Intervention study on the effect of vitamin K2 (Menaquinone-7) supplementation on the vascular stiffness in subjects with poor vitamin K-status.

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The primary objective of this study is to investigate the effect of MK-7 supplementation on vascular stiffness in a subgroup of subjects with poor vitamin K status.For this follow-up study the primary objective is to investigate the correlation...

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

Summary

ID

NL-OMON47354

Source
ToetsingOnline

Brief title
Vitamin K2 and vascular stiffness

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
vascular stiffness, vitamin K deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: NattoPharma,R&D group VitaK

Intervention

Keyword: Menaquinone-7, vascular stiffness, vitamin K status, vitamin K2

Outcome measures

Primary outcome

The primary study parameters of this study is to investigate the effects of MK-7 supplementation on vascular characteristics. The main study parameters are the percentage of changes in the clinical end points: pulse-wave velocity, carotid elasticity and intima-media thickness after one year of treatment between the two treatment groups (placebo and MK-7).

Primary study parameter of the follow-up study is to investigate the correlation between the 3 different non-invasive measurements for vascular stiffness among healthy subjects.

Secondary outcome

The secondary study parameter is the relative changes in the biochemical parameters i.e. dp-ucMGP fraction after one year of treatment.

Study description

Background summary

Population-based studies have shown that low dietary vitamin K intake is associated with increased risk of coronary calcification and cardiovascular morbidity & mortality. The mechanism behind this marked correlation between

K-intake and CVD is probably based on the strong calcification-inhibitory activity of the vitamin K-dependent Matrix-Gla protein (MGP). MGP is synthesized by vascular smooth muscle cells and chondrocytes. MGP is thought to exert its function as a calcification inhibitor by binding to crystal nuclei in hydroxyapatite, thereby preventing crystal growth. In order to acquire its calcification-inhibitory activity, MGP must be activated in a vitamin K-dependent post-translational carboxylation reaction. In many prospective studies in unrelated patient cohorts it appeared that dp-ucMGP (inactive MGP) is the strongest risk marker for unfavorable cardiovascular outcomes. Patient groups included aortic stenosis, heart failure, chronic kidney disease and hemodialysis, kidney transplant recipients, diabetics, coronary artery disease and peripheral artery disease. In a recent study among 2500 healthy adults with a follow-up period of 15 years it turned out that poor vitamin K status (as concluded from high circulating dp-ucMGP levels) is a strong risk marker for cardiovascular mortality, and that the risk is especially high in the upper quartile of circulating dp-ucMGP, i.e. above 400 pM.

Accelerated Plethysmography (APG) has been described as a non-invasive technique to measure vascular stiffness and aging. Due to the process of arteriosclerosis, vessel stiffness increases with age, resulting in changes in the peripheral pulse wave. These changes can be measured using the APG technique. Several studies show that parameters of the APG wave signals can be used to determine characteristics of vascular aging. APG ratios have also been found to be correlated with vessel distensibility and atherosclerotic changes in the carotid artery, blood pressure and gender. Several other studies also showed that APG and Pulse Wave Velocity (PWV) are correlated with each other. In this follow-up study we compare this APG-technique with two existing techniques (ultrasound of the carotid artery and PWV) to determine the correlation between the 3 measurements concerning arterial stiffness.

Study objective

The primary objective of this study is to investigate the effect of MK-7 supplementation on vascular stiffness in a subgroup of subjects with poor vitamin K status.

For this follow-up study the primary objective is to investigate the correlation between the 3 different non-invasive measurements for vascular stiffness in healthy subjects.

Study design

This is a dubbel-blind randomized placebo-controlled intervention study among 240 healthy men and women in the age of 40 -70 year, who are preselected based on their circulating inactive MGP concentration (>400 pM):
- group 1: n=120 men and women; daily intake of 1 tablet containing 0 microgram

of MK-7 during 1 year;
- group 2: n=120 men and women; daily intake of 1 tablet containing 180 microgram of MK-7 during 1 year.

In order to include the subject the level of circulating inactive MGP has to be determined. At the first visit blood will be taken to measure this inactive form of MPG (dp-ucMGP). After inclusion the participants have to come to our trialcenter for their second visit. This visit is the start of the study, during which the vesselwall characteristics, the pulse wave velocity and the body composition will be measured. Also blood will be taken after an overnight fasting period. The placebo/MK-7 tablets will be given for 6 months. Tablets should be consumed together with breakfast or dinner. After 6 months our investigators will visit the participants at home/work to deliver the tablets for the next 6 months. Remaining tablets should be handed over to the investigator. After the total intervention period of 1 year all participants undergo the same measurements and the venapuncture. Remaining tablets have to be brought back to the trial center to check for their compliance. Participants haver to report all changes concerning medication, illness. For each subject a CRF will be recorded for each subject. The participants will be asked not to change their lifestyle, dietary habits or level of physical activity to a great extent during the intervention period.

From this study population eligible participants (men and women) will be selected. The study information will be send to them by mail or post (if they don*t have a mail address). If they are interested to participate they can contact us by mail/phone, If no reaction is given within 2 weeks we will send a reminder. Participants willing to participate will be contacted by phone and an appointment will be made to come to the site for the measurements if they meet the in- and exclusion criteria.In total 100 participants will be invited. Measurements will be performed at the same day (vessel wall characteristics of the common carotid artery, PWV and the measurement of the heart rate, oxygen saturation, stiffness score with the oxymeter).

Intervention

The total group of 240 men and women will be randomly assigned to 2 groups:
- n=120 men and women: daily intake of 1 tablet with 0 microgram of MK-7 during 1 year
- n=120 men and women: daily intake of 1 tablet with 180 microgram of MK-7 during 1 year.

Study burden and risks

In total, participants will undergo 3 venipunctures in a period of 1 year. The venipunctures will be made by experienced coworkers. For the first venipuncture a fasting condition is not necessary. A fasting period of at least 10 h is

necessary for the venipunctures during the study visits at baseline and after 1 year. The daily dosage of vitamin K2 (180 µg) for the intervention period of 1 year will not cause adverse side-effects. Previous studies on vitamin K intervention used dosages between 180 µg and 45 mg of vitamin K. No adverse side-effects were reported by these intervention studies. Another burden is the low dose of X-ray radiation participants receive during the WB-scan (Category 1: <0.1 mSv). No adverse effects are to be expected from the ultrasound technique. A personal benefit that participants may obtain from the study is that detailed information is obtained on vascular health and their body composition at baseline, and the changes after one year. Subjects with extensive carotid artery calcifications will be referred to their GP, but if no treatment is installed, they are eligible to participate in the study.The use of the fingertip oxymeter will not cause any adverse effects. In conclusion, the risks for the participants of this study are minimal.

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

Men and women between 40 and 70 years of age
Subjects having a BMI between 20 and 35 kg/m2
Subjects of the Caucasian race
Subjects having circulating values of dp-ucMGP higher than 400 pmol/L
Subjects given written consent to take part in the study

Exclusion criteria

Subjects with hyperlipedaemia
Subjects with cardiovascular disease
Women treated with estrogens
Subjects on oral anticoagulant therapy
Subjects with (a history of) metabolic or gastrointestinal disease
Subjects taking vitamin K containing (multi)vitamin supplements

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-10-2015
Enrollment:	240
Type:	Actual

Ethics review

Approved WMO Date:	23-06-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-01-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-03-2018
Application type:	Amendment
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	NCT02404519
CCMO	NL50741.068.14

Study results

Date completed:	22-09-2017
Actual enrolment:	243