Effect of Multiple healthy donor intestinal microbiota infusions on non Alcoholic Steatosis Hepatis (NASH) and vascular function in obese subjects

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine and glandular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON44842

Source
ToetsingOnline

Brief title
MASH study

Condition

- Endocrine and glandular disorders NEC
- Hepatic and hepatobiliary disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
non alcoholic hepatic steatosis (NASH), Non-alcoholic fatty liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: CVON-Nederlandse Hartstichting 2012

Intervention

Keyword: Fecal transplantation, Gut microbiota, inflammation, NASH/NAFLD

Outcome measures

Primary outcome

Effect op NAFLD/NASH:

- Primary outcome is reducting in hepatic steatosis without worsening of

fibrosis as determined by liverbiopsy (Bruntclassification) and liver MRI after

6 months

Secondary outcome

- Changes in bacerial composition of small intestine, large intestine and liver

- Changes in vascular function (normalized wall index en mean wall thickness as

measured with 3T MRI of the carotid artery

- Changes in inflammatory tone (plasma TMAO/betaine and TNFalfa/CD68 expression

on monocyte and in subcutanous adipose tissue)

Study description

Background summary

Non alcoholic fatty liver disease (NAFLD) is intricately related to obesity, insulin resistentance and dyslipidemia. The worldwide prevalence of this disease is increasing at a rapid pace. When NAFLD progresses into non alcoholic steatohepatitis (NASH) it is strongly associated with increased cardiovascular disease risk as well as that it can lead to livercirrhosis and subsequent livercancer. It is expected that within 20 years this will be the number 1 reason for orthotopic livertransplantation. Despite several efforts, there is

no effective treatment option for NASH .

Recent animal and human data have implicated that the intestinal microbiota may play an important rol in the development of NAFLD/NASHas well obesity thus implying a potential therapeutic treatment target. Underlying mechanisms including translocation of (small) intestinal bacterial strains that are transported via the blood to the lever and there cause chronic inflammation resulting in NASH. Earlier research from our group has shown that fecal transplantation using a lean donor (allogeneic fecaltransplant cures clostridium difficile associated diarrhea and reduces chronic inflammation and insulin resistance in obese subjects . Using an algorithm to calculate NASH in obese subjects treated with allogeneic fecal transplantation showed a significant reduction in NASH upon treatment .We thus hypothesize that repetitive fecal transplantation can normalize (small) intestinal bacterial composition therefore reducing bacterial translocation and thus inflammation. This could provide us with novel therapeutic targets (bacterial strains) to treat NASH.

Study objective

In this study we would like to investigate whether repetitive allogeneic (lean donor) fecal transplantations can reduce liversteatosis and if so which (small) intestinal bacteria cause this inflammation in the liver resulting in subsequent chronic inflammation and vascular dysfunction.

Study design

This is a double blind single center randomized controlled trial.

Patients will be randomized to the following 2 treatment arms:
1. three allogenic (lean donor) fecal transplantations (at baseline, 8 and 16 weeks)
2. three autologous (own) fecal transplantations (at baseline, 8 and 16 weeks)

Intervention

Patients will be treated with infusion of either allogenic or autologous microbial transplantion by duodenal tube after bowel lavage.

Fecal transplantation therapy (week 0, 8 and 16 weeks) consists of:
1. Morning stool sample is collected by recipient & donor and handed over to study phycisian in the AMC for processing
2. Meanwhile, gastroduodenoscopy (0 en 6 months including biopsies) or Coretrack at 2 en 4 months) positioning of the duodenal tube will be performed, including an abdominal X-ray(only at 0. and 6 months) to ensure the intraduodenal position of the tube.

4. Thereafter, bowel lavage with 2-3 liters of Klean-prep (macrogol/electrolytes) through the duodenal tube (according to standard protocols) will be performed to ensure complete bowel lavage (duration 3-4 hours)
5. Finally, allogenic or autologous feces mixed in ~ 500 cc saline (filtered, < 2 hours after processing) will be infused in the duodenum through positioned duodenal tube.

Study burden and risks

in the last 5 years we have performed over 200 fecal transplantations at the AMC in several patientgroups without seeing any short/long term complications . Although in theory there is always the risk of transferring (unknown) infectious diseases (just like with bloodtransfusions), however using a thorough donor screening protocol can minize this risk. Risk of complications during gastroduodenoscopy and liver biopsy is low (<0.01%). There is currently no effective treatment for NASH and this disease is strongly associated with increased cardiovascular disease as well as cirrhosis and livercancer, Since at the one hand animal studies have implicated translocation of intestinal microbiota in the developement of NASH and on the other we have shown beneficial metabolic effect of fecal transplantation in human obese subjects , we hypothesize that this study can provide us with pathophysiological mechanisms leading to a potential treatment for NASH We therefore think that the data from this study are very important to understand and treat NASH in the future that they outweight the intermediate risk of participating in this study

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Recipients:
- Caucasian
- Male or postmenopausal female
- Aged 21-69 years
- Scheduled for liver biopsy on clinical indication (suspicion of NASH)
- No concomitant medication;Donors
- Male / postmenopausal female
- Lean (BMI 20-25 kg/m2)
- Aged 21-69 years
- No concomittant medication

Exclusion criteria

Recipients:
- Cardiovascular disease
- Cholecystectomy
- Use of any concomittant medication including PPI , oral anticonceptivesand antibiotics in the past three months
- Plasma ALAT / ASAT > 2.5 times the upper limit of normal
- Other causes of liver disease besides NAFLD/NASH (e.g. hemachromatosis, auto-immune hepatitis, viral hepatitis, alcoholic steatohepatitis).
- History of heavy alcohol use (>12 to 15 gram / day).
- Renal disease (creatinin clearance < 60 ml/min)
- Fasting glucose > 13.3 mmol/l
- History of anaphylaxis, known allergy for gadolinium of other contrast agents, or other contra-indication for the use of gadolinium;Donors:
- Diarrhea

- Cholecystectomy
- Unsafe sex practice
- Any medication use including PPI, oral anticonceptives and antibiotics in the past three months
- Serological presence of HIV, hepatitis A, B and/or C, active cytomegalovirus (CMV), active Eppstein-Barr virus (EBV), lues, amoebiasis or strongyloides
- Presence of fecal bacterial pathogens (Salmonella, Shigella, Campylobacter, Yersinia, enteropathogenic E. coli), transmittable viruses (Rotavirus, Norovirus, enterovirus, parechovirus, sapovirus, adenovirus 40/41/52, astrovirus) or parasites
- Positive C. difficile stool test
- Individuals with an increased risk for one of the above conditions (e.g. homosexual contacts, recent blood transfusions) will be excluded.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-04-2014
Enrollment:	81
Type:	Actual

Ethics review

Approved WMO

Date:	08-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	29-05-2015
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	NL45172.018.13