The role of skin sodium accumulation in chronic kidney disease

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Main objectivesCohort study:To investigate the prognostic implications of skin sodium accumulation for CKD patients.Sodium excretion intervention study:To study the effect of increased renal sodium excretion, with and without ...

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON53426

Source
ToetsingOnline

Brief title
SKIN-CKD

Condition

- Renal disorders (excl nephropathies)

Synonym
Chronic kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: NWO-talentprogramma Veni ZonMw (Sub studie: waterinname interventie),Collectebussenfonds

Intervention

- Other intervention
- Life style intervention

Keyword: CKD, Skin sodium, Sodium MRI

Explanation

N.a.

Outcome measures

Primary outcome

Cohort study:
Incidence of cardiovascular events and renal replacement therapy.

Sodium excretion intervention study:
Skin sodium content difference between different treatments.

Sodium intake intervention study:
Skin sodium content difference between diets.

Water intake intervention study:
Incidence of hyponatremia and hypervolemia.
Skin sodium content and TEWL difference between habitual and increased water
intake.

Secondary outcome

Cohort study:
- The relation between tissue sodium content, changes in tissue sodium content,
and micro- and macrovascular function.
- The association between skin sodium content and traditional cardiovascular
risk factors.
- The association between skin sodium content and quality of life.

Water intake intervention
- The effect of high water intake on blood pressure, copeptin, systemic
vascular resistance and microcirculation.

Study description

Background summary

Recent studies demonstrated that sodium can be stored in high concentrations in the skin without water retention. This was mainly observed in medical conditions associated with systemic sodium overload and water excess such as in patients with chronic kidney disease (CKD). In this group of patients, increased skin sodium content is associated with left ventricular hyperthrophy and increased mortality in dialysis patients.
However, the exact pathophysiology and consequences of elevated tissue sodium

in CKD remains unclear. The exact link between skin sodium and hypertension is also not understood. Skin sodium accumulation may results in hypertension due to endothelial dysfunction and microvascular rarefraction. But one may also argue that skin sodium is merely the result of hypertension.
In other words, sodium accumulation under the skin in CKD patients is related to cardiovascular disease and complications. However, only a few studies have addressed the relationship between sodium storage under the skin and long-term disease outcomes in renal patients.

A relatively new hypothesis regarding skin sodium storage in CKD is that it is a compensation mechanism for increased renal water loss. At an eGFR of 15-29 ml/min/1.73m2 the median fasting urine osmolality declines to 400 mOsm/kg, whereas the maximum concentrating capacity of a healthy kidney is 1200 mOsm/kg. In rat studies, researchers have demostrated that fluid intake did not compensate fully for the increased renal water loss, indicating that other compensatory mechanisms are involved. These mechanisms included cutaneous vasoconstriction and skin electrolyte accumulation, which together reduced transepidermal water loss.

Previous intervention studies have demonstrated that sodium stored in the skin can be mobilized by loop diuretics, sodium-glucose co-transporter-2 (SGLT-2) inhibitor and dialysis. Furthermore, high sodium intake was associated with an increased skin and muscle sodium content in healthy volunteers. To present date, it is unknown whether tissue sodium content in CKD patients can be lowered by increasing renal sodium excretion or water intake or limiting sodium intake. We hypothesize that skin sodium content in CKD patients can be lowered by increasing renal sodium excretion, increasing water intake or limiting sodium intake, and that lower skin sodium content is associated with better micro- and macrovascular function in CKD.

Study objective

Main objectives
Cohort study:
To investigate the prognostic implications of skin sodium accumulation for CKD patients.

Sodium excretion intervention study:
To study the effect of increased renal sodium excretion, with and without aldosterone blockade, on tissue sodium content in CKD.

Sodium intake intervention study:
To define the effect of high and low sodium intake on tissue sodium content in CKD.

Water intake intervention study:
To assess safety of increasing water intake in CKD stage 4.

To study the effect of increased water intake on skin sodium content and transepidermal water loss (TEWL).

Secondary objectives
Cohort study:
- To study the micro- and macrovascular consequences of tissue sodium accumulation and changes in tissue sodium content in CKD patients.
- To test whether skin sodium accumulation is correlated with the quality of life in CKD patients.

Water intake intervention study:
- The effect of water intake on blood pressure, copeptin, systemic vascular resistance and microcirculation.

Study design

This project is divided in four studies:
- 1 cohort study
- 1 open label randomized crossover sodium intake intervention
- 1 open label randomized crossover sodium excretion intervention
- 1 open label randomized crossover water intake intervention.

Intervention

Sodium intake intervention
The participants in this group will receive 2 weeks high sodium diet (>200mmol) and 2 weeks low sodium diet (<50mmol). Between both diets, participants will have to 2 weeks washout period.

Sodium excretion intervention
In a randomized crossover method, we will compare the effect of two sodium depleting antihypertensive drugs (hydrochlorothiazide, spironolactone) and a non-sodium depleting antihypertensive agent (lercarnidipine).This in order to determine whether tissue sodium content is dependent on systemic sodium overload, hypertension or both and to study the role of aldosteron in this proces.

Water intake intervention
The participants in this group will receive a water intervention in which they drink their habitual water intake for 4 weeks and a high water intake (1L more than their mean 24-hour urine volume at screening and baseline) for 4 weeks. Between both water intakes, participants will have a 2-week washout period.

