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

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Objectives: To investigate the effect of a daily sachet of probiotics on vitamin K status for 12 weeks vs placebo.

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46101

Source
ToetsingOnline

Brief title
ProVitaK

Condition

- Other condition
- Vitamin related disorders

Synonym
nutritional status, vitamin K status

Health condition

vitamine status

Research involving
Human

Sponsors and support

Primary sponsor: Winclove B.V.
Source(s) of monetary or material Support: Winclove B.V.

Intervention

Keyword: matrix gla protein, probiotics, vitamin K

Outcome measures

Primary outcome

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.

Secondary outcome

Secondary study parameters/endpoints after 12 weeks

Vitamin K metabolites in 24-urine collection: metabolites 5C en 7C-aglycone.

Vitamin K metabolites in stool: vitamin K1 and MK4 and MK-7 after 12 weeks in participants.

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 the substantial 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.
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. This study will explore whether probiotics are an effective vehicle to increase vitamin K status and might be an alternative to diet and supplements. This study will assess whether supplementation with probiotics that produce vitamin K2 can improve vitamin K status as measured by inactive MGP in middle-aged adults with high risk of metabolic disturbances.

Study objective

Objectives: To investigate the effect of a daily sachet of probiotics on vitamin K status for 12 weeks vs placebo.

Study design

Study design: Double-blind, placebo-controlled, randomized controlled pilot 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 a previous study that showed a 31% decrease of dp-ucMGP after 12 weeks of supplementation with 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.

Intervention

A daily sachet of 4 gram freeze-dried probiotics producing 180 µg vitamin K2 to be dissolved in lukewarm water with a slight vanilla taste.

Study burden and risks

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 not considered harmful. The participants will follow a vitamin K low diet for 2 weeks. This means low intake of fermented dairy (cheese, buttermilk, yoghurt) and green leafy vegetables (such as spinach, endive, kale, lettuce). After the 2 week run-in diet no dietary restrictions are necessary. 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 out 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. Each visit a total amount of up to 25 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.

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

* High 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 * 2 hour glucose levels of 7.8 to 11.0 mmol/L after 75 gram oral glucose tolerance test
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 < 60 ml/min
* No gastrointestinal tract problems/stool problems

Exclusion criteria

* Pregnancy, lactation or a female planning to conceive within the study period
* 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.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Ethics review

Not approved

Date:	26-04-2019
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL67643.029.18