ISRCTN25169606 https://doi.org/10.1186/ISRCTN25169606

The impact of dietary salt intake and kidney disease on aldosterone regulation

Submission date
17/12/2013

Recruitment status
No longer recruiting

Registration date
10/01/2014

Overall study status
Completed

Last Edited
25/06/2020

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
It is recognised that patients with chronic kidney disease have an increased risk of cardiovascular disease such as heart attack and stroke. The reasons for this are not entirely clear. It is possible that aldosterone, a natural steroid hormone produced by the body, plays a key role in this. Our research group has shown that there is a difference in levels of aldosterone in patients with CKD when compared to people with high blood pressure and normal kidney function, and that this might be made worse by high dietary salt intake. There are medications available that can lower aldosterone levels in the body and dietary education can lower salt intake. This study aims to develop a better understanding of how dietary salt intake and aldosterone levels interact.

Who can participate?
Three groups of patients will participate in this study. The first group of patients will have high blood pressure but normal kidney function, the second group will have kidney disease with or without high blood pressure, and the final group will have normal blood pressure and normal kidney function.

What does the study involve?
If you take part in this study you will be required to attend the research centre for 3 separate morning visits over a 6-week period. We will ask you to fast from midnight before each visit. Visits will last no more than 3 hours during which time a number of blood and urine samples will be taken. You will also be connected to a drip and given an infusion of either saline (salt water) or a drug called Angiotensin II, following which further blood tests will be taken. At your second and third visits you will undergo measurement of muscle sympathetic nerve activity. This involves placing a small needle in a nerve in the leg. Measurements will then be taken for 5 minutes. Between visits you will be asked to follow a low salt diet or a high salt diet for 5 days at a time. A taxi will be provided to take you to and from each of your study visits if necessary and you will be provided with a light breakfast on completion of the tests.

What are the possible benefits and risks of participating?
There is no direct benefit to you from taking part in this study. However, the information we get from this study may help us improve treatment of patients who have CKD in the future and reduce their risk of heart disease and stroke. Taking blood samples in some cases can result in

the formation of a small bruise. The amount of blood taken for this research does not place you at any risk. When following the high salt diet your normal diet will be supplemented with salt tablets (Slow Sodium®). These tablets are well accepted with very few side effects. Due to the salt load you will get from these tablets there is a risk of temporarily developing mild ankle swelling; however, this would resolve on stopping the tablets. To minimise this risk we are only asking you to take the tablets for 5 days and we will carefully assess your fluid status before and after you take these tablets. Angiotensin II is a hormone produced naturally in your body. It is well tolerated but there are recognised potential side effects. Occasionally, it can lead to facial flushing, increased blood pressure and an increased heart rate. A more serious side effect can be chest tightness. These symptoms resolve quickly when the infusion is stopped. Your blood pressure and heart rate would be monitored carefully during this infusion and the drug would be stopped if the doctor supervising you has any concern. To minimise the risk of side effects the infusion will be started at a very slow rate and only increased if you are feeling well. Measurement of muscle sympathetic nerve activity (MSNA) is an established technique in which a small needle is inserted into the nerve just below the knee. Most patients experience minimal discomfort during this. Side effects of the procedure are rare and include a tingling sensation, numbness, or pain/tenderness at the site of electrode insertion. Studies have shown that where side effects do occur, the majority resolve within 7 days of recording, and long-term complications are very uncommon.

Where is the study run from?
The British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, UK. All evaluations will be performed in this facility.

When is the study starting and how long is it expected to run for?
The study started in December 2013 and will run for 12 months or until the required number of 48 patients have been recruited and evaluated.

