Translating the Adipose Tissue-liver axis in Metabolic dysfunction associated SteatoHepatitis: finding inflammatory therapeutic targets and biomarkers

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Primary Objective:To identify the immunological changes and associated mechanisms in the AT-liver axis in overweight and obesity-related NASH. Secondary Objective(s): - Develop novel biomarkers of NASH- Discover novel therapeutic targets for NASH

Ethical review	Approved WMO
Status	Pending
Health condition type	Hepatic and hepatobiliary disorders
Study type	Observational invasive

Summary

ID

NL-OMON56912

Source
ToetsingOnline

Brief title
translATe-MASH

Condition

- Hepatic and hepatobiliary disorders

Synonym
Metabolic Dysfunction associated steatohepatitis (MASH)

Research involving
Human

Sponsors and support

Primary sponsor: Zuyderland Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: adipose tissue, inflammation, liver, obesity

Outcome measures

Primary outcome

- Immune cell signature in blood, AT and liver

- Inflammatory mediators in blood, AT and liver

- Liver phenotype: MASLD activity score (histology), composite scores (MASLD fibrosis score, FIB-4) and ALAT/ASAT plasma levels

Secondary outcome

Potential confounders:

- BMI, waist circumference

- Metabolic profile: fasting glucose, HbA1c, fasting insulin, HOMA-IR, plasma lipids

- Age

- Sex

- Ethnicity

- Alcohol consumption

- Smoking

- Medication use

- Blood pressure

Study description

Background summary

Metabolic dysfunction associated steatotic liver disease (MASLD) is a condition where fat accumulates in the liver (steatosis) occurring in 25% of people worldwide (1). In obesity, MASLD risk rises to 90% (2). In 7-30%, steatosis progresses to an inflammatory state called metabolic dysfunction associated steatohepatitis (MASH), increasing the risk for developing fibrosis, cirrhosis and liver failure (1), necessitating liver transplantation (3). MASH patients also develop more hepatocellular cancers, cardiovascular disease and type 2 diabetes. These cardiometabolic diseases account for the majority of global morbidity and mortality (WHO, 2020). Developing liver inflammation is thus a crucial step in disease progression and clinical outcomes.

There are two major clinical problems with MASH. First, diagnosis of MASH is difficult. MASH is a very dynamic condition, requiring multiple times of assessment. Although elevated liver enzymes indicate hepatocyte damage, ALT levels have disappointing 50% sensitivity and 61% specificity for MASH and some patients retain normal ALT levels during disease progression. The so-called *MASH test*, combining demographic parameters like age, sex and BMI, with several serum parameters, has a negative predictive value of 81% for MASH, but very poor sensitivity (4). The gold standard, i.e. a liver needle biopsy, is invasive and with a significant risk of complications. Hence, less than 50% of endocrinologists and general practitioners refer patients at risk for a biopsy (5). Thus, many MASH cases remain undiagnosed. Nevertheless, even after a biopsy, diagnosis is not straightforward. Such needle biopsies are very small while the liver often displays heterogeneity, risking sampling bias. Moreover, the dichotomy of MASH vs non-MASH based on histological scoring systems fails to capture borderline cases, and leaves subtle inflammatory changes in the liver that may precede MASH unrecognized. As a result, the true nature of MASH in humans remains elusive. Second, there are currently no treatments for MASH (6). These limitations are least partially due to a knowledge gap about the mechanisms of liver inflammation in MASH development in humans.

MASH is influenced by crosstalk with other tissues (7). Given the high incidence of MASH in obesity, the AT-liver axis is particularly interesting (8). Our previous work in experimental animals showed that AT expansion induces neutrophil and monocyte recruitment to the liver from the circulation, causing inflammation and liver damage, independent of other risk factors (9). These data Illustrate the causal contribution of AT to hepatic inflammation and the involvement of circulating immune cells herein. Other groups also showed a role for circulating immune cells in hepatic inflammation using experimental mouse models (10-12).

We hypothesize that circulating immune cells are key mediators in the AT-liver axis, and are therefore a promising biomarker and target for treatment of MASH. Unfortunately, almost no data are available on the contribution of immune cells

to MASH development in the human AT-liver axis. This knowledge gap hampers the development of diagnostic and therapeutic strategies targeting inflammation in MASH. Here, we propose to investigate the role of immune cells in the AT-liver axis during MASH development in humans.