Study burden and risks

Cohort

Subjects will visit the clinic once for an extensive baseline measurements (3 hours). The measurements are not harmful or painful and no adverse events are expected. Patients will be asked consent for follow-up until the start of renal replacement therapy or a maximum of 15 years. At baseline and every 12 months during follow up, we will take the Kidney Disease Quality of Life (KDQOL-36) questionnaire. The questionnaire mentioned above possess no risk for the subject and has no consequences for the regular outpatient care that they will receive.

Sodium intake intervention
The patients will receive a 2-week low and a high sodium diet with a wash out period in between of at least 2 weeks. Subjects will visit the clinic 7 times (+/- 12 hours) for the measurements including 23Na-MRI. 24-hour urine will be checked 7 times to check dietary adherence. 24-hour blood pressure will be measured 3 times. We do not expect any adverse events related to the dietary interventions due to the short study duration.

Sodium excretion intervention
All participant will receive 3 different antihypertensive drugs for a 6-week period to alter renal sodium excretion. All drugs are extensively used in daily clinical practice of hypertension treatment and the safety has been proven. We will include hypertensive subjects with an eGFR >30 ml/min/1.73m2 and a plasma potassium <5.0 mmol/L to limit the risk of adverse events such as hypotension and hyperkalemia. The participants will visit the clinic in total 8 times (+/- 15 hours) to perform various measurements, including 23Na-MRI, blood sampling and evaluation of adverse effects. 24-hour urine and 24-hour blood pressure measurements will be collected in total 4 times.

Water intake intervention
The patient will receive a 4-week habitual and increased water intake with a wash out period in between of at least 2 weeks. Subjects will visit the clinic 9 times (+/- 12 hours in total) to perform various measurements, including three 23Na-MRIs (during the 3 long visits), blood sampling and evaluation of adverse effects. 24-hour urine will be checked 11 times. 24-hour blood pressure will be measured 3 times. As the ability to excrete free water is not substantially impaired when eGFR is >15 ml/min/1.73m2, the risk for hypervolemia or hyponatremia is low. Nevertheless, we will exclude patients with a history of heart failure, dysnatraemia or medications known to influence the concentrating capacity of the kidney to further limit the risk of these adverse events.

Contacts

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Trial sites

Trial sites in the Netherlands

Amsterdam UMC
Target size: 60

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria
1. Chronic kidney disease with an eGFR between 15 and 60 ml/min/1.73m2.
2. Stable diuretic and antihypertensive treatment in the 6 weeks prior to the study.

Additional inclusion criteria for the sodium excretion intervention
1. Office systolic blood pressure (SBP) >135 mmHg

Additional inclusion criteria for the water intake intervention
1. Chronic kidney disease with an eGFR between 15 and 29 ml/min/1.73m2

2. Office blood pressure >=140/90 mmHg or use of antihypertensive medication
3. Fasting morning urine osmolality <425 mOsm/kg for men and < 400 mOsm/kg for women

Exclusion criteria

Exclusion criteria
1. Age <18 years.
2. The patient is expected to start renal replacement therapy or is planned to receive a kidney transplantation within 3 months
3. An active diagnosis of nephrotic syndrome at inclusion.
4. (Recurrent) acute glomerulonephritis within 1 year prior to the study.
5. Salt losing nephropathy.
6. Use of oral or intravenous glucocorticoids with an equivalent of prednisolone >5mg/day.
7. Contra-indication for MRI i.e. metallic foreign body, claustrofobia
8. Cardiovascular event or procedure during the previous 3 months.
9. Pregnant women, women of childbearing age planning to conceive for the study duration, women of childbearing age who do not use an effective contraception.
10. Participation in other intervention studies.
11. Presence of significant comorbidities (e.g. advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.
12. A psychiatric, addictive or any disorder that compromises the participants' ability to give truly informed consent for participation in this study.
13. Patients with an active infection and/or auto-immune diseases with involvement of the lower extremities.
14. Any other issues that in opinion of the investigator could be harmful to the subject or compromise interpretation of the data.

Additional exclusion criteria for sodium intake intervention
1. Chronic use of NSAID

Additional exclusion criteria for sodium excretion intervention
1. Serum potassium concentration >5.0 mmol/l.
2. eGFR <30 ml/min/1.73m2
3. Uncontrolled hypertension (>180/100mmHg)
4. Contra-indication for drugs used during this study e.g. drug intolerance (side effect, hyperkalaemia hypersensitivity to sulphonamides) and drug interaction.
5. Chronic use of NSAID.

Additional exclusion criteria for the water intake intervention
1. Recent history of severe hyponatremia (outpatient plasma sodium < 130 mmol/L in the last 6 months)
2. Plasma sodium <135 mmol/L at screening
3. History of heart failure
4. Use of lithium, vasopressin analoga, vasopressin antagonists, oral or intravenous

glucocorticoids, thiazide diuretics.
5. 24-hour urine volume > 2L
6. Chronic use of NSAID

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Other type of control
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	07-01-2025
Enrollment:	60
Duration:	6 months (per patient)
Type:	Anticipated

Medical products/devices used

Product type:	N.a.
Registration:	No

IPD sharing statement

Plan to share IPD: Undecided

Plan description
N.a.

Ethics review

Approved WMO Date:	18-04-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2025
Application type:	Amendment
Review commission:	METC Amsterdam

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	NL82810.018.23
Research portal	NL-004973