Quantification of trans-intestinal cholesterol excretion in patients with familial hypobetalipoproteinemia

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON35578

Source
ToetsingOnline

Brief title
TICE-FHBL

Condition

- Metabolic and nutritional disorders congenital
- Lipid metabolism disorders

Synonym
Familial hypobetalipoproteinemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cholesterol, Excretion, FHBL, Intestines

Outcome measures

Primary outcome

Via the quantity of cholesterol isotopes in blood, gall and feces, we will be

able to measure how these fluxes add to the total amount of cholesterol that is

fecally excreted.

The different fluxes are:

A) dietary cholesterol that is not absorbed by the intestines

B) cholesterol that is excreted in the feces via the blood stream

B1) cholesterol excreted via gall

B2) cholesterol excreted directly via the intestines

C) cholesterol from hepatic de novo synthesis

D) intestinal de novo cholesterol synthesis and shedding via enterocytes

B2 should be regarded as a derivative of TICE

Secondary outcome

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Study description

Background summary

Reverse cholesterol transport (RCT) is an important anti-atherogenic mechanism, as it mediates the elimination of excess cholesterol out of the body into the

faeces. Recently, the concept of RCT has been revisited. In the *classical* concept, the liver is considered to be the only organ capable to eliminate cholesterol via excretion into the bile. However, evidence from animal models suggests that the intestine is also an important secretory organ for cholesterol 1-4. In fact, direct trans-intestinal cholesterol excretion (TICE) accounted for 33% of total faecal sterol excretion in mice 4 and activation of the Liver X Receptor (LXR) has been found to induce a 6-fold increase in trans-intestinal cholesterol secretion in mice 4. This suggests that TICE might be a novel therapeutic target for cholesterol excretion and thereby for cardiovascular disease prevention.
Previous human perfusion studies suggested that secretion of cholesterol in the small intestine also occurs in humans 5. In order to establish the existence of such a direct intestinal cholesterol-excreting pathway, we studied the contributions of various cholesterol fluxes to total fecal sterol elimination in healthy humans and found that approximately one third of total fecal sterol excretion in healthy mildly hypercholesterolemic men was eliminated via TICE (Storc-Extra study, METC 10/092).
The next step in elucidating the mechanisms involved in human trans-intestinal cholesterol excretion is the evaluation of differences in TICE across populations. From animal studies it can be hypothesized that triglyceride-rich particles in the VLDL-range are likely to be the so-called *donor particles* for TICE 4,6. These lipoproteins are thought to deliver the plasma-derived cholesterol to the enterocyte for elimination via TICE. Individuals lacking such particles would exhibit impaired TICE as compared to healthy unaffected controls. Therefore, we propose to investigate the role of VLDL-particles as a determinant of human TICE by studying the contribution of TICE to fecal sterol loss in patients with familial hypobeta-lipoproteinemia (FHBL).
Familial hypobetalipoproteinemia (FHBL) is a rare disorder of lipoprotein metabolism (estimated prevalence of 1 in 500 - 1 in 1000) and is characterized by LDL-cholesterol and total apolipoprotein B (apoB) levels below the 5th percentile 7,8. Approximately 50% of FHBL subjects are carriers of a mutation in the apoB gene7 leading to the formation of a dysfunctional form of apoB. Since apoB is the main component of VLDL, mutations in the apoB gene give rise to a defective VLDL-export system. As a consequence, plasma VLDL-concentrations are extremely low in these patients. In case blood-derived cholesterol destined for elimination via TICE, is truly mediated via VLDL-particles, patients with FHBL should exhibit a significant reduction in TICE, as compared to unaffected age, gender and BMI-matched controls.

Study objective

The purpose of the current study is to evaluate the difference in TICE in FHBL-patients as compared to unaffected controls, according to the previously developed stable isotope method with minor modifications (METC 10/092). This way we can prove the hypothesis dat VLDL is the donor particle for TICE in humans.

Study design

It is a cross-sectional cohort study. Both patients with FHBL as healthy controls will be recruited. The study starts with a screening visit

Day -7, AMC, morning: obtaining informed consent; fasting blood sample (lipoproteins, liver-, renal- function); physical examination

Day -2, at home: start taking sitostanol capsules (1 capsule per meal, 3 meals per day); start cholesterol-restricted diet; start dietary record; collecting feces sample as control sample

Day 0, AMC, 09.00u: baseline blood sample withdrawal

Day 0, AMC, 06.00pm: start study; standardized meal with 2 hours hereafter ingestion of two bile acid isotopes

Day 1, AMC, 09.00am: insertion of venous catheter and fasting blood sample (bile acid isotopes); admission of intravenous cholesterol isotope; ingestion of oral cholesterol isotope togetehr with breakfast; two hours after breakfast blood sample (bile acid isotopes); start collecting feces samples
Day 1, AMC, 06.00pm: fasting blood sample (cholesterol isotopes); standardized meal; 2 hours hereafter blood sample (bile acid isotopes); providing enterotest (to be taken in before going to sleep)

Day 2, AMC, 08.00am: admission in the hospital; fasting blood sample (bile acid isotopes) every 30 minutes until 01.00pm; administration of 0,05ug/kg cholecystokinin intravenously to contract gallbladder at 08.00am; 1 hour hereafter withdrawal of enterotest and analysis of enrichment with bile acids; standardized lunch at 01.00pm; blood sample (bile acid isotopes) at 03.00pm

Day 3, AMC, 09.00am: fasting blood sample (cholesterol isotopes); hereafter standardized breakfast and blood sample again at 11.00am (bile acid isotopes)
Day 3, AMC, 06.00pm: fasting blood sample (cholesterol isotopes); hereafter standardized meal and blood sample again at 08.00pm (bile acid isotopes)

Day 4: identical to day 3

Day 6, AMC, 09.00am: fasting blood sample (cholesterolisotopes)

Day 8: identical to day 6

Day 9: last day of ingesting sitostanol capsules

Day 10: last day of cholesterol-restricted diet, recording diet and collecting feces

Day 11, at home: collecting feces samples, dietary records etc. End of study

Study burden and risks

The total study will take place within a period of two weeks time. It will include 11 visits to the hospital and one visit at home. This will be preceded by a screening visit to the hospital. Total duration of all visits is approximately 25 hours. During the study, participants will need to follow a cholesterol-restricted diet, keep a dietary record and collect their feces samples.

Administration of the three isotopes expectedly will not have any side effects, as the isotopes behave like their natural (endogenous) counterparts, without causing harm to their 'hosts'. Infusion of cholecystokinin can cause mild transient nausea or abdominal discomfort. In rare cases, it can lead to an allergic reaction.

We don't expect any AEs or SAEs

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

FHBL patients: Male; caucasian origin; 18-65 years old; documented FHBL
Healthy controls: Male; caucasian origin; 18-65 years old; matched for age, BMI and possible medication use, depending on included FHBL subjects

Exclusion criteria

Use of cholesterol influencing medication; BMI > 35 kg/m2; Diabetes mellitus type 1 and 2; Uncontrolled hypertension; History of arterial disease including acute coronary syndrome (ACS), recent transient ischemic attacks (TIAs) or cerebro-vascular accident (CVA); Alcohol or drug abuse; Hepatic transaminases, yGT or bilirubin > 2 ULN at screening visit; History of gallstones or gallbladder resection; Having received an investigational drug in the last 3 months before the screening visit; Unable or unwilling to comply with the protocol requirements or deemed by the investigator to be unfit for the study; Likely to leave the study before its completion

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Will not start

Enrollment:	22
Type:	Anticipated

Ethics review

Approved WMO Date:	12-01-2012
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	NL37537.018.11