Validation of plasma plant sterol levels as markers of cholesterol absorption

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What is the difference in fractional cholesterol absorption, measured by means of the dual isotope method, between mildly hypercholesterolemic subjects with high plasma campesterol/TC ratios compared to subjects with low plasma campesterol/TC ratios...

Ethical review	Approved WMO
Status	Pending
Health condition type	Lipid metabolism disorders
Study type	Observational invasive

Summary

ID

NL-OMON33370

Source
ToetsingOnline

Brief title
DAHLIA-2A

Condition

- Lipid metabolism disorders

Synonym
mild hypercholesterolemia, slightly elevated cholesterol

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: cholesterol absorption, hypercholesterolemia, non-cholesterol sterols (plant sterols)

Outcome measures

Primary outcome

1. The difference in fractional cholesterol absorption, determined by the dual isotope method, between 40 subjects with high and 40 subjects with low baseline campesterol/TC ratios (combined results of Dahlia-2 and Dahlia-2a study).

2. Correlation of plasma campesterol/TC ratios with cholesterol absorption, determined by the dual isotope method in 80 subjects with mild hypercholesterolemia (combined results of Dahlia-2 and Dahlia-2a study).

Secondary outcome

Correlation of cholesterol absorption as measured by the dual isotope method with cholesterol absorption as measured by the continuous feeding method.

Study description

Background summary

Intestinal cholesterol absorption varies considerably in the general population, ranging between 20 and 80%. Previous studies have suggested a classification of subjects with high or low cholesterol absorption. In omost studies, levels of non-cholesterol sterols have been used as markers of cholesterol absorption and synthesis respectively. Bssed on these markers, a classification of subjects with high or low cholesterol absorption, the so-called high and low absorbers, has been suggested. The high absorbers are thought to have elevated cholesterol levels due to high absorption, whereas the low absorbers have elevated levels based on high synthesis. Subsequently, it has been suggested that high absorbers do not or hardly benefit from statin treatment alone, either with respect to cholesterol reduction and the

recurrence of coronary hear disease. Therefore, the high absorbers may benefit form the addition of cholesterol absorption inhibitors.

This underscores the need to identify high absorbers in order to treat them accurately. Therefore, easy accessible markers are essential in clinical practice. However, whether high and low absorbers indeed can be identified based on plasma levels of non-cholesterol sterols has bever been verified by means of actual cholesterol absoption measurements. Besides the fact that the validity of these markers may be questionable, they also do not provide any indication regarding the quantity of cholesterol that is absorbed.

In a previous study, we investigated the actual cholesterol absorption rates by means of stable isotope methods, in 12 mildly hypercholesterolemic subjects, who were predefined as high or low absorbers, based on their rplasma campesterol/TC ratios (Dhalia-2 study). We expected to find a difference of 20% between the so-called high and low absorbers. Although we found a broad range of cholesterol absorption (12-98%), to our surprise, cholesterol absorption rates did not correlate with plasma campesterol/TC ratios in these 12 subjects. This implies that plasma campesterol/TC ratios are not valid markers of cholesterol absorption, in contrast to what was previously suggested based on only 80 subjects and which has been used throughout literature ever since. Another explanation might be that the Dahlia-2 study was underpowered to show the expected results. Therefore, we will expand our study population by investing cholesterol absorption rates in a larger population of 80 mildly hypercholesterolemic subjects. Data of the present Dahlia-2a study will be combined with those of the previous Dahlia-2 study.

Study objective

What is the difference in fractional cholesterol absorption, measured by means of the dual isotope method, between mildly hypercholesterolemic subjects with high plasma campesterol/TC ratios compared to subjects with low plasma campesterol/TC ratios?

Study design

This is a cross-sectional single measurement of cholesterol absorption, by means of the dual isotope method in 34 subjects with high campesterol/TC ratios and 34 subjects with low campesterol/TC ratios. These results will be combined with previous results of the Dahlia-2 study in 12 hypercholesterolemic subjects.

First, subjects will attend a screening visit, consisting of a medical history, physical examination and blood sampling to determine lipid profile. At the second study visit, the actual cholesterol absorption measurement will start, consisting of a blood sample with ensuing single intravenous administration of

13C2 cholesterol and an oral administration of 2H7 cholesterol via a stardardized breakfast. Subjects will return to their homes and will attend the AMC in the subsequent three mornings for additional blood sampling. Percent intestinal cholesterol absorption will be calculated by dividing the plasma ratio of 13C2 and 2H7 enrichment by the ratio of 13C2 and 2H7 cholesterol species administered to the subjects.

To rule out that the method of cholesterol absorption measurement might be of influence on our study question, we will repeat a cholesterol absorption measurement in 20 subjects according to a diffent method. These subjects will attend the AMC for an additional measurement, in which cholesterol absorption will be measured in fecal samples instead of in blood samples.

This substudy will take a week, in which participants will attend the AMC twice (day) and 8). On Day 0, subjects will start taking two sets of capsules three times daily for a period of 7 days. These capsules contain 3mg 2H7 cholesterol and 3mg 2H4 sitostanol respectively. During the last 4 days, subjects will be asked to collect daily stool samples. Percent absorption is calculated from the fecal ratio of 2H7 cholesterol and 2H4 sitostanol, divided by their ratio which was administered to the subjects.

Study burden and risks

Hardly any risks are involved in this study. At screening, a single blood sample will be obtained. At the second visit, an intravenous catheter will be inserted, followed by four blood drawings, during the following three days. This may lead to a hematoma at the site of venepuncture. Furthermore, two kinds of cholesterol markers will be administered to the study subjects, both orally and intravenously. These so-called stable isotopes are not harmful, as they behave as their natural substrates. This also applies to the oral sitostanol which is used in the substudy. In this substudy, no blood samples are obtained, however, subjects are asked to collect stool samples for a period of 4 days. Finally, we do not expect any unfavorable effects of discontinuation of any possible cholesterol lowering medication, neither from a possible 8-week cessation of fish oil or fibrates.

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

Healthy male and female subjects, aged 18-65 years old, with an LDL-cholesterol concentration between 3.0 and 5.0 mmol/l, who participated in the Dahlia-1 study and belong to the 40 subjects with the highest or to the 40 subjects with the lowest plasma campesterol/TC ratios respectively.

Exclusion criteria

Excluded are persons with a genetic hyperlipoproteinemia like familial hypercholesterolemia, LPL-deficiency, familial dysbeta lipoproteinemia and familial hypertriglyceridemia. Also people with diabetes mellitus, severe hypertriglyceridemia, uncontrolled hypertension or history of arterial disease including unstable angina, myocardial infarction, recent transient ischaemic attacks or a cerebro-vascular accident, will be excluded.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2009
Enrollment:	68
Type:	Anticipated

Ethics review

Approved WMO

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	NL29302.018.09