Treatment of vascular stiffness in patients with autosomal dominant polycystic kidney disease

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This study has been transitioned to CTIS with ID 2024-512544-27-00 check the CTIS register for the current data. We aim to investigate if arterial stiffness is exacerbated due to a high-salt diet in patients with ADPKD. We also intend to explore…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON55149

Source
ToetsingOnline

Brief title
TRAMPOLINE

Condition

- Renal disorders (excl nephropathies)

Synonym
Polycystic kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Nederlandse nierstichting

Intervention

Keyword: Amiloride, Hypertension, Polycystic kidney disease, Salt

Outcome measures

Primary outcome

The three primary outcomes of this study are a difference in central arterial stiffness, measured as the pulse wave velocity (PWV), in highsalt group versus low-salt group, and before versus after amiloride treatment in both groups.

Secondary outcome

Secondary outcomes include ambulatory (24-hour) blood pressures, markers of inflammation, salt tasting test and skin sodium content through 23Na-MRI.

Study description

Background summary

Autosomal dominant polcystic kidney disease (ADPKD) is the most common inherited kidney disease characterized by cystic kidneys and caused by mutations in the polycystin genes. It is associated with salt-sensitive hypertension, which accounts for the majority of morbidity and mortality. About 70% of patients with ADPKD develop hypertension, prior to the onset of kidney function decline.

Early onset hypertension, despite its treatment, is independently associated with rapid kidney function decline, and is therefore used as a marker for those with rapid disease progression. Knowledge of its etiology is therefore crucial for its targeted therapy.

Although incompletely understood, arterial stiffness and sodium-retention are thought to precede hypertension in ADPKD. Recent insights show that the endothelial glycocalyx (a protein layer) localized on arteries plays a significant role in development of vascular stiffness. In normal situation, glycocalyx buffers sodium and prevents hypernatremia. A high-salt diet disrupts the glycocalyx, which leads to sodium influx into endothelial cells through the

so-called epithelial sodium channel (ENaC). This results in interstitial sodium accumulation in the skin and vascular stiffness.

We hypothesize that a high-sodium diet in patients with ADPKD is required for the development of hypertension and inhibition of the ENaC reverses this phenomenon.

Study objective

This study has been transitioned to CTIS with ID 2024-512544-27-00 check the CTIS register for the current data.

We aim to investigate if arterial stiffness is exacerbated due to a high-salt diet in patients with ADPKD. We also intend to explore whether treatment with amiloride prevents the effect of high salt on arterial stiffness.

Study design

Randomized, double blinded and placebo-controlled clinical trial with open-label treatment with amiloride

Intervention

After obtaining informed consent, patients will be subjected to a low-salt diet (3,5 grams/day) for 6 weeks, and randomized into two treatment groups for 4 weeks:

Group 1: Sodium chloride capsules (6 grams/day) + additional amiloride (20 mg/day) in last two weeks
Group 2: Placebo capsules + additional amiloride (20 mg/day) in last two weeks

Furthermore, the following measurements will be performed during the trial:
- 3x non-invasieve measurements of vascular stiffness, using pulse wave velocity
- 4x office bloodpressure measurements
- 3x 24-hours ambulatory blood pressure measurements
- 4x blood withdrawals
- 4x spot urine measurements
- 3x 24-hours urine collections
- 4x Salt tasting test
- For a subgroup patients (n=8): 3x MRI scans in AMC, Amsterdam

Study burden and risks

The burden of participation includes:
- A dietary salt restriction of 3,5 grams/day for a total period of 6 weeks
- Salt supplement intervention as mentioned above for a total period of 4 weeks

- Additional drug intervention with amiloride during the last 2 weeks
- Five visits to the hospital and one phone call
- The following measurements:

Screening visit (week 0):
Office blood pressure measurement
Blood samples
Spot urine samples

Duration: 45 minutes

Dietician visit (week 0):
Salt tasting test

Duration: 45 minutes

Baseline visit (week 3) :
Pulse wave velocity measurement
Office blood pressure measurement
Blood samples
Spot urine samples
24-hours blood pressure measurement
24-hours urine collection
Salt tasting test
23Na-MRI (Amsterdam UMC) (n=8 per group)

