Disease mechanisms and markers for non-alcoholic steatohepatitis in a population with non-alcoholic fatty liver disaese: a prospective cohort study with biobank

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

Summary

ID

NL-OMON47388

Source
ToetsingOnline

Brief title
Prospective cohort and biobank of nonalcoholic fatty liver disease patients

Condition

- Gastrointestinal conditions NEC
- Hepatic and hepatobiliary disorders

Synonym
fatty liver, Non-alcoholic fatty liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: (diagnostic) markers, biobank, non-alcoholic fatty liver disease, prospective cohort

Outcome measures

Primary outcome

The primary outcome of this cohort is the diagnosis NASH

Secondary outcome

Furthermore different parameters ([epi-]genetic, lifestyle, metabolic,

inflammatory and microbial parameters) associated with NASH in a cohort NAFLD

patients will be investigated cross-sectionally and longitudinally. The degree

of hepatic steatosis and/or fibrosis (e.g. using MRI and Fibroscan) and the

presence of hepatic inflammation (e.g. using biochemical parameters and MRI)

will be assessed. Additionally, the prevalence of (extra)hepatic complications

of NAFLD will be evaluated.

Study description

Background summary

Non-alcoholic fatty liver disease (NAFLD) is with 20-30% the most prevalent liver disorder in Western society and is associated with overweight and obesity in 50-100%. NAFLD has been described as the hepatic component of the metabolic syndrome. The majority of patients have simple steatosis, in about 15-30% non-alcoholic steatohepatitis (NASH) develops, which leads to an overall increase in morbidity and mortality due to the progression to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The term NAFLD comprises both simple steatosis and NASH. Most patients with NAFLD have no or few, mainly aspecific symptoms; and generally there is a silent progression of simple

steatosis to NASH and in the end liver-related morbidity and mortality.
NASH is a chronic systemic inflammatory disease of multifactorial origin. In the pathogenesis of simple steatosis to NASH, oxidative stress plays a crucial role in the initiation and the progression of the inflammatory cascade. Genetic susceptibility, activated white adipose tissue with adipocytokine secretion, altered intestinal microbiota and an increased intestinal permeability are also involved, but their exact contribution and interaction in the occurrence of NASH still has to be determined. Further insight in factors contributing to the initiation of NASH in patients with simple steatosis and early diagnosis are essential for identifying future therapeutic options and to limit the risk of complicated NASH (i.e. fibrosis, and cirrhosis with portal hypertension) HCC, liver-related mortality and extrahepatic morbidity.

Study objective

Objective: The objective of the prospective NAFLD cohort study with biobank is:
1. In a cross-sectional design (a) to determine which factors are associated with the presence of NASH in a population of NAFLD patients and (b) to identify and validate non-invasive markers to identify patients with NASH. 2. In a longitudinal design (a) to define factors contributing to the development and progression of NASH in patients with simple steatosis, and (b) to identify and validate non-invasive markers to identify patients with NASH.
Therefore, the role of metabolic, systemic and local inflammatory, intestinal (i.e. microbiota and barrier function) and/or lifestyle factors will be studied both cross-sectionally and longitudinally in a cohort of NAFLD patients. Furthermore, non-invasive diagnostic tools and/or markers associated with NASH will be investigated.

Study design

Study design: A cohort study, with both a cross-sectional and a longitudinal part, of obese subjects with proven NAFLD based on liver biopsy and/or imaging (any form). Eligible subjects will be included via the MUMC+ outpatient clinic and second line obesity clinic, Zuderland MC and general practitioners in South-Limburg. The majority of eligible subjects will undergo/have undergone imaging or liver biopsy for clinical reasons. It is to be expected that about 33% of subjects will be asked to undergo a MRI for study purpose only. Subjects with a suspected diagnosis of NAFLD (no prior imaging or biopsy) need to undergo a CAP measurement to confirm the diagnosis, before the other measurements are scheduled.
All participants will be asked to complete several questionnaires (i.e. demographics, clinical data, SF-36, GAD-7 and PHQ-9, FFQ, SQUASH, and Baecke), to undergo anthropometric measurements. Furthermore, blood, urine, faeces and exhaled air will be collected and a fibroscan and DEXA-scan will be performed. This will be the standard to be collected data set. Additionally, participants will be asked to participate in a multi-sugar test for intestinal permeability.

