Cardiometabolic consequences of Hereditary Fructose Intolerance

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

Summary

ID

NL-OMON43427

Source
ToetsingOnline

Brief title
HFI study

Condition

- Hepatic and hepatobiliary disorders
- Inborn errors of metabolism
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Hereditary fructose intolerance (genetic fructose intolerance); Nonalcoholic fatty liver disease (fatty liver)

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Stofwisselkracht Grant

Intervention

Keyword: Cardiovascular disease, Hereditary fructose intolerance, Nonalcoholic fatty liver disease

Outcome measures

Primary outcome

- Degree of hepatic fat accumulation in patients with HFI and age, sex and BMI matched controls.

Secondary outcome

- Degree of hepatic fibrosis in patients with HFI and age, sex and BMI matched controls.

- Lactate response to an oral glucose tolerance test in patients with HFI and age, sex and BMI matched controls.

- Changes in fingerpressure during peripheral applanation tonometry in patients with HFI and age, sex and BMI matched controls.

- Changes in skin blood flow during laser doppler flowmetry in patients with HFI and age, sex and BMI matched controls.

- Carotid-femoral pulse wave velocity in patients with HFI and age, sex and BMI matched controls.

- Plasma hepatokines in patients with HFI and age, sex and BMI matched controls, patients with glycogen storage disease 1a (GSD1a) and familial hypobetalipoproteinemia (FHBL).

- Plasma lipids, biomarkers of low-grade inflammation and biomarkers of endothelial function in patients with HFI and age, sex and BMI matched controls, patients with GSD1a and FHBL.

- Fat distribution (visceral and subcutaneous fat) in patients with HFI and

age, sex and BMI matched controls.

- 24 hours urinary fructose in patients with HFI and age, sex and BMI matched

controls.

Study description

Background summary

Improved treatment strategies for inborn errors of metabolism (IEM) have resulted in better survival of many patients. However, longer lifespan also confronts patients and physicians with new complications of IEM that were not known before, simply due to the fact that patients succumbed before these complications could develop. This demands a thorough long-term follow-up of the natural history of all patients with IEM.

Hereditary fructose intolerance (HFI) is an inborn error of fructose metabolism as a consequence of a defect in Aldolase B. Ingestion of fructose can result in gastrointestinal discomfort, hypoglycaemia and liver/renal failure. These adverse reactions can be avoided by the adherence to a complete fructose restricted diet through which HFI patients can live a relatively normal life. Long-term follow-up of HFI patients, however, strongly suggests that patients with HFI develop nonalcoholic fatty liver disease (NAFLD) despite fructose restriction.

NAFLD is a liver condition that is characterized by a histological spectrum ranging from simple steatosis, to hepatitis, fibrosis and cirrhosis that can eventually lead to end-stage liver failure and hepatocellular carcinoma. Moreover, scientific evidence is accumulating that NAFLD is a cardiovascular risk factor per se. Accumulation of fat in the liver (i.e. simple steatosis) results from increased flux of free fatty acids from adipose tissue or de novo lipogenesis, or decreased secretion of VLDL particles or beta-oxidation. NAFLD is frequently observed in obese subjects, as a consequence of sedentary lifestyle and unhealthy dietary habits, such as consumption of fructose enriched food products, which induce hepatic de novo lipogenesis.

Why then do patients with HFI * whose diet is devoid of lipogenic fructose * develop NAFLD as well? We postulate that the susceptibility to develop NAFLD in patients with HFI is caused by a continuous activation of hepatic glucokinase by fructose-1-phosphate.

There is always endogenous production of fructose from glucose through the polyol pathway. The accumulated fructose-1-phosphate (as a consequence of Aldolase B deficiency in HFI) acts as a strong disruptor of the binding between glucokinase regulatory protein and glucokinase, which causes glucokinase to facilitate the conversion of glucose to glucose-6-phosphate. Increased glucose-6-phosphate can have different fates. In the postprandial state it is mainly stored as glycogen or converted to fatty acids and stored as fat accounting for NAFLD.

Of interest, genetic studies have shown that this complex is relevant in the development of NAFLD, since carriers of a missense variant in GCKR (that encodes for a GKRP protein that binds glucokinase less effectively) are prone to develop NAFLD.

Thus, increased de novo lipogenesis appears to be responsible for the development of NAFLD in HFI. However, to study this research question/hypothesis, expensive complex stable isotope studies are required. We believe that measurement of plasma hepatokines might provide an alternative. Hepatokines are proteins that are released by the liver into the systemic circulation and are known to affect metabolic processes. If hepatokines are measured in patients with HFI and subsequently compared with patients with NAFLD of which the metabolic pathway has been elucidated, such as glycogen storage disease type 1a (de novo lipogenesis) and familial hypobetalipoproteinemia (impaired VLDL secretion), then the patterns will provide more information of the metabolic pathways in HFI.

Study objective

Based on the gaps in our knowledge (as stated above), we have formulated the following objectives:

- To quantify the degree of hepatic fat accumulation and fibrosis in patients with HFI.
- To gain more insight in the mechanism leading to NAFLD in patients with HFI
- To study the cardiovascular risk profile of patients with HFI.

Study design

This will be an observational study with a cross-scetional design.

This study will focus on the long term consequences of HFI.

For this, the following measurements will take place:

- Magnetic resonance spectroscopy of the liver, to quantify the degree of hepatic fat accumulation.

- Fibroscan of the liver, to quantify the degree of liver fibrosis.
- Oral glucose tolerance test, to gain more insight in the mechanism responsible for the development of NAFLD.
- Peripheral applanation tonometry and laser doppler flowmetry (as measure for endothelial function), and carotid-femoral pulse wave velocity (as measure for arterial stiffness) to study the cardiovascular effects of NAFLD.
- Blood withdrawal (hepatokine level, to gain more insight in the mechanism responsible for the development of NAFLD and biomarkers of inflammation and endothelial function, to study the cardiovascular effects of NAFLD).

Study burden and risks

The risks of this study are minimal, since no interventions are imposed. The only invasive test is blood withdrawal, which is associated with minimal health risk.

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

Age * 18 years
Diagnosis HFI (with the exception of the control groups)

Exclusion criteria

Inability to give informed consent
Contraindications for MRS (i.e. claustrophobia, heart pacemaker or other electronic appliances implanted in the body, history of collapse or seizures, or pregnancy < 12 weeks)

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):	06-07-2016
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	25-04-2016
Application type:	First submission
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
CCMO	NL55849.068.16

Study results

Date completed:	05-02-2018
Actual enrolment:	30