Effects of vitamin K2 supplementation on [18]F-NaF PET/MRI in patients with carotid and coronary artery disease

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To test our hypothesis that vitamin K2 supplementation will induce a clinically relevant reduction in the degree of micro-calcification from carotid artery disease patients, when comparing to a placebo, after 3 months.

Ethical review	Approved WMO
Status	Pending
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON47981

Source
ToetsingOnline

Brief title
INTRICATE

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
carotid artery disease, narrowing of the arteries of the neck

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: European Union□s Horizon 2020 research and innovation programme under the Marie Sk□odowska-Curie grant agreement No 722609

Intervention

Keyword: hybrid PET/MRI, micro-calcification, NaF, vitamin K

Outcome measures

Primary outcome

We hypothesize that intervention with vitamin K2 will lead to a regression or at least to non-progression of micro-calcifications compared to treatment with a placebo. Therefore, the main parameter/end point of this study is The main parameter/end point of this study is the mean rate of progression of vascular micro-calcifications in the carotid arteries, measured as a difference between the intervention group and placebo group in 18F-NaF uptake via hybrid PET/MRI at baseline and after the 3 months follow-up.

Secondary outcome

1. Investigating whether vitamin K2 supplementation can diminish, halt or even reverse the development of arterial micro-calcification in the coronary arteries, measured as a difference between the intervention group and placebo group in CAC score at baseline and after the 3 months follow-up.

2. The mean rate of progression of vascular calcification, measured as a difference in CAC score at baseline and after a follow-up of 3 months.

3. The mean rate of progression of vascular calcification, measured as a difference in carotid 18F-NaF uptake at baseline and after a follow-up of 3 months.

4. The correlation between the uptake of 18F-NaF at 3 months and the CAC score.

5. Investigating whether vitamin K2 supplementation can influence MRI parameters such as normalized wall index (i.e. measurement of plaque burden), intra-plaque haemorrhage volume, lipid-rich necrotic core volume, and fibrous cap status.

6. The correlation between 18F-NaF uptake and cIMT.

7. The correlation between vitamin K2 supplementation and cIMT.

8. The correlation between vitamin K2 supplementation and the plasma levels of MGP

9. The correlation between acute events (i.e. myocardial infarction and stroke) and the plasma levels of MGP

10. The correlation between serum vitamin K2 concentrations and PIVKA-II plasma level, PT, and the INR value.

Study description

Background summary

Coronary and carotid arteries are the first two causes of cardiovascular (CV) mortality in Global Burden of Disease 2013 Study, leading to more than

10.000.000 deaths worldwide in 2013. Atherosclerosis is the underlying pathophysiological process of almost 90% of all CV diseases. The high-risk features of any atherosclerotic plaque include micro-calcifications within the arterial wall, which has been proven to act as an independent CV risk factor. Arterial calcification is an active process and results from imbalance between calcification promoting and inhibiting factors. In the last two decades, a series of proteins that are able to bind calcium ions and to inhibit calcification have been discovered, including matrix Gla protein (MGP). These circulating proteins share a common feature, the *-carboxyglutamic acid (Gla) rich domain, which requires vitamin K to become biologically active. Vitamin K supplementation is associated with several positive outcomes. All together, these studies support the idea that vitamin K protects against calcification. After an extensive literature research, the fluorine-18 sodium fluoride positron emission tomography/magnetic resonance imaging (18F-NaF PET/MRI) emerged as the safest and most reliable clinical imaging platform that can noninvasively detect micro-calcifications in the arterial wall. Therefore, we will use 18F-NaF PET/MRI to assess the influence of vitamin K supplementation in the development of arterial micro-calcification in the context of atherosclerosis.

Study objective

To test our hypothesis that vitamin K2 supplementation will induce a clinically relevant reduction in the degree of micro-calcification from carotid artery disease patients, when comparing to a placebo, after 3 months.

Study design

This will be a prospective double blind randomized controlled feasibility study, in which one group will receive a vitamin K2 supplementation compared to a control group receiving a placebo.

