The search for biomarkers to enable detection and monitoring of disease progression from NAFLD to NASH and NASH itself; Amsterdam NASH cohort

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We aim to identify hepatic, plasma, genetic and gutmicrobial markers that, alone or in combination, enable detection and monitoring of disease progression from NAFLD to NASH and subsequent progression from NASH to cirrhosis.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON52739

Source
ToetsingOnline

Brief title
Amsterdam NASH cohort (ANCHOR) study

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Hepatic and hepatobiliary disorders

Synonym
non-alcoholic fatty liver disease; steatohepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: EU horizon 2020 (LITMUS consortium)

Intervention

Keyword: biomarkers, gut microbiota, NAFLD, NASH

Outcome measures

Primary outcome

primary outcome is identification of new riskfactors in patients with steatosis hepatis on abdominal ultrasound that develop NASH from NAFLD This includes study of specific hepatic gene expression (RNAseq), plasma markers (metabolites), DNA methylation and intestinaal microbiota composition to identify rapid and slow NAFLD-NASH progressors.

Secondary outcome

to apply a systems biology approach to identify the hierarchy of driving mechanisms (microbial and metabolic markers) involved in the conversion of NAFLD-NASH and NASH-Cirrhosis after 5 years that can be used for the development of novel treatment options in NASH

1. dietary and satiety lists and excreted metabolites (24h faeces and urine as well as BIA and questionnaires)

2. Faecal and oral microbiota composition in relation to plasma metabolites in NAFLD-NASH progression as well as NASH-Cirrhosis progression

Study description

Background summary

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of liver dysfunction in the Western world and is strongly associated with obesity, insulin resistance and the metabolic syndrome. NAFLD is defined as hepatic fat accumulation (hepatic steatosis) in the absence of excessive alcohol consumption. It represents a spectrum of liver disease that ranges from simple steatosis, through non-alcoholic steatohepatitis (NASH) to advanced fibrosis and cirrhosis, which may ultimately be complicated by hepatocellular carcinoma (HCC). Transition from NAFLD to NASH gives an increased risk of cardiovascular disease and increases mortality of liver-related disease and can only be diagnosed based on histological examination of liver tissue obtained by biopsy. Furthermore, liver cirrhosis originated from NASH is expected to become the primary indication for liver transplantation in the USA in the next 10 years. However, since no treatment options are available at this moment to prevent progression of NAFLD to NASH, identified patients are not regularly followed at an outpatient clinic. This as most patients with NAFLD only exhibit steatosis and do not progress towards NASH, whereas a distinct subgroup advances to overt liver disease like NASH and fibrosis with the mechanisms underlying this distinctive disease course remaining poorly understood. Since progression from NAFLD to NASH is associated with significantly increased risk of morbidity and mortality, there is a clinical imperative to identify the NAFLD patients that rapidly progress to NASH from those who will remain in the NAFLD stage, in order to better monitor these patients and to reduce their risk. Our study aims to identify novel risk factors in subjects with hepatic steatosis, as well as to validate noninvasive imaging modalities, in order to better discern the patients who progress to NASH from non-progressing NAFLD patients. Our rigorous baseline biomarker validation against biopsy proven NAFLD-NASH progression over 5 years has the goal to reduce the need for future liver biopsies in NAFLD-NASH in the clinical setting. As there are currently no registered treatment modalities for NASH besides dietary intervention, improved understanding of the pathophysiological mechanisms as well as their relationship to metabolic disturbances are of crucial importance to discover new diagnostic and therapeutical targets in NAFLD/NASH.

Study objective

We aim to identify hepatic, plasma, genetic and gutmicrobial markers that, alone or in combination, enable detection and monitoring of disease progression from NAFLD to NASH and subsequent progression from NASH to cirrhosis.

Study design

prospective cohort study.

Study burden and risks

Participants will be recruited from patients that visited the outpatient clinic

of internal medicine and gastroenterology at AMC in the last 6 years and in whom an ultrasound was made that reports presence of hepatic steatosis. After informed consent, biological samples (including saliva, blood and faeces sample) will be collected; also, subjects will undergo MRI of the liver and visceral fat. The study participation is estimated to take a total of 8 hours. Despite ample noninvasive efforts in small groups of NAFLD/NASH patients over the last decade, a liver biopsy is still regarded as the gold standard for discerning between NAFLD and NASH. Moreover, there is currently no registered treatment that helps to prevent neither progression from NAFLD to NASH nor progression from NASH to cirrhosis. Our study participants will be referred to our AMC intervention radiology department for liver biopsy to assess liver histology and gene expression (RNAseq) in liver tissue. Thereafter, subjects are seen again at the AMC after 5 years to measure the same parameters and a repeated ultrasound guided liver biopsy will be taken to study histological progression. Currently, about 25% of all adults in USA has NAFLD whereas 5-6% has NASH. Smaller studies have suggested that about 25% of NAFLD patients progresses per 5-10 years into NASH, of whom subsequent 25% develops fibrosis and cirrhosis in the next 5-10 years thereafter (Petäjä et al., 2013). When participants are found to have NASH in their baseline liver biopsy, they will be referred to the department of gastroenterology and hepatology for clinical follow-up and dietary counselling.
As an experienced interventional radiologist or hepatologist will perform the liver biopsy ultrasound-guided, the risk (comprising mostly bleeding from the biopsy sites) of complications will be very low (<0.1%). Moreover, local hemostasis after the procedure will be observed and bleeding disorders are an exclusion criterion. Taken together with the fact that there is no other method to diagnose NASH and progression from NAFLD to NASH is associated with significantly increased risk of morbidity and mortality, we feel that the benefits outweigh the risks of study participation. Moreover, our study will help to provide (noninvasive) algorithm based risk scores validated against gold standard diagnostics (biopsy) to improve identification of subjects that will rapidly move from NAFLD to NASH (progressors) and those that have no progression at all (non-progressors). This will reduce the necessity for liver biopsies for NAFLD-NASH patients in the future. Total blood volume collected over 5 years is 100 ml.

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 steatosis hepatis on ultrasound or by biopsy or on Fibroscan with CAP >280dB/m
• >18 years of age
• ASAT and/or ALAT levels above upper limit of normal in six months prior to inclusion
• BMI >25 kg/m2

Exclusion criteria

• Abusive alcohol use (>20 IU/week)
• Hepatitis B and/or C
• Auto-immune hepatitis
• Wilsons disease/ alpha-1-antitripsine deficiency
• Haemachromatose
• Bleeding disorder, including the use of anticoagulant therapy and platelet aggregation inhibitors. Except for subjects using platelet aggregation inhibition monotherapy for the prevention of cardiovascular disease and without a history of any coronary events. In this case the platelet aggregation inhibitor will be discontinued for 7 days before the liver biopsy is performed.
• Use of drugs with a potential role in aggravation of pre-existing NAFLD

• Not able or willing to undergo MRI (for example claustrophobia, ICD, pacemaker).
• Diagnosis of liver cirrhosis and/or hepatocellular carcinoma.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-09-2018
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO Date:	11-04-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	07-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
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: 19935
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL63975.018.17
OMON	NL-OMON19935