Natriuresis following an acute oral versus IV sodium load in type 2 diabetes patients with and without DKD: an incretin effect?

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27521

Source
NTR

Brief title
REALITY study

Health condition

Chronic Kidney Disease, T2DM

Sponsors and support

Primary sponsor: None
Source(s) of monetary or material Support: Rembrandt grand

Intervention

Outcome measures

Primary outcome

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 healthy individuals and T2DM patients with/without renal impairment on urinary sodium excretion after 24h, determined by the cumulative sodium balance.

Secondary outcome

The most important secondary efficacy parameters include the effect of an acute oral versus intravenous sodium load on:
• Variation in blood pressure, determined by a non-invasive, automated, beat-to-beat blood pressure monitor (Nexfin®) measurements and 24h ABPM device
• Differences in total and fractional urinary sodium excretion after 2,4 and 6 hours
• Differences in plasma, urine and systemic hemodynamic markers

Study description

Background summary

In recent decades, the gastro-intestinal tract has been recognized as one of the largest endocrine organs in the human body. This entero-endocrine system has a key function in detecting signals from the external environment and in communicating these signals in order to maintain endocrine and neural homeostasis.
Several gut-derived neuroendocrine hormones have been identified in recent decades. The most widely studied hormones in this regard include the so-called incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones have been found to regulate (postprandial) glucose metabolism1,2. Both hormones are secreted in a physiological response to nutrients by secretory granules from entero-endocrine cells located in the small intestinal mucosa. The main effect of GLP-1 is stimulation of glucose-dependent insulin release from pancreatic islets (e.g. insulinotropic effects)3. The result of these actions is the phenomenon that an oral glucose load triggers higher levels of insulin secretion than a similar intravenous glucose load would. Other known effects of GLP-1 are delaying gastric emptying, reducing appetite by affecting the hypothalamic appetite centers in the brain and reducing the release of inappropriately secreted post-meal glucagon; all of these actions contribute to reductions in postprandial hyperglycemia4,5.
Several studies have shown that the incretin effect is reduced in type 2 diabetes mellitus (T2DM) patients and can be restored by increasing GLP-1 to pharmacological levels6,7. However, GLP-1 is quickly degraded by the enzyme dipeptidyl peptidase (DPP)-4 and therefore not suitable for therapy in patients. Thus, new incretin-based therapies in T2DM patients have been developed two decades ago and now take an important role in the pharmacological management of T2D. GLP-1 receptor agonists, which are resistant for cleavage by DPP-4, are administered as a subcutaneous injections and are available for combination therapy with oral antihyperglycemic agents and basal insulin8. In general, GLP-1 receptor agonists reduce HbA1c levels by approximately 1% compared to placebo9,10. The other group of incretin-based therapies concerns the selective and competitive DPP-4

inhibitors. The glucose-lowering effect of oral DPP-4 inhibitors is most notably mediated by preventing the postprandial fall of endogenous GLP-111.
Besides the above-indicated effects, GLP-1 receptor agonists have several effects beyond glucose lowering; so called pleiotropic effects. They improve hard cardiovascular outcome as studied in large cardiovascular outcome trials, likely through improvement of cardiovascular risk factors such as dyslipidemia, blood pressure, obesity and low-grade inflammation12. The mechanisms behind the blood-pressure lowering effects of GLP-1 receptor agonists are currently unknown, however it is known that GLP-1 receptor agonists improve endothelial function and vascular stiffness in patients with T2DM.
In recent years, there has also been increasing interest in the renal effects of GLP-1 receptor agonists. In phase-3 trials and in large cardiovascular outcome trials, GLP-1 receptor agonists have consistently shown to lower albuminuria, which is known to correlate with hard renal outcomes in the long-term, but which needs confirmation in a large ongoing trial in T2D patients with kidney disease that receive the GLP-1 receptor agonist semaglutide. The mechanisms behind this apparent renoprotection remain currently also unknown, but may involve changes in sodium homeostasis. 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 kidney5. 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 state1,5. This could be of importance given the association of increased sodium intake and both cardiovascular13 and renal disease14. As such, in Western countries, the average salt intake ranges between 8 and 12 g daily, which exceeds the daily limit of 5 g recommended by several health care organizations. The pathogenesis underlying the relationship between excessive salt intake and cardiorenal complications remains debated, but the leading hypothesis for decades has been that, in so called salt-sensitive individuals, excess sodium intake with concomitant impaired renal sodium excretion results in extracellular volume (ECV) expansion and hypertension. Particularly in patients with CKD, decreased glomerular filtration rate (GFR) reduces the rate of sodium and fluid excretion leading to activation of the renin-angiotensin system. Yet, carefully designed sodium balance studies in salt-resistant participants, i.e. individuals in whom increased salt intake does not increase blood pressure or body water/weight, much of the ingested sodium excess is in fact not excreted in the urine15,16. Rather it was shown that sodium may be stored non-osmotically (i.e. without altering ECV) at extrarenal locations, which serve to act as osmotic sodium buffer17. A site which binds sodium in a non-osmotic way is the endothelial surface layer (ESL) or glycocalyx located on the luminal side of the vascular endothelium17. Interestingly, ESL damage has been observed in participants with T2DM18 and CKD19, which could be speculated to contribute to the salt-sensitivity that is often observed in these people. Although non-osmotic sodium storage seems beneficial in the short term, saturated sodium depots have been linked to both hypertension and left ventricular hypertrophy, however, indicating the risks of chronic sodium overload. Accordingly, strategies to reduce tissue and interstitial sodium by facilitating renal excretion will likely contribute to improved cardiorenal health.