After 5 and 10 years, participants will be invited to undergo in the same study procedures, data and sample collection to study the factors responsible for the development of NASH in the group with simple steatosis at baseline, and the development of (extra)hepatic complications in the group with NASH at baseline. The time load for the different investigations is estimated 5 hours, consisting of completing the questionnaires at home and one visit to the hospital to collect to collect the anthropometric data, blood/stool/urine/air samples, perform a fibroscan and DEXA-scan. In case of participating in the intestinal permeability test, the time load will be another 24 hours, for collecting urine.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The measurements, data and sample collections will be planned with the participant. Anthropometric data collection, hand grip strength, blood, urine and faeces collection, exhaled air (VOC), and fibroscan will be performed during study visit 1 (after a pre-visit for signing the informed consent). The participant can fill out the questionnaires at home and bring the forms when visiting the research physician. The DEXA-scan will be planned in agreement with the participant. MRI for study purposes only, is needed in a subset of subjects. CAP to confirm a suspected diagnosis is needed in a subset of patients. The DEXA-scan and, if possible, also the MRI will be combined with study visit 1. The multiple sugar permeability test will be performed at home by participants who consented (and signed informed consent) for this.

No side effects of the investigations are expected, apart from a small bruise of taking the blood samples. Three tubes (21 ml) will be collected for research purposes; if possible this will be combined with regular blood sampling. If participants are not regular patients at the outpatient clinic, a maximum of 4 extra tubes (max.17,5 ml in total) will be collected to determine (part of) the standard clinical laboratory investigations (e.g. liver function tests, cholesterol) for research purposes only.
Radiation exposure during the DEXA scan is 0.01 mSV per procedure. No side effects are expected with this minimum dose of radiation exposure.
The time burden associated with participating in the research is: 90 minutes to fill out the questionnaires, 2 hours for the first visit to collect samples and anthropometry and perform a fibroscan. The DEXA-scan will take approximately 15-30 minutes. If an MRI is needed, this will take 45-60 minutes.
Subjects participating in the intestinal permeability test will have to collect their urine for 24 hours. In case of unexpected findings, awareness of normally unknown pathology may affect a person*s perception of his own health condition negatively. On the other hand, early detection is likely to have favourable effects on disease progression and enable early intervention

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

- NAFLD diagnosis based on evidence of hepatic steatosis, either by imaging (any form) or by histology
- BMI >= 25
- Between 18 - 65 years of age

Exclusion criteria

- Incompetent to understand and/or sign the informed consent.
- Causes for secondary hepatic fat accumulation such as significant alcohol consumption, medications, Wilson*s disease, viral infections, starvation or parenteral nutrition, among others, and conditions associated with microvesicular steatosis (excluding hemochromatosis)

- Ethanol consumption exceeding more than 14 standard beverages per week for males and more than 7 standard beverages per week for female.
- Unwilling to collect biosamples
- Pregnancy and breastfeeding.
- A history of bariatric surgery.
- Diagnosis of liver cirrhosis and/or hepatocellular carcinoma.
- Diagnosis of extrahepatic malignancies
- Individuals about to undergo or recovering from a surgical or otherwise medical procedure that will interfere with data collection and analyses planned within the current cohort, will initially be excluded from participation, but are offered the opportunity to participate at a later moment in time (e.g., after 3 months are myocardial infarction patients are eligible for participation).

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:	Recruitment stopped
Start date (anticipated):	01-02-2015
Enrollment:	500
Type:	Actual

Ethics review

Approved WMO

Date:	25-03-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-12-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-05-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
ClinicalTrials.gov	NCT02422238

Register	ID
CCMO	NL50683.068.14