The effect of consecutive fecal microbiota transplantation on Non-Alcoholic Fatty Liver Disease (NAFLD) - a randomized-controlled trial -

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

Summary

ID

NL-OMON48776

Source
ToetsingOnline

Brief title
NAFLD and Fecal microbiota Transplantation (the NAFTx study)

Condition

- Hepatic and hepatobiliary disorders
- Lipid metabolism disorders

Synonym
hepatic fat accumulation, Non-Alcoholic Fatty Liver Disease (NAFLD)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Vendanta

Intervention

Keyword: fecal microbiota transplantation, liver steatosis, microbiota, NAFLD

Outcome measures

Primary outcome

Prior to randomization, and at 12 weeks, patients will undergo LiverMultiscan

to non-invasively quantify liver fat accumulation and other features of NAFLD.

Secondary outcome

Secondary objectives are weight, waist, blood pressure, metabolic parameters

(including glucose, cholesterol, pancreatic beta-cell function, HOMA-IR),

liver enzymes, gut-microbiota, bile composition, objective and subjective

stress. Stool samples will be collected for microbiota analysis at time point

0, 3, 6 and 12 weeks.

Study description

Background summary

Nonalcoholic fatty liver disease (NAFLD) is a disease of alarmingly increasing prevalence, linked to metabolic, cardiovascular and malignant morbidity and without any officially approved treatment. It is considered to be more than a single entity, since it compasses a range of phenotypes, starting from nonalcoholic simple steatosis, in which the predominant histological characteristic is lipid accumulation in the hepatocytes, to nonalcoholic steatohepatitis (NASH), characterized by the addition of hepatic inflammation and/or fibrosis, and NASH-related cirrhosis and hepatocellular carcinoma. Abdominal, particularly visceral, obesity leading to insulin resistance is strongly associated NAFLD, both via increased delivery of free fatty acids to the liver and through increases of hepatic lipogenesis associated with

hyperglycemia and hyperinsulinemia.
It is increasingly recognized that the gut microbiome is implicated in the pathogenesis and progression of numerous chronic diseases, including NAFLD. Through the so-called gut-liver axis, the liver is exposed to gut-bacterial-derived products, including toxins (lipopolysaccharides), enzymes (methylamines), alcohol, and short-chain fatty acids (mainly acetate, propionate, and butyrate), that may lead to accumulation of triglycerides, inflammatory responses, oxidative stress and accompanying damage to the hepatocytes.
Previously, an obese microbiome has been demonstrated in mice models, which has an increased capacity to harvest energy from the diet. Moreover, this obesity trait is transmissible, as colonization of germ-free mice with the *obese microbiome* results in a significantly greater increase in total body fat than colonization with a *lean microbiome*. Interestingly, this concept has been tested in humans recently, showing similar findings. Although weight loss could not be proven, fecal microbiota transplantation (FMT) of lean males to obese males resulted in improved hepatic insulin sensitivity.

Study objective

The primary objective is to study the effect on consecutive FMT on liver fat accumulation measured by Magnetic Resonance Images (MRI) LiverMultiscan at 12 weeks. Secondary objectives are weight, waist, blood pressure, metabolic parameters (including glucose, cholesterol, pancreatic beta-cell function, HOMA-IR), gut-microbiota and bile composition, objective and subjective stress, and liver enzymes. Stool samples will be collected for microbiota analysis at time point 0, 3, 6 and 12 weeks.

Study design

Single center double-blind randomized placebo-controlled pilot study.

Intervention

Patients will be randomized for infusion of allogenic (lean donor) or autologous (own) feces through a nasoduodenal tube at time points 0, 3 and 6 weeks.

Study burden and risks

Nonalcoholic fatty liver disease (NAFLD) has been recognized as a global public health problem, affecting 6-45% of the general population, rising up to 70% in patients with type 2 diabetes mellitus (T2DM) and 90% in morbidity obese patients. It is considered to be more than a single entity, since it compasses a range of phenotypes, starting from non-alcoholic simple steatosis, in which the predominant histological characteristic is lipid accumulation in the

hepatocytes, to nonalcoholic steatohepatitis (NASH), characterized by the addition of hepatic inflammation and/or fibrosis, and NASH-related cirrhosis and hepatocellular carcinoma (HCC). At present, NAFLD is among the leading causes of liver cirrhosis, HCC and liver transplantation. Multiple factors (*hits*) contribute to the pathogenesis of NAFLD, considered to be a multiple-hit disorder. Abdominal, particularly visceral, obesity leading to insulin resistance is strongly associated NAFLD, both via increased delivery of free fatty acids to the liver and through increases of hepatic lipogenesis associated with hyperglycemia and hyperinsulinemia. Other pathogenetic factors are divided into those with an established association with NAFLD, including genetic [e.g. polymorphism of patatine-like phospholipase domain-containing protein 3 (PNPLA3) gene, dietary factors (e.g., fructose), and adipokines, as well as those with a potential association needing validation, including endocrine disruptors and dysbiosis of the gut microbiota. Although it is a disease of alarmingly increasing prevalence, linked to metabolic, cardiovascular and malignant morbidity, NAFLD is at present without any officially approved treatment.

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

- Obese (BMI > 27 kg/m2)
- Males and postmenopausal females
- Aged 18 to 70 years
- Hepatic steatosis defined as increased hyperechogenicity of the liver on abdominal ultrasound and/or histological signs of steatosis
- Written informed consent

Exclusion criteria

- Exclusion criteria for MRI (claustrophobia, pacemaker, metal implants, etc)
- Any other liver disease than NAFLD/NASH
- Present excessive alcohol use defined as > 2 units/day
- Recent use (< 3 months) of antibiotics
- use of possible drugs interfering microbiota or recent (< 3 months) changes in dosages
- Recent (< 3 months) weight change (>5%)
- Cardiovascular co-morbidity defined as heart failure, coronary insufficiency and hypertension in past history
- Previous use of glucocorticosteroids, hormonal substitution, pagitaxel, theofyllin, amiodarone, myelosuppresive agents.
- A psychiatric, addictive or any other disorder that compromises the subjects ability to understand the study content and to give written informed consent for participation in the study

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-12-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	22-07-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-02-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
Other	ClinicalTrials.gov
CCMO	NL66705.058.18