Reversal Of Arterial Disease by modulating Magnesium And Phosphate

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Primary Objective:- Determine the effect of 24 weeks of oral magnesium supplementation and/or the phosphate binder sucroferric oxyhydroxide on arterial wall stiffness in CKD patients, as measured by pulse wave velocity.Secondary Objectives:-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone, calcium, magnesium and phosphorus metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON55005

Source
ToetsingOnline

Brief title
ROADMAP trial

Condition

- Bone, calcium, magnesium and phosphorus metabolism disorders
- Vascular disorders NEC

Synonym
calcification, vascular stiffness

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Health Holland (Ministerie van Economische Zaken),Bedrijven: Fresenius Medical Care;Calciscon en NedMag,Calciscon,Fresenius Medical Care,NedMag

Intervention

Keyword: Chronic kidney disease, Magnesium, Phosphate binder, Pulse wave velocity

Outcome measures

Primary outcome

The difference in PWV over 24 weeks between groups

Secondary outcome

Secondary

- The difference in plasma T50 and CPP concentrations over 24 weeks

- The difference in Mg, Phosphate, Klotho, FGF-23 and hsCRP concentrations over

24 weeks

Explorative

- In a subsample: the difference in 18F-FDG and 18F-NaF-PET scans over 24 weeks

- Change in T50, CPP concentrations, FGF-23 and hsCRP 4 weeks after cessation

of the intervention (T4).

Study description

Background summary

Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). Accumulating evidence suggests that CVD and mortality are partially driven by inflammation and an increased calcification propensity, both features that affect arterial stiffness. Recently, clinical quantification of calcification propensity, i.e. the tendency to develop calcifications, has become feasible by measuring calciprotein particle (CPP) maturation time in-vitro from patient samples (T50). Besides their direct effect on vascular mineralization, CPP*s seem to induce inflammation, that contributes to vascular calcification and endothelial dysfunction, contributing to increased arterial stiffness as well. Importantly, both magnesium deficiency

and excess phosphate are associated with increased arterial stiffness as can be measured by pulse wave velocity (PWV). The influences of lower magnesium and higher phosphate concentrations on arterial stiffness are possibly explained by their modulating, detrimental effect on endothelial function and their ability to aggravate CPP formation, respectively. Moreover, multiple observational studies among CKD patients have linked magnesium deficiency to cardiovascular events and mortality.
The previous NIGRAM consortium (Nijmegen, Groningen, Amsterdam) addressed the role of mineral metabolism markers and the renin-angiotensin-system (RAS) in relation to vascular disease, demonstrating that deregulated mineral metabolism, i.e. high plasma phosphate concentration, but also novel players such as high concentrations of fibroblast growth factor-23 (FGF-23) and low Klotho, contribute to vascular calcification and dysfunction. Within the NIGRAM 2+ consortium, of which the current protocol is part, this focus will now be expanded by the role of magnesium as a powerful endogenous calcification inhibitor, examining the effect of magnesium supplementation on arterial stiffness and calcification propensity. In addition, we will determine whether phosphate binding therapy in CKD patients without overt hyperphosphatemia can amplify the presumed beneficial effect of magnesium. By focusing on the role of magnesium and phosphate as targets that can modulate arterial stiffness, this research aims to improve cardiovascular outcomes in the CKD population. Moreover, the hypothesis will be tested, if the effects on arterial stiffness and inflammation, are mediated by changes in calcification propensity. If this hypothesis can be confirmed, this will enable personalized medicine on this aspect of CKD, by directing interventions on the T50 score.

Study objective

Primary Objective:
- Determine the effect of 24 weeks of oral magnesium supplementation and/or the phosphate binder sucroferric oxyhydroxide on arterial wall stiffness in CKD patients, as measured by pulse wave velocity.

Secondary Objectives:
- Determine the effect of 24 weeks of oral magnesium supplementation and/or the phosphate binder sucroferric oxyhydroxide on calcification propensity and vascular inflammation in CKD patients, measured by markers including T50, CPP concentrations, FGF-23, Klotho and hsCRP.
- Explore the effect of 24 weeks of oral magnesium supplementation and/or the phosphate binder sucroferric oxyhydroxide on vascular calcification and vascular inflammation, assessed by 18F-NaF-PET scans and 18F-FDG-PET, respectively, in a subsample of 40 participants.

Study design

Randomised Controlled Trial, multi center

Intervention

This study has 4 intervention arms:

A) Magnesium citrate
B) Magnesium Placebo
C) Magnesium citrate + sucroferric oxyhydroxide
D) Magnesium Placebo + sucroferric oxyhydroxide

Concluding: a doubble blind placebo controlled magnesium intervention with addition of an open label phosphate binder (sucroferric oxyhydroxide) intervention

Study burden and risks

An extensive overview on burden risk and benefits can be found in the ROADMAP protocol, paragraph 11.4 and 13.1. Reference numbers relate to the references used in the protocol.