Who is the main contact:
Dr Alison Taylor
Alison.Taylor@glasgow.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Alison Taylor

Contact details
Room 312
British Heart Foundation Glasgow Cardiovascular Research Centre
126 University Place
Glasgow
United Kingdom
G12 8TA
-
alison.taylor@glasgow.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
GN12RE427 (NHS Greater Glasgow and Clyde - sponsor)

Study information

Scientific Title
MINeralocorticoid Dysregulation in Chronic Kidney Disease

Acronym
MIND CKD

Study objectives
Levels of the hormone aldosterone are abnormally high in chronic kidney disease (CKD) resulting in heart and kidney damage. We will study why levels of this hormone are high and see if this relates to salt intake and sympathetic nerve activity (nerves involved in fight or flight). We hope this study will help define treatment choices for high blood pressure in CKD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West of Scotland Research Ethics Service WoS REC 3, 15/02/2013, ref: 13/WS/0018

Study design
Mechanistic unblinded crossover study with patients acting as their own control

Primary study design
Interventional

Secondary study design
Non randomised controlled trial

Study setting(s)
Other

Study type(s)
Diagnostic

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Hypertension in chronic kidney disease (CKD)

Interventions
This is a mechanistic unblinded crossover study with patients acting as their own control. This study will include three age and sex matched groups of CKD, essential hypertension (HTN) and normal controls. For those patients who are on antihypertensive therapy an attempt will be made to match them with patients on a similar class of therapy in other groups. A total of 48 patients will be recruited; 24 patients with CKD, 12 patients with essential hypertension (and PCR <20 mg/mmol), and 12 normal controls. The CKD group will include patients with CKD stages 3 and 4 (eGFR 15-60 ml/min). There will be a subdivision in the CKD group; 12 patients will have proteinuria (PCR ≥100 mg/mmol) and 12 patients will have no proteinuria (PCR <50 mg /mmol). Patients will be given a container in which to complete a 24-hour urine collection prior to visit one.

Visit 1 Baseline tests:

1. Patient height, weight, history of cardiovascular disease or diabetes, and a full list of their current medications will be documented. Clinic BP (mean of three, seated position) will be recorded and an electrocardiograph will be taken.
2. Using the completed 24-hour urine collection, albuminuria, electrolytes, urinary steroids (THALDO, THDOC, cortisol metabolites [THE, THF, aTHF], THS, urinary free cortisol [F], urinary free cortisone [F]) will be measured. A sample to the 24-hour collection will be frozen and stored for LC-MS multi-steroid analysis.
3. Having fasted since midnight and after 20-30 minutes rest in a semi-recumbent position serum for routine urea and electrolytes, albumin, calcium, phosphate, renin, aldosterone, cortisol, ANP, BNP, renalase and prorenin will be taken. An extra sample will also be frozen and stored for LC-MS multi-steroid analysis and DNA analysis of genes involved in the regulation of blood pressure.
4. At the end of the first visit the patient will undergo a modified saline suppression test. A peripheral venous catheter will have been inserted at the time of venepuncture. 1000 ml of 0.9% NaCl (3600 mg sodium/9 g salt) will be infused over two hours, following which serum aldosterone, renin, ANP, BNP. A sample will be frozen and stored for LC-MS multi-steroid analysis. BP will be measured every 15 minutes throughout the infusion.

The entire visit should take no longer than 3 hours and patients will be provided with a light breakfast on completion of tests.

To minimise the sequence effect patients will be divided into two groups for the remainder of the study. The first group will start on the low salt diet. Patients will be provided with a low salt diet sheet advising them how to lower salt intake to less than 2000 mg sodium (87 mmol sodium or 5 g salt) per day. The second group will start on the high salt diet. Along with their normal diet patients will take two Slow Sodium® tablets twice daily. Each Slow Sodium® tablet contains 600 mg sodium. The supplements will therefore provide an extra 2400 mg sodium (104 mmol sodium or 6 g salt) per day.

Following the first visit, patients will be asked to follow each dietary intervention in turn for 5 days and then after each 5-day period, return for a further visit. There will be a two-week wash out period between dietary interventions.

Further visits (visit 2 and 3):

During these visits patients will undergo the same tests as on the baseline visit; however, they will also undergo measurement of muscle sympathetic nerve activity using microneurography, and instead of the saline suppression test they will undergo an Angiotensin II stimulation test.

With the patient in the recumbent position an intraneural recording of muscle sympathetic nerve activity will be made using a tungsten microelectrode. The microelectrode will be placed in the peroneal nerve following which burst frequency and burst incidence will be recorded. The criteria for adequacy of recording will be based on pulse synchrony, facilitation during Valsalva straining, increase in response to breath holding and intensivity to startle (loud noise). Probe time will be limited to less than 30 minutes to minimise the risk of complication.

