VLDL1, VLDL2, and LDL apolipoprotein B-100 kinetics in patients with familial hypercholesterolemia of unknown origin (FH4)

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON45448

Source
ToetsingOnline

Brief title
APPRECIATION

Condition

- Lipid metabolism disorders

Synonym
Familial hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Vidi grant [016.156.445] from the Netherlands Organisation for Scientific Research (NWO)

Intervention

Keyword: apolipoprotien, hypercholesterolemia, kinetic, LDL

Outcome measures

Primary outcome

Tracer/tracee ratio, pool size, fractional catabolic rate, and production rate

in FH4 subjects compared with (family) controls and/or dyslipidemic patients

with mutations in established lipid genes.

Secondary outcome

n.v.t.

Study description

Background summary

Familial hypercholesterolemia (FH) is characterized by increased low density lipoprotein (LDL) cholesterol and increased cardiovascular risk. There are 3 known genes (LDLR, ApoB, PCSK9) in which mutations can lead to the FH phenotype (FH1 to 3 respectively). However, in approximately 5-10% of patients such a mutation cannot be found, despite family-based linkage studies (the so called FH4 group). Therefore, a more elaborate approach is deemed necessary, where data derived from transcriptome, proteome, and metabolome studies are combined to find novel genes and metabolic pathways in lipid metabolism. We aim to acquire in depth phenotyping in selected FH4 patients by extensive lipoprotein kinetic flux studies yielding insights into the pathophysiological mechanism of FH4.

Study objective

To study *in vivo* lipid and apolipoprotein metabolism in patients with FH4, and to compare the results with healthy family controls and dyslipidemic patients with mutations in established lipid genes(i.e. FH1 * FH3). This will ultimately help to answer the fundamental question as to whether FH4 is a result of overproduction or a decreased catabolism of ApoB containing

lipoproteins.

Study design

Matched case-control study

Intervention

n.v.t.

Study burden and risks

Participants will visit the AMC for 1 or 2 full day(s) (7.30 am till 6.00 pm). Metabolic fluxes will be measured with stable isotope tracers that behave like their natural substrates and are therefore not harmful. At 21 timepoints blood samples will be collected, in total 279 ml. In the week prior to the admission participiants will be asked to keep track of their daily diet. On the day after the study day a last blood sample will be collected at the patients home at 8.00 am.
Patiënts with FH4 will be asked to participate in 2 study days, 1 after a 4 week wash-out period of lipid lowering therapy.
We state that the scientific insight of our findings will outweigh the minimal burdens and risks in this study.

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

- Diagnosis of familial hypercholesterolemia of unknown origin (FH4) based on Dutch Lipid Clinic Network criteria (Nordestgaard et al. 2013) and negative DNA-testing (mutations in LDLR, ApoB, PCSK9).
- Untreated LDL-cholesterol levels of > 95th percentile for affected members
- 18-65 years of age;Controls:
- Unaffected family member with untreated LDL-cholesterol between 20-60th percentile
- 18-65 years of age
Or:
- Persons with mutations in LDLR, APOB, or PCSK9 gene or other genes involved in lipid metabolism.
- 18-65 years of age

Exclusion criteria

· Heavy alcohol use
· Dysthyroidism
· Pregnancy, breastfeeding
· Renal insufficiency (creatinine >150 µmol/L)
· Diabetes mellitus

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-05-2017
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	31-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2017
Application type:	Amendment
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

ID: 26254
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL61012.018.17
OMON	NL-OMON26254

Study results

Date completed: 20-04-2020

Actual enrolment: 2

Summary results
Trial ended prematurely