Study objective

Primary Objective:
To identify the immunological changes and associated mechanisms in the AT-liver axis in overweight and obesity-related NASH.

Secondary Objective(s):
- Develop novel biomarkers of NASH
- Discover novel therapeutic targets for NASH

Study design

This research will be an observational cross-sectional study with invasive measurements. Overweight and obese patients undergoing abdominal (bariatric, gallbladder and other) surgery will be recruited. Biopsies of liver, subcutaneous AT and visceral AT will be collected for histological evaluation, as well as experimental measurements of immune cells (flow cytometry), gene expression (qPCR, RNAseq), and biochemical measurements. Based on the hepatic biopsies, MAFLD/MASH will be diagnosed. In addition, blood is collected for immunological characterization and for measuring circulating plasma proteins. Participants will be divided into the following groups, including expected incidence based on previous research (09T30):
- Overweight and obese individuals without MAFLD (20% of individuals)
- Overweight and obese individuals with steatosis only (60% of individuals)
- Overweight and obese individuals with MASH without diabetes type 2 (10% of individuals)
- Overweight and obese individuals with MASH with diabetes type 2 (10% of individuals)

These groups will be compared to a control group of lean individuals undergoing abdominal surgery, in which the occurrence of MAFLD is not expected. In this way, we can evaluate the immunological and inflammatory changes in the tissues and circulation that are specific to MASH in a background of overweight and obesity. In addition, using the control group, we can delineate which changes are specific for overweight and obesity. Patients with MASH are stratified based on the presence of type 2 diabetes, since it is known that type 2 diabetes status impacts hepatic inflammation (13).

Study burden and risks

The research may have limited adverse effects. Patients will not notice

anything from the removal of pieces of fat and liver tissue as this will occur during surgery while they are under anesthesia. There will be no additional pain or scarring from the removal of the fat and liver tissue, and the patient will not need to stay in the hospital longer because of it. Any minor bleeding that occurs due to the removal of the fat will be immediately stopped by the surgeon. In total, we will take (2 tubes) 10 ml of blood. This amount poses no problems for adults and will be done during anesthesia.

Given the steep rise in obesity, the rate of MASLD and MASH is expected to rise to worrying levels, while there is no cure available. MASH is associated with increased risk of liver complications, i.e. cirrhosis, liver failure and hepatocarcinoma. Furthermore, MASH greatly elevates the risk of developing extrahepatic complications, including cardiovascular disease. Although weight loss often leads to improvement of this condition, attaining and sustaining weight loss are notoriously hard to achieve and do not always cure the condition. Given the high chance of developing both hepatic and extrahepatic complications in NASH and fibrosis patients, alternative intervention strategies are urgently warranted. In addition to the lack of approved treatments, there are no trustworthy biomarkers for MASH. This project will identify novel biomarkers based on immune cell measurements that can ultimately lead to a better identification of those patients at risk of developing MASH. This will lead to improved risk stratification and patient care.
Thus, the participants in this study will contribute to increasing our understanding of inflammation development in MASH in potentially finding novel biomarkers and treatments for the disease. On the other hand, the proposed procedures imposes no or very little additional burden on the participants as the blood and tissue samples will be collected during already scheduled clinical procedures and visits.
Potentials risks include small bleedings due to taking the biopsy, these will immediately be stopped by the surgeon

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

subject must be eligible for abdominal surgery (bariatric, gallbladder or other) and between 18 and 75 years of age. The additional inclusion criterion for the control group will be BMI<25 and for the overweight/obese patients BMI>25.

Exclusion criteria

- Evidence of MASLD (based on biopsy or fibroscan measurements) for lean (BMI<25) control individuals
- Alcohol consumption > 2 per day for women; >3 per day for men
- Drug abuse
- Known viral hepatitis or other infection
- Hepatic cancer
- Elevated CRP levels (>10)
- Diabetes mellitus type 1 or other autoimmune diseases
- Use of anti-inflammatory drugs (specifically corticosteroids)
- For patients without type 2 diabetes: use of anti-diabetes drugs due to their known effect on inflammation (e.g. metformin, GLP1 mimetics)
- - Pregnancy or breastfeeding

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:	Pending
Start date (anticipated):	01-06-2024
Enrollment:	308
Type:	Anticipated

Ethics review

Approved WMO

Date:	10-07-2024
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	NL85870.096.24