A randomized study on probiotics and their effect on vitamin K2 status

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20242

Source
NTR

Brief title
ProVitaK

Health condition

Cardiovascular disease

Sponsors and support

Primary sponsor: VU University Medical Centre Department of Epidemiology & biostatistics Prof. J. Berkhof, department head
Source(s) of monetary or material Support: Health Holland and Winclove B.V.

Intervention

Outcome measures

Primary outcome

To investigate the effect of a daily sachet of 4 gram freeze-dried probiotics producing 180 µg vitamin K2 on plasma dp-ucMGP concentrations after 12 weeks in participants aged (50-70 years).

Secondary outcome

To determine the effect of a daily sachet of 4 gram freeze-dried probiotics producing 180 µg vitamin K2 in 24-hour urine on vitamin K metabolites 5C en 7C-aglycone, and vitamin K1 and MK4 and MK-7 in stool samples after 12 weeks in participants aged (50-70 years).

Study description

Background summary

Rationale: Vitamin K is mainly known for its function in blood coagulation, but recently other functions in bone metabolism and vascular health have become apparent. Vitamin K is a fat-soluble vitamin present in green vegetables in the form of vitamin K1 (phylloquinone) and as vitamin K2 (menaquinones) in animal products (meat, cheese). Vitamin K2 is the most active form of vitamin K and another part of vitamin K2 is derived from gut bacteria biosynthesis. Besides the production in the gut, vitamin K2 is also present in fermented dairy (cheese, yoghurt) and fermented soy beans (natto). Vitamin K is a cofactor involved in the carboxylation (activation) of several proteins, such as matrix Gla-protein (MGP) and reduces the inactive form of MGP, dephosphorylated uncarboxylated matrix gla protein (dp-ucMGP), and could thereby inhibit ongoing calcium deposition in the vascular system and eventually arterial calcification. Recently, it has been discovered in-vitro that certain probiotics – normally used for other indications– can also produce vitamin K2. These probiotics are currently approved as over-the-counter supplements and are safe according to EFSA. Observational studies have shown that a high vitamin K2 intake is associated with reduced coronary calcification and a reduced risk of coronary heart disease. The available randomized controlled trials have mainly used vitamin K1 supplements and these studies indicated that vitamin K1 supplements improved the elastic properties of the vessel wall and inhibit progression of coronary artery calcium. To date, few randomized controlled trials showed that vitamin K2 supplementation reduced dp-ucMGP with approximately 40% within 3 months and among postmenopausal women, vitamin K2 supplementation improved arterial stiffness among women with high arterial stiffness at baseline.
Furthermore, probiotics are often prescribed in nursing homes for older adults on long-term antibiotic use to increase intestinal health and reduce obstipation. These people are often deficient in vitamin K and could benefit from a probiotic formulation that increases intestinal health as well as vitamin K status. This study will explore whether probiotics are an effective vehicle to increase vitamin K status by a broad range of menaquinones and might be an alternative to diet and supplements.
Objectives: To investigate the effect of a daily sachet of probiotics on vitamin K status for 12 weeks vs placebo in middle-aged adults with high risk of metabolic disturbances.
Study design: Double-blind, placebo-controlled, randomized controlled trial. Participants will be randomized into two equal groups, one group receives probiotics with bacteria that can produce up to 180 µg vitamin K2 daily and the other group receives placebo sachets daily for 12 weeks. The dose is based on multiple studies that showed a decrease in dp-ucMGP between 17-40% after 6-12 weeks of supplementation with approximately 180 microgram

MK-7 daily. The duration of the present study is 12 weeks, which will be long enough to achieve similar reductions in dp-ucMGP levels. Dp-ucMGP can be influenced after 2-4 weeks of supplementation, however, the effects of probiotics with vitamin K producing properties are currently unknown.
Study population: 20 participants will be recruited, aged 50-70 years, that participated in previous studies such as the DIRECT Study, New Hoorn Study and/or via an advertisement in the local newspaper in the vicinity of Hoorn.
Main study parameters/endpoints: The main study parameter is the difference in vitamin K status as assessed by plasma dp-ucMGP between the 2 groups after 12 weeks.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
The participants are requested to use a daily sachet dissolved in lukewarm water with vanilla taste.
The probiotics can lead to changes in bowel frequency and movement, however this will stabilize after 2 weeks. The dose of the vitamin K producing probiotics is within the physiologic borders and therefore safe. For the study, 4 visits to the DCS VUmc will take a total time of 2-3 hours. During the visits the participants are asked to fill some questionnaires regarding medical history including a short diet questionnaire to estimate the main vitamin K sources via diet. In addition, a physical examination will be performed including anthropometry (height, weight, blood pressure), blood collection. In each visit a total amount of up to 18 ml blood will be collected by means of vena puncture. Vena puncture can cause discomfort and can result in bruising that continues up to a few days after the examinations. Also during the visits, participants will hand in a 24-hour urine collection and a frozen stool sample. Participants gain no individual benefit from their participation in the study. However, the study is expected to increase our understanding of vitamin K metabolism and contributes to developing vitamin K requirements and may ultimately lead to a new therapeutic intervention.

Study objective

We hypothesize that probiotics with vitamin K2 producing properties can improve vitamin K status, which will eventually reduce the risk of coronary calcification.

Study design

Baseline, six weeks, twelve weeks

Intervention

This study aims to assess whether a daily sachet of probiotics producing vitamin K2 for 12 weeks vs placebo improves vitamin K status in middle-aged adults between 50-70 years with high risk of developing cardiovascular disease risk.

Contacts

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Eligibility criteria

Inclusion criteria

• Higher cardiovascular risk without type 2 diabetes – at least 1 of the following risk factors:
o systolic blood pressure > 140mm Hg, diastolic blood pressure > 90 mmHg or use of blood pressure lowering medication and/or
o impaired glucose tolerance
o Family history of cardiovascular disease < 65 years
o Total cholesterol > 6.5 mmol/l or use of statins
o Smokers ≥ 50 years
o Estimated glomerular filtration rate > 30 and < 60 ml/min
• No gastrointestinal tract problems/stool problems
• Written informed consent

Exclusion criteria

• Pregnancy, lactation or a female planning to conceive within the study period
• Any significant medical reason for exclusion as determined by the investigator
• Unable to give written informed consent
• Unable to speak, read and/or write Dutch
• Diabetes of any type.
• Age <50 or ≥ 70 years
• Body mass index < 20 or > 39 kg/m2
• Using vitamin supplements that contain vitamin K, or unwilling to stop two weeks before randomization.
• Using probiotic supplements
• Natto or goose liver consumers
• Use of vitamin K antogonists such as warfarin, acenocoumarol or coumarin derivates

• Use of antibiotics
• Colectomy
• Crohn's disease/ Ulcerative Colitis
• Use of more than 3 alcoholic beverages per day

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2021
Enrollment:	20
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	02-11-2020
Application type:	First submission

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
NTR-new	NL9013
Other	METc VUmc : 2019.638 - NL71758.029.19

Study results