Role of endothelial surface layer in regulating the sodium balance and extracellular fluid volume

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In this study we will identify the role of the endothelial GAGs in Na+ and volume homeostasis. Is there a link between the ESL and individual susceptibility to Na+-excess?

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

Summary

ID

NL-OMON46844

Source
ToetsingOnline

Brief title
SALT-2 study

Condition

- Other condition
- Vascular hypertensive disorders

Synonym
blood pressure, extracellular volume, sodium and volume homeostasis, sodium buffering capacity of ESL

Health condition

fysiologie van natrium- en volumebalans

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW en Nierstichting

Intervention

Keyword: blood pressure, endothelial surface layer, extracellular volume, natrium

Outcome measures

Primary outcome

We will primarily study the effects of a salt load on the haemodynamics, ECV and ESL in patients with acquired and congenital loss of the ESL. Primary endpoint will be the ECV as represented by body weight, BP and iohexol measurements.

Secondary outcome

Other study paramaters consist of indirect measurements of the ESL dynamics and function assessed by imaging of the sublingual microvasculature, measurement of ESL shedding products and determination of the transcapillary escape rate (TER) of I125-albumine. The kidney function will be studied by estimating the glomerular filtration rate (eGFR) and measurement of the fractional Na+ excretion and albuminuria. Finally, skin biopsies will allow studying the role of interstitial GAGs and macrophage influx in response to a salt load.

Study description

Background summary

Sodium (Na+) plays a key role in maintaining volume homeostasis and blood pressure (BP). The difference between Na+ intake and excretion, the Na+ balance, is regulated by the kidney. Regulation of the Na+ balance by the

kidney is believed to be the main determinant of extracellular fluid volume (ECV). Recent studies have revealed that the Na+ balance is not only regulated by the kidney, but also in the interstitium of the skin. Here, binding of Na+ to glycosaminoglycans (GAGs) allows non-osmotic handling of Na+, thereby acting as a Na+ buffer. Based on these findings, we hypothesize that the endothelial surface layer (ESL), representing a complex sugar layer principally composed of negative-charged GAGs lining the endothelium, is an important determinant of volume homeostasis and BP by its ability to act as an immediate non-osmotic Na+ buffer. A perturbed ESL might therefore lead to an increase in ECV and BP after a salt load. The volume of the ESL varies highly between individuals (0.5-2.3 L) and is known to be smaller in specific patient groups such as diabetic patients and patients with chronic kidney disease.
The putative non-osmotic buffer capacity of the endothelial GAGs without commensurate water retention has only been limitedly studied yet, but seems particularly relevant in clinical conditions characterized by volume overload (e.g., heart failure, hypertension, chronic kidney disease). If the endothelial GAGs are involved in non-osmotic Na+ storage, treatment strategies directed to restoration of the ESL would lead to improved BP and ECV control and, conceivably, to better cardiovascular outcome. This study focuses on a novel function of the ESL, namely the capacity to store Na+ non-osmotically.

Study objective

In this study we will identify the role of the endothelial GAGs in Na+ and volume homeostasis. Is there a link between the ESL and individual susceptibility to Na+-excess?

Study design

In this project, we plan to conduct an experimental interventional cross-over study to investigate the Na+ storing capacity of the endothelial GAGs. For this, the effect of different Na+ conditions on ESL, ECV and BP, will be studied in diabetic and hereditary multiple exostosis (HME) patients.

Intervention

High salt diet (>200 mmol Na+ daily) for 1 week, and low salt diet (<50 mmol Na+ daily) for 1 week, each in random order. Furthermore, all subjects will receive a hypertonic salt infusion at day 15 of the low salt diet to study the effects of an acute salt load.

Study burden and risks

The burden of this study consists of a total of 3 visits in which they will spend about 17 hours in the hospital. All subjects will be asked to adhere to a low and a high Na+ diet and collect 24-hour urine samples during the diet. The

study comprises extra venous blood drawing and various extra diagnostic tests. Invasive measurements with different tracers for ECV and GFR (iohexol), plasma volume (PV) and TER (125I-albumin) will take place. The radiation exposure is *minor* (maximum 0,1 mSV). At present, the function of the ESL in relation to salt intake and CVD is not well understood. Novel strategies for targets for treatment of complex diseases with concepts of volume overload are prevalent. For the patients there is no direct benefit when participating in this study, but the outcome of the study is essential for further investigations on this topic. The findings of this study might influence future treatment for diseases characterized by an expanded ECV.

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. Diabetic patients (n<=12)
- Male between 18 and 40 years old
- Known with Diabetes Mellitus - type 1
- With or without microalbuminuria defined as:
o either albuminuria 20-200 mg/L in a morning urine sample
o or albuminuria 30-300 mg/24 hrs collected in a 24-hours urine collection
o or albumin-to-creatinin ratio 2,5-25 mg/mmol in a morning urine sample.
- Stable renal function (creatine 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
- Multiple injections of insulin a day
- Able to provide written informed consent and to comply with the requirements and restrictions listed in the informed consent form;2. HME patients (n<=12)
- Male between 18 and 40 years old
- Documented Hereditary Multiple Exostoses
- Stable renal function (creatinin clearance > 60 ml/min and < 6 ml/min per year decline, no proteinuria)
- Able to provide written informed consent and to comply with the requirements and restrictions listed in the informed consent form

Exclusion criteria

- An office blood pressure >140/90 mmHg
- A body mass index > 30 kg/m2
- 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
- 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 any renal disease
- 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 of primary hyperlipoproteinemias
- A history of hypersensitivity or allergy to iodium or to shell fish
- 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
- Any clinically relevant abnormality noted on the 12-lead ECG as judged by the Investigator or an average QTcB or QTcF > 450 millisec

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-06-2014
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	25-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2014
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

ID: 28711
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL48278.018.14
OMON	NL-OMON28711