Burden
For all participants there will be 4 or 5 study visits over a period of approximately 9 to 12 months (5th visit is optional). All study visits will take place at the hospital where participants are included, except for the two visits including additional PET scans that will be performed at the VUmc (only concerning a subsample of participants). If possible some visits will be combined with regular CKD or other hospital visits. During the screening an electrocardiography (ECG) will be taken a single X-ray of the abdominal aorta (lateral and anterior/posterior) will be performed. Fasting blood samples will be collected by venepuncture during all visits (a total of 65 or 86 ml blood will be withdrawn). PWV measurements will be performed 3 times, which is non-invasive nor painful. Within each allocation arm 10 out of 45 participants will undergo a 18F-NaF-PET or 18F-FDG-PET scan twice, combined with a low-dose computer tomography (CT). For this subsample of participants, time investment will be approximately an additional 2,5 hours both times, to perform the PET scans at location VUmc. 18F-FDG-PET and 18F-NaF-PET are imaging techniques that can capture unexpected, incidental findings such as questionable, possible malignant nodule*s. Although these techniques can facilitate detection at an early stage, it can potentially be a burden if it leads to false positive findings. The PET requires overnight fasting and PWV measurements will be preceded by only some minor restrictions. Pill burden consists of 3 or 5 pills a day: 3 capsules of magnesium citrate or matching Mg-placebo (intervention A and B), or 3 capsules of magnesium citrate or Mg-placebo with 2 tablets of SFOH (intervention C and D), in addition to regular medication use. Capsule intake will be divided over breakfast, lunch and dinner. Magnesium citrate and SFOH can both cause bowel discomfort and sometimes diarrhoea, although mostly these symptoms will disappear or decrease after the first 2 weeks. Another possible

side effect of SFOH is dark stools, however, this is only seen in some users and because of the low dose of SFOH, dark colouration may be minimal. 24-hour urine will be collected twice during the study, and participants will be ask to fill in a very short questionnaire concerning medication tolerability and compliance during two of their study visits.

Risks:
Knowledge of both magnesium citrate and SFOH are sufficient, as an over-the-counter supplement without safety concerns and a registered, frequently used phosphate binder in clinical practice, respectively. This study is in continuation to other studies in which CKD patients have been exposed to increasing magnesium levels and (higher doses of) SFOH [40, 69, 75, 76].
A daily dose of 350 mg magnesium citrate is not expected to raise plasma magnesium to unacceptably high levels (> 1.5 mmol/L). A meta-analysis demonstrated a significant rise of plasma magnesium concentration of 0.04 mmol/L (95% CI: 0.02, 0.06) at a median dose of 365 mg/day (range: 197-994 mg/day) after 12 weeks. A recent intervention study by Joris et al., showed a 0.02 mmol/L rise in plasma magnesium with a similar dose and formulation after 24 weeks of supplementation [25]. Risk of hypermagnesemia includes gastro-intestinal manifestations such as nausea and vomiting and in more severe hypermagnesemia it can induce bradycardia, arrhythmia, low blood pressure, ileus, hyporeflexia and respiratory depression. Symptomatic hypermagnesemia is not expected by oral intake of magnesium, since plasma magnesium levels are not expected to exceed 2.0 mmol/L, with the threshold when symptomatic hypermagnesemia typically develops. Therefore, we do not expect any of these symptoms during our study related to inacceptable high magnesium concentrations. Magnesium citrate intake is expected to increase plasma magnesium levels, yet it is very unlikely magnesium concentration will rise to unacceptable concentrations (>1.5 mmol/L). In case of hypermagnesemia (>1.5 mmol/L) the magnesium citrate supplementation frequency will be reduced. The risk for severe hypermagnesemia and/or hypophosphatemia is minimized by regular monitoring (at week 0, week 6, week 12 and week 24). By means of a ECG during the screenings visit we will detect participants at risk of cardiac arrhythmia*s due to (minimally) increased plasma magnesium.
SFOH is a registered product, clinically used as one of the phosphate binding agents in CKD for patients with high plasma phosphate concentration. Although, literature does not describe any specific phosphate level at which phosphate binding therapy should be started, it is suggested that phosphate binding therapy should only focus on CKD patients with hyperphosphatemia. Therefore, SFOH prescription in this study will be mostly off-label, since participants will have normal to moderately elevated phosphate concentration. A clinical trial doubting the safety of phosphate binding agents in CKD patients with normal phosphate concentrations did not distinguish calcium containing phosphate binders from non-calcium containing phosphate binders in their analysis. Although not proven, it is suggested that the safety concern (higher incidence of coronary calcification) is due to calcium loading within the calcium-containing phosphate binder group. Since SFOH is a non-calcium