While we know that GLP-1 receptor agonist treatment/infusion increases sodium excretion in the fasted state, the question at hand is whether GLP-1 functions a feedforward sodium sensor in the gut (so called gut-kidney axis) following an oral sodium load. In addition the

question is whether GLP-1 could provide non-osmotic sodium buffering as they are known to reduce blood pressure and improve endothelial function20. There are scant data in literature at present regarding this topic. Singer et al. studied the endocrine responses to acute oral compared with intravenous sodium loading in humans. They observed there was a trend for an early delay in sodium excretion, followed by increased natriuresis after the oral load compared with the intravenous sodium load21. Carey et al. attempted to define the difference in renal sodium excretion after the two routes of sodium repletion in man. It was found that healthy individuals given the oral sodium load excreted greater quantities of sodium in their urine than those repleted intravenously. The differential natriuresis was significant as early as 2 hours after sodium loading22. Lennane et al. made a comparison of natriuresis after oral and intravenous sodium loading in sodium-depleted man. The results showed that those who received their sodium orally excreted it more rapidly than those who received it intravenously. The difference was most pronounced in the first 8 hours after the dose The rapidity of this response suggests that the gastrointestinal tract is involved in early recognition of changes in sodium intake and in mediation of the compensatory response23. A limitation of these studies is that they were all conducted in heathy humans, who are known to be resistant to the deleterious effects of sodium loading, possibly by gut-derived factors which regulate excretion and/or mediate non-osmotic storage. In addition, blood pressure response to sodium loading where not recorded, leaving the sensitivity to the sodium effect in terms of blood pressure response completely unknown.
We hypothesize that gut-kidney signaling may be impaired in patients with T2D and in patients with T2D and diabetic kidney disease who are more salt sensitive, compared to healthy volunteers. These subjects, in contrast to healthy individuals, are characterized by sodium sensitivity and susceptibility to hypertension. To the best of our knowledge there are no oral versus intravenous sodium load studies in patients with chronic kidney disease or/and T2DM performed; in addition, the role of GLP-1, the major gut-derived hormone, is unknown. Also, the relation between an acute sodium load and blood pressure has not been investigated yet. Recently studies concerning salt homeostasis showed that an excessive sodium intake can be buffered by a non-osmotic sodium storage24.
In this study we will examine the renal effects of an acute oral versus intravenous sodium load. Our primary outcome will be fractional and cumulative 24 hour natriuresis and our co-primary outcome will be blood pressure, determined by a 24 hour ambulatory blood pressure device. We further hypothesize that these effects may be reversed by increasing GLP-1 to pharmacological levels similarly as for the pancreatic incretin effect.

Study objective

In T2DM patients with DKD, an acute oral sodium load results in less renal sodium excretion than in healthy individuals and non-DKD T2DM, which can be restored by administration of a GLP-1 receptor agonist.

Study design

-30, 0, 60, 120, 180, 240, 300, 360, 1440 minutes

Intervention

Three arms:

1. Oral + placebo:
- Oral: 154 mmol sodiumchloride (9 gram) diluted in 254 cc water
-Intervenous: glucose 5% diluted in 46 mL 0.9% isotonic saline

2. Oral + GLP-1
- Oral: 154 mmol sodiumchloride (9 gram) diluted in 254 cc water
- Intravenous: 10 µg GLP-1 diluted in 46 ml 0,9% isotonic saline

3. Intravenous
- Intravenous: Nacl 3% diluted in 300 cc

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Eligibility criteria

Inclusion criteria

Group 1: T2DM patients with DKD

• 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
• One of the following criteria:
o Microalbuminuria defined as either albuminuria >20 mg/L in a morning urine sample or albuminuria >30 mg/24 hrs collected in a 24-hours urine collection or albumin-to-creatinine ratio >3 mg/mmol in a morning urine sample
o Creatinine clearance <50 ml/min
• Stable renal function (< 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

Group 2: T2DM patients without DKD
• 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 microalbuminuria defined as albumin-to-creatinine ratio < 3 mg/mmol in a morning urine sample.
• Stable renal function (creatinine clearance > 75 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

Group 3: Healthy subjects
• Male, age between 40 and 75 years of age
• Caucasian
• Average daily sodium intake of 150 mmol/day
• Healthy, as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination (PE) and laboratory tests carried out in the screening visit.
• eGFR > 75 ml/min, without microalbuminuria
• Non-treated office blood pressure ≤ 140/90 mmHg
• Normal glucose tolerance as assessed by a 75-g oral glucose tolerance test (OGTT) according to ADA criteria
• Capable of giving written informed consent and able to comply with the requirements and restrictions listed in the informed consent form

Exclusion criteria

A potential subject of any of the three groups who meets one or more of the following criteria will be excluded from participation in this study:
• 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

• 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, percutaneous 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

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-01-2020
Enrollment:	33
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	13-01-2020
Application type:	First submission

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
NTR-new	NL8293
Other	METC VUmc : METc_2019.530

Study results