Those patients who have a BP of ≥160/90 mmHg on the day of the visit will be excluded from the Angiotensin II stimulation test. To minimise the potential adverse effect of Angiotensin II on BP a graded dose (1.5 ng/kg/min then 3 ng/kg/min) infusion will be used with increments in drug dose after 30 minutes if tolerated by the patient. Patients will remain in the semi-supine position throughout the test. The patients will be connected to a cardiac monitor throughout this test and BP will be measured every 10 minutes. The infusion will be stopped if the patient's BP rises above 180/100 mmHg or the patient develops adverse effects. Serum aldosterone, renin, ANP and BNP will be measured at 0 min, 30 min and 60 min (completion) or at the point the infusion is discontinued.

The second and third visits should take no longer than 3 hours. Patients will be provided with a light breakfast and monitored in the department for a further 30 min on completion of the Angiotensin II stimulation test.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Difference in urinary aldosterone (THALDO) excretion after dietary salt loading between the three groups of patients (CKD, hypertension and control) will be measured from urine samples using gas chromatography-mass spectrometry (GC-MS)

Secondary outcome measures
1. Difference in serum aldosterone levels in response to acute salt loading (modified saline suppression test) at baseline between the three groups of patients.
2. Difference in response to angiotensin II stimulation test (serum aldosterone measurements) between the groups in the low and high salt environment. This test will be carried out at study visit number 2 and study visit number 3.
3. Influence of dietary salt intake on level of muscle sympathetic nerve activity (MSNA). An intraneural recording of MSNA will be made using a tungsten microelectrode after dietary salt loading and dietary salt reduction. This will be carried out at study visit number 2 and study visit number 3 before the angiotensin II stimulation test.

Overall study start date
18/12/2013

Completion date

18/02/2015

Eligibility

Key inclusion criteria
1. Individuals aged between 18 and 80 years
2. Individuals with capacity
3. Renal group:
3.1 Patients with CKD who attend the Western Infirmary renal unit and its satellite units CKD stage 3 and CKD stage 4 [decline in glomerular filtration rate (GFR) <5ml/min in preceding 6 months]
3.2 Proteinuric [polymerase chain reaction (PCR) ≥100mg/mmol] and non proteinuric (PCR <50mg /mmol) patients will be included
3.3 Patients' blood pressure (BP) should be controlled <160/90 mmHg (where applicable patients should be on a stable dose of antihypertensive for four weeks prior to consent for study)
4. Hypertensive group:
4.1 Patients who attend the hypertension clinic at Western Infirmary Glasgow (WIG) or Glasgow Royal Infirmary (GRI)
4.2 Patients' BP should be controlled <160/90 mmHg (where applicable patients should be on a stable dose of antihypertensive for four weeks prior to consent for study)
4.3 No significant proteinuria (PCR <20 mg/mmol)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
48

Key exclusion criteria
1. Individuals unable to give informed consent
2. Diabetes mellitus (possibility of type 4 renal tubular acidosis hyporeninaemic hypoaldosteronism)
3. Patients with nephrotic range proteinuria (PCR ≥300 mg/mmol)
4. Patients on aldosterone antagonist or direct renin inhibitor
5. Individuals pregnant or breast feeding
6. Patients with a history of Conns syndrome, Cushings disease or Addisons disease
7. Patients who require maintenance corticosteroids or patients who have had corticosteroid treatment within 3 months prior to study commencing
8. Renal group - patients with progressive (decline in eGFR of >5 ml/min) renal disease in the six months leading up to study start date

Date of first enrolment
18/12/2013

Date of final enrolment
18/02/2015

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
British Heart Foundation Glasgow Cardiovascular Research Centre
Room 312
126 University Place
Glasgow
United Kingdom
G12 8TA

Sponsor information

Organisation
NHS Greater Glasgow and Clyde (UK)

Sponsor details
c/o Dr Maureen Travers
Academic Research Coordinator
Research & Development Management Office
NHS Greater Glasgow and Clyde
The Tennent Institute
38 Church Street
Glasgow
Scotland
United Kingdom
G11 6NT

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Charity

Funder Name
Kidney Research UK (UK)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No