Duration: 90 minutes for patients without MRI;
120 minutes for patients with MRI

Mid-term visit (week 5):
Pulse wave velocity measurement
Office blood pressure measurement
Blood samples
Spot urine samples
24-hours blood pressure measurement
24-hours urine collection
Salt tasting test
23Na-MRI (Amsterdam UMC) (n=4 per group)

Duration: 90 minutes for patients without MRI;
120 minutes for patients with MRI

Final visit (week 7):
Pulse wave velocity measurement
Office blood pressure measurement
Blood samples
Spot urine samples

24-hours blood pressure measurement
24-hours urine collection
Salt tasting test
23Na-MRI (Amsterdam UMC) (n=4 per group)

Duration: 90 minutes for patients without MRI;
120 minutes for patients with MRI

Total study duration: 360 minutes for patients without MRI;
450 minutes for patients with MRI

Risks:
Although expected risks are limited, side effects of treatment may include exacerbated hypertension and hyperkalemia:
1. Hypertension: an increase in mean arterial blood pressure (MAP) of 7 mmHg was observed after an exceptionally high-salt diet of 18 grams/day in patients with ADPKD (Doulton et al., J Hypertens, 2006). Several studies have shown an average blood pressure increase of 8/4 mmHg in hypertensive patients after discontinuation of their hypertension treatments. Together with cessation of antihypertensive drugs, the expected maximum rise of MAP is ±15 mmHg for those receiving salt capsules (group 1). Considering the short duration of the trial, this will unlikely be harmful. Blood pressure will be monitored during the trial (visit 3 = safety visit) and study will be terminated prematurely if an office blood pressure of >=190/>=100 mmHg is reached.

2. Hyperkalemia: using a daily dose of 20 mg amiloride increased serum potassium levels by 0.52 mmol/L in hypertensive patients, without serious adverse events (Williams et al., Lancet 2018). A mild hyperkalemia occurred in 7% of hypertensive patients when treated with amiloride 20 mg per day, with highest potassium concentration of 5.8 mmol/L (Brown et al., Lancet 2016). Only those with renal function decline and concomitant ACE-inhibitor use are at a mild risk of hyperkalemia ((Oxlund et al., J Am Soc Hypertens, 2014). We therefore do not expect any severe events of hyperkalemia.

Possible benefits:
1. Regular blood pressure and arterial stiffness measurements/monitoring. After finishing/deblinding of the study, participants and their physicians will receive reports on outcomes, which may facilitate better treatment.

2. Insight into the compliance of a low-salt diet, which may be beneficial for blood pressure measurements.

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

Inclusion criteria:
- Adults with ADPKD diagnosis based on Ravine criteria and/or a documented Pkd 1 or 2 mutation
- CKD-EPI eGFR >=60 ml/min/1.73m2
- Ability to provide informed consent

Exclusion criteria

Exclusion criteria:
- Uncontrolled hypertension, defined as an office blood pressure of >=160/ >=90 mmHg with or without antihypertensive treatment
- Concomitant use of >=3 antihypertensive medications
- When antihypertensive treatment is prescribed for any other treatment indication than hypertension (e.g. cardia arrhythmia)

- Serum potassium levels >5.5 mmol/L (measured within last 6 months)
- History of liver disease (excluding liver cysts due to ADPKD)
- History of heart failure (cardiac ejection fraction < 35%) or cardiac arrhythmia
- History of diabetes mellitus
- Active infection or antibiotic therapy
- Immunosuppressive therapy within the last year
- Concomitant use of drugs that could influence blood pressure and/or disease progression (Tolvaptan/non-steroidal anti-inflammatory drugs (NSAIDs)/chemotherapy), excluding <3 antihypertensive drugs
- Actual pregnancy or unwillingness to adhere to reproductive precautions during the duration of the study

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-03-2022
Enrollment:	54
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	03-08-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-12-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EU-CTR	CTIS2024-512544-27-00
EudraCT	EUCTR2020-000433-40-NL
CCMO	NL72836.078.21