Luminal Fructose Kinetics

Published: 02-05-2024
Last updated: 21-12-2024

To elucidate host/microbial intestinal (postprandial) fructose kinetics (by 13C incorporation in glucose and ethanol as well as other metabolites) in small intestinal fluid as well as plasma, urine and breath samples (whole body metabolism) and...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56753

Source
ToetsingOnline

Brief title
MARTINI

Condition

- Other condition

Synonym
Hepatic steatosis, metabolic dysfunction associated liver disease

Health condition

MASLD /MASH

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ethanol, Fructose, MASLD, microbiome

Outcome measures

Primary outcome

Changes in host/microbial intestinal (postprandial) fructose kinetics (by 13C incorporation in glucose and ethanol as well as other metabolites) in small intestinal fluid as well as plasma, urine and breath samples (whole body metabolism) and establish the role of (small) intestinal luminal pH (which is increased upon proton pump inhibitor for 4 weeks of oral omeprazole 2dd 40mg) in biopsy proven MASLD/MASH subjects versus healthy (BMI<25) subjects (n=11 per group).

Secondary outcome

- Differences in expression of small intestinal biopsy RNAseq based genes (including host alcohol dehydrogenase genes) before and after omeprazole
- Changes in oral, small intestinal as well as in fecal microbiota including bacterial alcohol dehydrogenase genes and intestinal pH + alcohol dehydrogenase in feces (since elevated ADH in feces is a measure for increased ethanol exposure)
- Changes in Dietary intake between two vistis (by online Eetmeter at week 0 and week 3)
- To model differences in 13C- fructose whole body handling between the healthy and MASLD/MASH patients by tracking the label in metabolites (mainly glucose) in peripheral circulation, breathe, and feces and urine for excretion.

Study description

Background summary

Metabolic dysfunction associated steatotic liver disease (MASLD) has been on the rise worldwide, with a prevalence of approximately 30% . It is the number one cause of liver transplantation and patients with MASLD have an increased risk of death by cardiovascular diseases . Major contributing factors include obesity, insulin resistance and diabetes mellitus type 2 (T2DM). In recent years, the role of the gut microbiome in the development of MASLD has become increasingly evident.

Studies have revealed that lactic acid and streptococci bacterial strains in the (small) intestine are responsible for significant ethanol production, and our research has further demonstrated a correlation between endogenous ethanol production and the presence of fatty liver disease. Additionally, it was shown that oral proton pump inhibitor use was associated with elevated ethanol levels. From in vitro experiments we know that fructose serves as a substrate for lactic acid bacteria . Over the past few years, there has been a substantial increase in dietary fructose consumption, contributing to the incidence of obesity and related conditions, including MASLD. Fructose,derived from fruits and honey, is also a prominent component of commonly used sweeteners such as sucrose and high-fructose corn syrup, commonly found in soda beverages. This widespread use results in a substantial fructose intake worldwide. Conventionally fructose is catabolized in the liver through fructose-1 phosphate pathway, and a recent study in mice showed that in low dose, approximately90% of the fructose is metabolised in the small intestine primarily into glucose. However, in higher doses this small-intestinal fructose clearance capacity was saturated leading to unmetabolized fructose to spill over in both the colon and liver. Furthermore, this saturation can also lead to a longer residence time of fructose in the small intestine, which could affect the small intestine microbial fructose mixed acid fermentation. This can subsequently drive production of toxic metabolites, such as ethanol, which may contribute to the accumulation of hepatic fat following fructose consumption.

In this regard, intestinal gluconeogenesis (IGN) appears to be a protective mechanism as it converts dietary fructose into glucose thereby preventing fructose fermentation by microbes. However it remains unclear whereas this process can also occur in the human (small) intestine following fructose intake. This as most of our understanding of the (small) intestinal lumen comes from in vitro experiments or measuring final products in feces or peripheral blood samples, since there are difficulties to access the (small) intestinal lumen. However, these in vitro samples do not translate to human (small) intestinal metabolism since they only represent the net result of metabolites production, excretion, absorption and hepatic passage, underestimating the

actual contribution of (small) intestine.
In this study we therefore aim to elucidate (small) intestinal microbial and host fructose catabolism by the use of 13C tracking techniques and directly sampling of the intestinal lumen in healthy and MAFLD/MASH subjects. Furthermore, we will test if postprandial fructose and ethanol kinetics depend on the intestinal pH by administration oral PPIs to the participants.

