Natriuresis following an acute oral versus IV sodium load in type 2 diabetes patients without CKD: An incretin effect

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To assess the timed effects of a matched acute oral sodium load (in the absence or presence of GLP-1 receptor agonist) or an acute intravenous sodium load in T2DM patients with/without renal impairment on urinary sodium excretion after 24h,...

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

Summary

ID

NL-OMON54982

Source
ToetsingOnline

Brief title
REALITY

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Nephropathies

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: Rembrandt grant

Intervention

Keyword: CKD, Natriuresis, Sodium, T2DM

Outcome measures

Primary outcome

Urinary sodium excretion 24h after a matched acute oral sodium load (in the absence or presence of GLP-1 receptor agonist) or an acute intravenous sodium load in T2DM patients with/without renal impairment, determined by the cumulative sodium balance.

Secondary outcome

Variation in blood pressure, determined by non-invasive, automated, beat-to-beat blood pressure monitor (Nexfin®) measurements and 24h ABPM device, differences in total and fractional urinary sodium excretion and total sodium balance after 2, 4 and 6 hours, differences in plasma, urine and systemic hemodynamic markers, which include plasma hematocrit, hemoglobin, MCV, sodium, potassium, creatinine, urea, bicarbonate, chloride, glucose and GFR, urine creatinine, albumin, urea, osmolality, glucose, Na+, K+, Cl- (fractional and 24h collection), systemic hemodynamic; Cardiac output, peripheral vascular resistance, central blood pressure, heart rate and pulse wave velocity by application tonometry

Study description

Background summary

In healthy individuals, the incretin effect (i.e. insulinotropic effects of the gut-hormone glucagon-like peptide (GLP)-1) plays an important role in the

regulation of postprandial glucose metabolism. Several studies have shown that the incretin effect is reduced in diabetes mellitus type 2 (T2DM) patients and can be restored by raising GLP-1 concentrations to pharmacological levels. It has been proposed that GLP-1, in addition to acting as a glucose/nutrient sensor, may also be a major regulator of water and electrolyte balance in the postprandial state through rapid feed-forward effects on the kidney. In line with these observations, our research group has published several papers in which short-term and long-term treatment with GLP-1 receptor agonists was shown to induce renal sodium excretion in the fasted state. This could be of importance given the association of increased sodium intake and both cardiovascular and renal disease. Although the incretin effect in relation to glucose has been studied thoroughly, the role of sodium in GLP-1 production remains unclear. To our knowledge there are no sodium load studies in patients with chronic kidney disease or/and T2DM, in which the relation between GLP-1 and the renal effects were studied.

Study objective

To assess the timed effects of a matched acute oral sodium load (in the absence or presence of GLP-1 receptor agonist) or an acute intravenous sodium load in T2DM patients with/without renal impairment on urinary sodium excretion after 24h, determined by the cumulative sodium balance.

Study design

This is an randomized open label cross-over study design

Study burden and risks

Possible benefits for participants: There are no benefits expected for the participants.

Possible inconvenience for participants:
With regard to the used testagents, the Infusion of Iohexol can lead to a warm, sometimes painful sensation. Most common but rare adverse effects are headache, stiffness, nerve pain, nausea, vomiting, fever, hives, stomach pain, hallucinations and neurological changes. In patients with an allergy for iodide it can elicit hypersensitive reactions, therefore we specifically check a for this allergy at screening.
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.

Iohexol administration will not cause an increased discomfort, however patients who have an allergy for iodine are not allowed to participate due to the risk on an allergic reaction.

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 all the participants the total duration
of the visits is estimated at 24 hours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Group 2: T2DM patients without impaired kidney function
* Male between 40 and 75 years old
* Caucasian

* Average daily sodium intake of 150 mmol/day
* Known with Diabetes Mellitus - type 2, according to the ADA criteria
* Without macroalbuminuria defined as albumin-to-creatinine ratio >300 mg/mmol in a morning urine sample.
* Stable renal function (creatinine clearance > 60 ml/min and < 6 ml/min per year decline) with or without stable therapy with RAAS inhibiting agents
* HbA1c levels between 6.0 and 10.0% (42-86 mmol/mol) during the 6 months preceding the study
* Hypertension should be controlled, i.e. * 140/90 mmHg.
* Able to provide written informed consent

Exclusion criteria

* An office blood pressure >160/90 mmHg
* A major illness in the past 3 months or any significant chronic medical illness that the Investigator would deem unfavourable for enrolment, including chronic inflammatory diseases
* Current use of the following medication: thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, oral glucocorticoids, immune suppressants, antimicrobial agents, chemotherapeutics, antipsychotics, tricyclic antidepressants, diuretics and monoamine oxidase inhibitors, short-acting insulin, < 3 months on stable dose of long-acting insulin, SGLT-2 inhibitors
* A history of any type of malignancy within the past 5 years with the exception of successfully treated basal cell cancer of the skin
* A history of cardiovascular disease (in the past 6 months) defined as documented coronary artery disease including myocardial infarction, (un-)stable angina pectoris or acute coronary syndrome, precutenaous transluminal coronary angioplasty, coronary artery bypass grafting, cerebrovascular disease including ischemic and hemorrhagic stroke or a subarachnodial bleeding, or peripheral artery disease including aortic aneurysmata
* A history of coagulation disorders
* A history, within 3 years, of drug abuse (including benzodiazepines, opioids, amphetamine, cocaine, THC, methamphetamine)
* A history of alcoholism and/or is drinking more than 3 units of alcohol per day. Alcoholism is defined as an average weekly intake of >21 units for males. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits
* Difficulty in donating blood or limited accessibility of a vein in left and right arm
* Subject has donated blood in last 3 months
* Use of tobacco products
* Any other issue that, in the opinion of the Investigator, could be harmful to the subject or compromise interpretation of the data
- Iodine allergy

Study design

Design

Study type: Observational invasive

Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-03-2021
Enrollment:	11
Type:	Actual

Ethics review

Approved WMO Date:	27-09-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2021
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
CCMO	NL70824.029.19