containing phosphate binder, we do not expect safety concerns related to this off-label use. Hypophosphatemia is not expected with the moderate dose prescribed in this study, however, if plasma phosphate concentration will reach the lower limit of 0.7 mmol/L, SFOH will be reduced or stopped to restore normal phosphate concentration. Since iron absorption from SFOH in the intestine is very low (in healthy subjects only 0.43%) there is minimal risk of iron accumulation or overload in the circulation [76, 79]. However, SFOH use in hemochromatosis or other iron storage diseases is not recommended and thus one of the exclusion criteria. SFOH may interfere with absorption of various types of antibiotics, therefore participants with a maintenance dose of antibiotics of multiple times a day will be excluded. Incidental use of antibiotics during the study will be evaluated per case. If the combination of the specific antibiotic and SFOH is not reliable, study exclusion will be the consequence in order to warrant safety of the concerning participant. SFOH is also known to influence thyroid replacement therapy if taken at the same time. However, because thyroid replacement medication intake is always (only) in the morning and SFOH will be prescribed during lunch time and diner, this will not interfere and therefore thyroid replacement therapy is not an exclusion criterion. The same applies to vitamin D containing medicine, because intake can be separated with a few hours from the SFOH intake without any consequence. Participants that will be prescribed SFOH (allocation arm C and D, open label) will be instructed for correct oral hygiene, because without proper oral hygiene participants using SFOH are at risk of permanent teeth discoloration. To reduce the risk of persistent diarrhoea with possible subsequent micronutrient deficiency, study medication will be reduced if not tolerated (see flow diagram paragraph 6.6, Figure 4).
Risk related to 18F-NaF-PET or 18F-FDG-PET scans are very limited. Both are commonly used and safe tracers for clinical practice without any serious side-effects. However, as with any injectable drug allergic reaction or anaphylaxis may occur and as any radioactive compound it may increase the almost negligible carcinogenic risk. Since it will be a low-dose CT with only radiation to the abdomen and thorax, radiation burden will be smaller to conventional CT scanning, reducing the carcinogenic risk that is known of high dose and cumulative radiographic radiation. Total radiation burden for combined 18F-NaF-PET + low-dose CT or 18F-FDG-PET + low-dose CT will be approximately 10 to 12.4 millisievert (mSv) in total, 5 to 6.2 mSv both times with 24 weeks in between. As a comparison, every person living in the Netherlands receives a natural background radiation dose of 2-2.5 mSv per year.

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

- Aged between 18-80 years and a life expectancy >1 year
- CKD patient with an eGFR 15-50 ml/min/1.73m2
- Plasma magnesium concentration 0.5-1.4 mmol/L
- Plasma phosphate concentration 0.8-1.6 mmol/L
- Provide informed consent

Exclusion criteria

- Any phosphate binding therapy (with exception of calcium carbonate)
- Unwilling to discontinue over-the-counter magnesium supplementation (for the study duration)
- Renal transplantation in medical history or expected transplantation within 6 months
- Prolongation of QTc interval of > 500 ms, 2nd or 3rd degree atrio-ventricular block on ECG or
bradycardia (heart rate below 50 bpm on screenings ECG)
- Atrial fibrillation or atrial flutter at last clinical or screenings ECG

- Known unstable carotid plaques
- Endoprothesis of the aorta
- Hemochromatosis or other causes of iron overload, or hemoglobin > 10.5 mmol/L
- Chronic diarrhea or gastrointestinal absorption disorders (ao gastric bypass surgery, partial resection of the small-intestines, Crohn disease etc).
- Chronic use of antibiotics
- Active malignancy
- Pregnancy or lactation
- Serious substance abuse
- Recurrent incompliance for medication intake or hospital visits, i.e. *no-shows*
- No sufficient understanding of the Dutch or English language
- Inability to measure PWV or to take blood samples for any reason, inability to swallow medication

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:	Recruitment stopped
Start date (anticipated):	15-07-2020
Enrollment:	180
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Velphoro

Generic name:	Sucroferric Oxyhydroxide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2021
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: 27899
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2019-001306-23-NL
CCMO	NL69613.029.19
OMON	NL-OMON27899

Study results

Date completed: 09-12-2022

Actual enrolment: 36

Summary results
Trial is onging in other countries