Study objective

To elucidate host/microbial intestinal (postprandial) fructose kinetics (by 13C incorporation in glucose and ethanol as well as other metabolites) in small intestinal fluid as well as plasma, urine and breath samples (whole body metabolism) and establish the role of (small) intestinal luminal pH (which is increased upon proton pump inhibitor for 4 weeks of oral omeprazole 2dd 40mg) in biopsy proven MASLD/MASH subjects versus healthy (BMI<25) subjects (n=11 per group).

Study design

This study is designed as a non-blinded single center intervention study in eleven healthy subjects and eleven MASLD/MASH patients performed in the Amsterdam UMC.

Intervention

Omeprazole orally given twice a day 40mg for four weeks

Study burden and risks

Omeprazole
omeprazol has been prescribed for more than twenty years. It is a relatively safe drug with a small risk of severe side effects. It prevents patients from getting gastric and duodenal ulcer or irritation of the stomach by gastric acid. Frequent reported side effects are gastro-intestinal complaints (i.e. nausea, vomiting, diarrhoea, constipation, stomach pain) and headache. Sometimes patients experience itch, rash, urticarial, malaise, insomnia and dizziness and very rare side effects that have been reported are allergic reactions, thrombocytopenia and leukopenia, muscle weakness, liver failure and hypomagnesaemia. However since patients only take the omeprazole for four weeks we don*t expect any side effects.

Nasal-intestinal catheter and gastroduodenoscopy
Gastroscopy will be performed by a gastroenterologist. Gastroduodenoscopy is a procedure associated with discomfort, but when participants are well fasted it is very safe. There is always a small risk of complications. For example bleeding. But this is less than 1% and often because participants use blood

thinners. We won*t include patients who use blood thinners. Positioning of the nasal intestinal catheter will be done during the gastroscopy.Participants may experience nausea or throwing up, but this feeling will fade after the catheter is placed.

Fomepizol
Fomepizol will be administered intravenously. Fomepizol blocks the ADH enzyme in the liver thereby preventing ethanol metabolism. We expect that ethanol concentrations will be higher especially in the MASLD group, but it is highly unlikely that these concentrations reach toxic values. Nontheless there will be a physican present during administration.

Blood samples
Participants will receive a catheter in a distal vein which enables multiple blood withdrawals. Of course they still have the discomfort of the placement but this will be only once per visit. Complications could be a bruise or a sore spot after placement. Risk of major complications is very small.

X-ray
After placement of the nasal-intestinal catheter we wille take a x-ray to check the position of the catheter. In total we will take two x-rays to determine and check the position of the catheter. Radiation exposure is 0.7 mSv per x-ray.

Contacts

Public
Amsterdam UMC

meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Amsterdam UMC

meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

In case of the healthy subject group:

- Adult individuals, age > 18 <65 years
- male / postmenopausal female
- BMI <25
- Ability to give informed consent

In case of the MASLD/MASH group

- Adult individuals, age > 18 <65 years
- BMI > 25
- male / postmenopausal female
- Biopsy proven MASLD/MASH
- Ability to give informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- History of sustained excess alcohol ingestion: daily consumption >30g/day (3 drinks per day) for males and >20 g/day (2 drinks per day) for females
- Patients with diabetes
- Bariatric surgery
- Other forms of liver disease (e.g. Hepatitis B,C, Wilson disease, hemochromatosis)
- Proton-pump inhibitor usage one year prior to study participation
- GLP1, SGLT2i or insulin use
- Antibiotic use for the past 3 months

- Probiotic or symbiotic usage
- Pregnant women
- Chronic illness (including a known history of heart failure, renal failure (eGFR <30 ml/min), pulmonary disease, gastrointestinal disorders, or hematologic diseases), or other inflammatory diseases
- Active infection
- Use of ascal, clopidogrel or other platelet inhibition
- Smoking
- Blood thinners
- Heart failure

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2024
Enrollment:	22
Type:	Anticipated

Ethics review

Approved WMO Date:	02-05-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2024
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	NL85966.018.23