and fluorescence activated cell sorting (FACS)

• Changes in erythropoietin (EPO) levels

• Changes in plasma substrates including glucose, free fatty acids, ketone bodies, and triglycerides

• Insulin sensitivity (OGIS, Matsuda Index) and beta-cell function (as derived from HOMA-B) during an oral glucose tolerance test (OGTT).

• Peripheral insulin extraction and total arterial insulin extraction

(extraction x arterial flow)

• Fasting energy expenditure by resting energy expenditure (REE)

Study description

Background summary

Diabetic Kidney Disease (DKD) is a major global health problem affecting ~35% of the patients with type 2 diabetes (T2DM) and it is the leading cause of chronic kidney disease (CKD) (Tonneijck et al., 2017; Wanner et al., 2016). Despite the advancements in treatment of DKD by controlling renal risk factors (e.g. hyperglycemia, hypertension, smoking) and widespread use of renin-angiotensin-aldosteron-system (RAAS) inhibitors, DKD still causes significant morbidity and mortality. This includes both the development of end-stage kidney disease (ESKD) as well as cardiovascular disease, which is strongly associated with DKD. Finding new, safe, and effective medication to halt DKD has proven to be challenging, which is partly due to the fact that the mechanisms underlying DKD are complex and not fully understood.

Former research indicates that chronic hypoxia can be the common pathway of chronic kidney disease. In patients with Diabetes the kidneys are highly susceptible to a disturbance in oxygenation due to several factors. Oxygen delivery can be compromised due to hyperglycemia associated microvascular damage. A decrease in tissue oxygenation induces deterioration of affected nephrons, which leads to hyperfiltration of the remnant nephrons and therefore oxygen demand. Additionally, workload is increased by upregulation of SGLT-2 and accompanied sodium reabsorption. This vicious cycle of gradual aggravation of oxygen delivery and demand mismatch can results in progressive tubulointerstitial fibrosis and loss of kidney function. Earlier studies, which is foremost comprised of animal research, has shown an increase in sodiumreabsorption accopanied by a state of renal cell hypoxia.

Study objective

Despite multifactorial treatment approaches residual risk for the development and progression of DKD remains high and novel therapies to halt renal burden in T2DM are urgently needed. SGLT-2 inhibitors are a relatively recent additions to the treatment armamentarium of T2DM, and are associated with renoprotective effects. Current study aims to elucidate whether targeting sodium-glucose cotransporter 2 improves renal tissue oxygenation and oxygen consumption. There are four main theories as to why it is proposed SGLT-2 inhibitors exert this positive effect:

-Oxygen demand might be decreased by:
(1) A decrease in GFR
(2) A a shift of fuel metabolites towards ketones, which produce ATP very oxygen-efficient in a state of relative starvation such as Diabetes.

-Oxygen supply might be increased by:
(3) a change in systemic and intrarenal hemodynamics and perfusion.
(4) an increase in EPO

Current research is designed to primarly study renal tissue oxygenation through BOLD-MRI and oxygen consumption by PET-CT in patients with diabetes mellitus and SGLT-2 intervention. The data will be compared with healthy participants matched for age and renal function. Secundary objectives are a change in fuel metabolites (such as ketone bodies), renal hemodynamics, cardiovascular function, EPO-levels, markers of damage and inflammation, and insulineresistance.

Study design

A phase 4, monocenter, prospective, randomized, placebo-controlled, double-blind, cross-over mechanistic intervention trial to assess effect of 4-week Ertugliflozin (SGLT-2 inhibitor) therapy on renal oxygenation as determined by BOLD-MRI

Intervention

Cross-over conditions:
(1) 4 weeks of ertugliflozin 15mg
(2) 4 weeks of matchted placebo

Study burden and risks

Over the last 10 years, we have gained ample experience with similarly demanding mechanistic drug intervention studies in T2DM patients on renal hemodynamics (SAFEGUARD 2012.391, RENALIS 2013.459, ELIXIRS 2014.275, RED 2015.421). Based on the positive feedback from our participants, the low drop-out rate (max 5%) and the large proportion of participants that returns to participate in yet another (similarly demanding) study, we are confident that the burden on participants is perceived as not being too high. Indeed, we have built in different ways to alleviate the burden for participants, including clear, repeated communication, frequent contacting, intensified (diabetes) care, 24-hour availability of research staff, study and travel reimbursement, enabling participants to receive the newest study medication (that for most of them would not be reimbursed in daily practice) and offering follow-up care in our out-patient clinic.

