The Role of microbial produced ethanol in etiology of Non-Alcoholic Steatohepatitis (ETHANASH trial)

Published: 20-01-2020
Last updated: 10-02-2024

To investigate whether microbial produced ethanol plays a role in the development of NASH.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON48065

Source
ToetsingOnline

Brief title
ETHANASH trial

Condition

- Gastrointestinal inflammatory conditions

Synonym
fatty liver disease, Non-alcoholic fatty liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: VIDI grand Max Nieuwdorp

Intervention

Keyword: Ethanol, Gut microbiome, Metabolites, NASH

Outcome measures

Primary outcome

Peripheral ethanol plasma concentrations in subjects undergoing a mixed meal tolerance test after receiving an infusion with and without fomepizole (15mg/kg in 30-45 min intravenously) .

1. Assessment of hepatic steatosis with ultrasonography of the liver prior to the mixed meal tolerance test.

2. 5h Mixed meal tolerance test for concentrations of plasma ethanol and insulin sensitivity (HOMA)

3. 5h Mixed meal tolerance test for concentrations of plasma ethanol after antibiotic treatment

4. Oral and faecal microbiota composition

5. Dietary and satiety lists

6. Clinical data (body weight, waist circumference, in addition information will be collected regarding medication, comorbidity, smoking,)

7. Causality of endogenous plasma ethanol production by intestinal microbiota as shown by reducted peripheral levels upon fomipizol infusion due to short term oral antibiotics course

Secondary outcome

-

Study description

Background summary

Changes in the composition of the gut microbiota have been associated with alterations in host metabolism and recent evidence suggest that gut microbiota might also be involved in the development of Non-Alcoholic Fatty Liver Disease (NAFLD) and subsequent Non-alcoholic steatohepatitis (NASH). So far, however, causality has not been demonstrated. Among many gut microbial metabolites, endogenous intestinally produced ethanol has gained interest in the past decade for its involvement in the development of NAFLD. Ethanol is produced by intestinal bacteria and it has been suggested that ethanol might play a role in the development of NAFLD, especially in the transition from NAFLD to NASH. When produced in significant amounts, hepatic ethanol metabolism inhibits beta-oxidation of fatty acids which will induce storage of lipids in the liver. Endogenously produced ethanol reaches the liver via the portal vein and is then rapidly removed from the circulation via extremely efficient hepatic mechanisms, leaving almost untraceable concentrations in the peripheral plasma if liver function is uncompromised. Several studies have showed that subjects with NASH (known to have a compromised liver function) have increased peripheral concentrations of ethanol, however these concentrations are so low that one might argue whether this is clinical relevant regarding the development of NASH. The first step in ethanol catabolism is the oxidation of ethanol to acetaldehyde using NAD+, mainly via the hepatic enzyme alcohol dehydrogenase. Fomepizole (4-methylpyrazole) is a specific inhibitor of the enzyme alcohol dehydrogenase. In a previous study, a significant elevation of peripheral plasma ethanol concentrations were observed in lean subjects who were treated with fomepizole after intake of lingonberry juice. Since subjects with NASH might have more ethanol producing bacteria, we anticipate to find increased concentrations of ethanol in subjects with NASH compared to healthy control subjects during a mixed meal test after the infusion of fomepizole.Moreover, when intestinal microbiota is temporarily eradicated by a short term oral antibiotic course, we expect to see no increase in peripheral plasma ethanol levels upon fomipizol infusion in all subjects.

Study objective

To investigate whether microbial produced ethanol plays a role in the development of NASH.

Study design

cross sectional cohort study

Study burden and risks

Subjects will be recruited from subjects that visited the outpatient clinic of internal medicine at AMC in the last year and in whom NASH was proven by biopsy. After informed consent, biological samples (including saliva, blood and feces sample) will be collected. In addition, subjects will undergo an ultrasonography of the liver. Prior to the mixed meal tolerance test, an infusion with fomepizole will be given to suppress the alcohol dehydrogenase enzyme in the liver. Repetitive blood samples will be drawn after the intake of the mixed meal. In total, 8 blood samples will be drawn during the 5-hour mixed meal tolerance test (total duration of study 15 h). The burden consists of the extra time invested in the measurements. This study will further investigate the role of endogenously produced ethanol in the development of NASH and more importantly, the relation with liver histology (already available from the biopsy taken at the outpatient clinic). We therefore believe that the scientific insight of our findings will outweigh the minimal risks for the participating subjects in this study. Total amount of blood taken is 70 ml per visit mixed meal test and 1x clinical lab (20ml) including hba1c, lipid profile, liver function 20ml) thus 230ml for all participants.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Diagnosis of NASH on liver biopsy taken on clinical grounds at the outpatient

clinic
- 18-65 years of age
- BMI > 25 kg/m2
- Subjects should be able to give informed consent,

Healthy controls:
- BMI >25 kg/m2
- 18-65 years of age
- Subjects should be able to give informed consent

Exclusion criteria

- Primary lipid disorder
- Known genetic basis for insulin resistance or glucose intolerance
- Ethanol intake
- Pregnancy, females who are breastfeeding
- Hepatitis B and/or C
- Auto-immune hepatitis
- Wilson disease/ alpha 1-antitripsine deficiency
- Hemochromatosis
- Use of drugs interacting with Fomepizole (products requiring CYP2E1 for metabolizing).
- Use of drugs interacting with Clindamycine, metronidazole or ciprofloxacin.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-05-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	29-03-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2020
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

No registrations found.

In other registers

Register	ID
CCMO	NL68634.018.18