Intervention

Subjects will be randomised into an intervention group (i.e.receive two daily capsules each containing 200*g of Menaquinone-7 and 40*g of vitamin D3) or into the control group (i.e. will receive a placebo capsule that will identical to the intervention capsule, but without Menaquinone-7). Both subjects and researchers will be blinded to the treatment allocation of subjects.

Study burden and risks

The duration of the trial is 3 months. After being randomised into one of the two arms of the study (i.e. treatment or placebo), the patients will have to visit the hospital after 3 months. During these visits, drug-compliance will be monitored, carotid intima-media thickness (cIMT) will be measured and blood

samples will be obtained via standard venous puncture. At baseline and after 3 months, an 18F-NaF PET/MRI will be performed in order to assess changes in calcium metabolism of carotid arteries. Moreover, the CAC score will be determined by a non-contrast enhanced CT scan of the heart at baseline and at 3 months, in order to assess changes in the degree of calcification.
There have been no side effects reported in subjects using a daily 360µg supplementation of vitamin K2 (i.e. MK-7). Vitamin K2 supplementation does not induce or increase a state of hypercoagulability. The proposed measurement of carotid intima-media thickness will add no burden to the patients. The average effective radiation exposures associated with the proposed two PET/MRI and two CAC scans are 3,15mSv/scan and 0,74mSv/scan, respectively. Each 18F-NaF PET/MRI scan will take about 1 hour, while each CAC scan will take about 2-3 minutes. Another burden of this study will be the venipunctures of 25mL each taken at baseline and at 3 months follow-up. The side effects of MRI contrast agent (i.e. Gadobutrol) are rare, amongst others nausea (0,25%), vomiting (0,05%), urticaria (0,04%), feeling of warmth, wheals (i.e. localized itchy oedema) (for each 0,03%), dizziness (0,02%), cough, dyspnoea (for each 0,01%), severe anaphylactic reaction (2 out of 14299 patients). The MRI contrast agent will be injected only in patients without any known allergy to gadolinium and with a GFR * 45mL/min/1,73m2 or * 60mL/min/1,73m2 in patients with diabetes mellitus. Menaquinone-7 supplementation may halt or even diminish the development of arterial calcification your plaques, but this is not certain.

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

* * Asymptomatic carotid artery disease on at least one side with a degree of stenosis > 25% (according to on the ECST criteria). If the patient has a symptomatic carotid artery disease on the contra-lateral side, he/she will still be included in the study., iIf intensified medical treatment for this symptomatic stenosis (e.g. statins, antiplatelet medication) was started * 6 month before inclusion of the patient, he/she will still be included in the study. This protocol was chosen in order to widely assure a stable situation on the plaque(s), which avoids an overspill from this medication on the assumed effects of the vitamin K supplementation.
* Age older than 18 years
* Signed informed consent provided

Exclusion criteria

* Antiplatelet or cholesterol lowering medication started in the past 6 months
* Chronic or paroxysmal atrial fibrillation
* Presence or scheduled coronary or carotid revascularisation procedure (e.g. stent implantation, coronary artery bypass graft, balloon-dilatation, endarterectomy, angioplasty)
* History of myocardial infarction or stroke
* Malignant disease (except for treated basal-cell or squamous cell carcinoma)
* Use of vitamin K antagonists or any other anticoagulation treatment
* A life-expectancy < 1 year
* Claustrophobia
* Presence of a pacemaker, intra-cardiac defibrillator, or metallic implant (e.g. vascular clip, neuro-stimulator, cochlear implant)
* Body weight > 130kg or body habitus that does not fit into the gantry
* Pregnancy or wish to become pregnant in the near future
* Breast feeding
* (History of) metabolic or gastrointestinal disease
* Use of vitamin K-containing supplements or vitamin K-rich foods (i.e. soya)

* Chronic inflammatory disease
* Systemic treatment or topical treatment likely to interfere with evaluation of the study parameters

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2019
Enrollment:	52
Type:	Anticipated

Ethics review

Approved WMO

Date:	18-12-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT04010578
CCMO	NL69450.068.19