QUANTIFICATION OF CHOLESTEROL FLUXES IN HUMANS: Assessment of hepatic cholesterol excretion, intestinal absorption and excretion and faecal sterol loss using quadruple stable isotope technique (STORC EXTRA)

Published: 17-11-2009
Last updated: 04-05-2024

To estimate reference values for reverse cholesterol transport, cholesterol absorption, hepatic cholesterol excretion and direct trans-intestinal cholesterol excretion in humans.

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

Summary

ID

NL-OMON33472

Source
ToetsingOnline

Brief title
STORC EXTRA

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: Ministerie van OC&W

Intervention

Keyword: cholesterol absorption, cholesterol excretion, stable isotopes

Outcome measures

Primary outcome

To estimate reference values for reverse cholesterol transport, cholesterol

absorption, hepatic cholesterol excretion and direct trans-intestinal

cholesterol excretion in humans.

Secondary outcome

not applicable

Study description

Background summary

Dylipidemia is one of the most important risk factors for cardiovascular disease. Roughly, the cholesterol that is present in the human body can be divided into 'good' HDL-cholesterol (HDL-C) and 'bad' LDL-cholesterol (LDL-C). In order to increase cardiovascular disease prevention, plasma levels of the bad LDL-C should remain low, whereas the good HDL-C should be as high as possible. The anti-atherogenicity of HDL-C is mainly attributed to its pivotal role within the reverse cholesterol transport (RCT) process. This is the transport of excess cholesterol from the periphery (including the arterial wall) to the liver for excretion into the faeces out of the body. We have recently found that this net cholesterol excretion is significantly diminished in patients with hereditary decreased HDL-C levels.
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, recent evidence in mice suggests that the intestine is also an important secretory organ for cholesterol. In fact, direct trans-intestinal cholesterol excretion (TICE) accounted for 33% of total fecal sterol excretion in mice. It is unknown whether TICE is present in humans.

However, sterols of non-dietary origin were found in fecal samples of patients with biliary obstruction, suggesting that TICE is present in these patients. TICE might be a novel therapeutic target for cholesterol excretion and cholesterol-lowering, as evidence in mice suggests that TICE can be stimulated by LXR-agonists. The latter are novel cholesterol lowering compounds which will soon become available for use in humans.
To date, no technique has been described to reliably estimate cholesterol homeostasis in humans. The latter requires simultaneous assessment of reverse cholesterol transport, cholesterol absorption, biliary cholesterol excretion and, as final common pathway, faecal sterol excretion. Daily biliary cholesterol output is the most difficult flux to assess non-invasively in humans. The purpose of the current study is to optimize a method in humans for combined assessment of the above mentioned cholesterol fluxes, in one single protocol by use of cholesterol and bile acid kinetic tracers. Moreover, this protocol will enable us to quantify TICE for the first time in humans. If valid, this experimental protocol can be used to estimate net-cholesterol efflux in patients following administration of novel pharmacological interventions, such as LXR-agonists.

Study objective

To estimate reference values for reverse cholesterol transport, cholesterol absorption, hepatic cholesterol excretion and direct trans-intestinal cholesterol excretion in humans.

Study design

The design of the study is cross-sectional cohort study, which comprises a single measurement of cholesterol fluxes in a period of 15 days.
Visit 1 (day -7, morning fasting state)
At the screening visit written informed consent will be obtained. Subsequently, a blood sample will be collected for the measurement of lipoprotein levels and safety parameters, such as liver and renal function. Additionally, a physical examination will be performed for a general health evaluation. In case subjects are eligible, they will start with a cholesterol-restricted diet, which they will monitor in a food diary until the end of study. In addition, subjects receive a box with 3mg 2H4-sitostanol capsules, which subjects will start using 3 times daily from day -2 for a period of 8 days.
Visit 2 (day 0, 06.00pm)
Subjects return to the AMC and ingest a standardized mealt, together with a single bolus of two bile acid tracers (dissolved in fruit juice), which are used to measure daily biliary output rate and enterohepatic cycling of cholesterol and bile acids.
Visit 3 (day 1, 09.00am)
The next day two cholesterol isotopes will be administered. A plastic intravenous (IV) catheter will be placed in the antecubital fossa of the

forearm, which will be used for a blood draw. Subsequently, this same catheter will be used for the infusion of a single dose of 50mg 13C2-cholesterol. Immediately thereafter, subjects will have a standardized breakfast, with which they will ingest a capsule containing 50mg of another cholesterol-marker (2H7-cholesterol). One and four hours after this meal, blood will be drawn and subjects return to their homes. At 06.00pm they return to the AMC for an additional blood draw. Finally, subjects receive the encapsulated Enterotest-thread which will be used for the bile sampling the next day, as described in section E6. Subjects will ingest this capsule before going to bed and the upper end of the thread is taped to the corner of the mouth.
Visit 4 (day 2, 08.00am-08.00pm)
This studyvisit comprises a 12-hour admission to the hospital ward for a single bile sample and in order to study bile acid and cholesterol kinetics. Again, a plastic intravenous (IV) catheter will be placed in the antecubital fossa of the forearm. This will be used to administer IV bolus of 0.05*g/kg cholecystokinin (Cerulotide, Takus®), which will induce gallbladder contraction. One hour thereafter, the Enterotest-thread is withdrawn. The catheter is then used for frequent bloodsampling (1ml every 30min) for the rest of the day. Starting from this visit, subjects will be asked to collect daily faecal samples, using a special specimen collection system, until the end of the study (day 8). At 08.00pm subjects return to their homes, where they continue to use the oral tracer capsules, keep the food diary and collect the faecal samples until day 8.
Visit 5 and 6 (day 3 and 4, 09.00am and 06.00pm)
Subjects will return twice to the AMC at day 3 and day 4 for a blood sample.
Visit 7 (day 8, morning fasting state)
At day 8, a blood sample is obtained and the diaries, faecal samples and remaining capsules will be collected at the subjects* homes.

Study burden and risks

At screening a blood sample will be obtained, as well as a medical history, aimed at dietary habits and cardiovascular riskfactors, combined with a general physical examination. In addition, subjects are asked to ingest a single solution of stable bile acid isotopes (dissolved in fruit juice), a single capsule of 50mg 2H7-cholesterol and to maintain a cholesterol restricted diet during the subsequent eight days, together with the use of 3mg sitostanol capsules three times daily.

In addition, subjects are asked to visit the AMC for frequent bloodsampling, including once during a 12-hour admission period. Other invasive actions include the administration of an iv dose of cholesterol tracer (13C2-cholesterol), the iv administration of cholecystokinin for the bile sample to be obtained. Finally, participants are asked to collect daily faecal samples in a special collection system for a period of 7 days.

Hardly any health risks are involved in this study. Stable isotopes of

cholesterol, sitostanol and bile acids behave like their natural substrates and therefore carry no health risks. The dose of isotopes administered to the subjects is small compared to the amount already present in the body. A hematoma can occur at the site of venepuncture. Ethanol can cause burning at the site of infusion, which usually disappears quickly. Administration of Takus® can cause slight transient nausea. In rare cases, the synthetic cholecystokinin (Takus®) can induce an allergic reaction. Withdrawal of the Enterotest® during bile sampling can cause transient nausea as well.

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 subjects, aged 18-65 years, with an LDL-cholesterol concentration between 3.0 and 5.0 mmol/l.

Exclusion criteria

Excluded are persons with 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 or subjects who use prescribed medication 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):	01-06-2009
Enrollment:	12
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	NL27670.018.09