We are aware of the fact that in the current study participants will undergo multiple tests that demand a considerable time investment from their end. For the participants in the studygroup the total duration of the visits is estimated at 40hours. For the participants in the control group the total duration of the visits is estimated at 12hours. These renal / cardiovascular test-days may be perceived as demanding that amongst others involves the placement of an arterial line. This procedure will be done by an experiences anesthesiologist to minimize the burden and risk of bleeding. Furthermore, during the cardiac autonomous nervous system function tests participants may experience transient dizziness or lightheadedness. As mentioned above, all possible measures will be taken to minimize the discomfort for the participants during the tests (e.g. comfortable beds are available which allow a semi-recumbent position).

The studymedication is considered to be safe and has been approved (FDA, EMA) for bloodglucose lowering treatment in type 2 Diabetes.Most common side effects are genital- or urinary tract infection, pruritus, pollakisuria, and nycturia.
The used test agents (i.e. Iohexol, PAH, 11C-acetate, Dotarem, and Sonovue microbubbles) are all considered to be safe in absence of allergy for any of the products. In case of an anafylactic reaction, appropriate actions will be undertaken.

Possible benefits for the participants include the positive effects of SGLT2-inhibitors on blood glucose levels. blood pressure, and weight.

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

Group 1:Participants with diabetes
* Provision of signed and dated, written informed consent prior to any study specific procedures.
* Caucasian*; female or male aged >=18 years and <80 years. Females must be post-menopausal (defined as at least 1-year post cessation of menses and follicle stimulating hormone (FSH) >31 U/L)*.
* Type 2 diabetes mellitus since at least 3 years with HbA1c >= 6.5% (>=57mmol/mol) and <10% (<94mmol/mol)
* An appropriate stable dose of Metformin and/or sulfonylurea as glucose-lowering therapy for the last 12 weeks
* Maximum tolerated antihypertensive dose of an ARB for at least 6 weeks prior to randomization.
* eGFR 60-90 ml/min/1.73m²
* BMI >=25 kg/m²
* In order to increase homogeneity.

Group 2:age-matched and eGFR matched non-diabetic controls
* Provision of signed and dated, written informed consent prior to any study specific procedures.
* Caucasian*; female or male aged >=18 years and <80 years. Females must be post-menopausal (defined as at least 1-year post cessation of menses and follicle stimulating hormone (FSH) >31 U/L)*.
* Normal glucose tolerance screening as confirmed by OGTT
* Maximum tolerated antihypertensive dose of an ARB for at least 6 weeks prior to randomization.
* eGFR 60-90 ml/min/1.73m²
* BMI >=25 kg/m²
* In order to increase homogeneity.

Exclusion criteria

Group 1: participants with diabetes
* Involvement in the planning and/or conduction of another study
* Participation in another clinical study with an investigational product during the last 3 months
* Diagnosis of type 1 diabetes mellitus
* CKD defined as eGFR<60 ml/min/1.73m² or macro-albuminuria (defined as UACR >30mg/mmol)
* Cardiovascular disease event in the last 6 months prior to enrollment, as assessed by the investigator: myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, heart failure, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmnia.
* Current/chronic use of the following medication: thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors, oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs), diuretics, and monoamine oxidase inhibitors.
* Current urinary tract infection and active nephritis
* History of ketoacidosis
* History of allergy/hypersensitivity to any of the testagents
* Contra-indication for MRI
* Any other condition that prevents participation as judged by the investigator

Group 2: age-matched and eGFR matched non-diabetic controls
* Involvement in the planning and/or conduction of another study
* Participation in another clinical study with an investigational product during the last 3 months
* CKD defined as eGFR<60 ml/min/1.73m² or macro-albuminuria (defined as UACR >30mg/mmol)
* Cardiovascular disease event in the last 6 months prior to enrollment, as assessed by the investigator: myocardial infarction, cardiac surgery or revascularization (CABG/PTCA), unstable angina, heart failure, transient ischemic attack (TIA) or significant cerebrovascular disease, unstable or previously undiagnosed arrhythmnia.
* Current/chronic use of the following medication: oral glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), immune suppressants, chemotherapeutics, antipsychotics, tricyclic antidepressants (TCAs), diuretics, and monoamine oxidase inhibitors.
* Current urinary tract infection and active nephritis
* History of allergy/hypersensitivity to any of the testagents.
* Contra-indication for MRI
* Any other condition that prevents participation as judged by the investigator

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2019
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ertugliflozin
Generic name:	Steglatro
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-11-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	05-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2022
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	EUCTR2019-000730-19-NL
ClinicalTrials.gov	NCT04027530
CCMO	NL69150.029.19