Role of bacterioPhages In gut Microbiome composition and glucose metabolism in Metabolic Syndrome subjects

Published: 26-10-2018
Last updated: 12-04-2024

Primary objective: to assess and compare the effect of lean-donor phage transplantation with placebo treatment (PBS) on glucose tolerance in obese, insulin resistant subjects at risk to develop diabetes. Secondary objective: to assess and compare...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON48768

Source
ToetsingOnline

Brief title
PIMMS

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
insulin resistance, metabolic syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW/Diabetes Fonds Grant (Doorbraakprojecten) 2018 aan Hilde Herrema

Intervention

Keyword: bacteriophages, glucose metabolism, Gut microbiome

Outcome measures

Primary outcome

To assess and compare the effect of lean-donor phage transplantation with placebo on glucose tolerance in obese, insulin resistant subjects at risk to develop diabetes. HbA1c, fasted glucose and insulin levels will be determined at baseline and 28days after the intervention (prior to the OGTTs). Area under the curve for glucose excursion during OGTTs will be the primary determinant of changes in glucose metabolism following the transplantations. Furthermore, insulin sensitivity will be estimated from the OGTT by oral glucose insulin sensitivity (OGIS) methodology. In addition, HOMA-IR and Matsuda index will be calculated as secondary readouts for insulin sensitivity.

Secondary outcome

To assess and compare changes in gut microbiota and phage composition following phage transplantation and placebo. In addition, microbiota and virome composition at baseline will be determined and compared between lean donors and obese recipients.

Bacterial and phage composition will be assessed by 16S rRNA analysis and

NanoPore technology, resp., in fecal samples of donors and recipients.

Study description

Background summary

Alterations in gut microbiota composition and bacterial metabolites have been increasingly recognized to affect host metabolism and are at the basis of metabolic diseases such as obesity and type 2 diabetes (T2DM). As shown by our group, modulation of the gut microbial composition by fecal microbiota transplantation (FMT) improves insulin sensitivity in insulin resistant subjects at risk to develop T2DM. Importantly, however, the effect of FMT is transient and effect size differs strongly between subjects. We have shown that subjects with lower diversity at baseline are more likely to benefit from donor FMT than subjects with higher bacterial diversity. In addition, the level of engraftment of the transplant (i.e., presence of donor bacterial composition in gut of recipient) might determine in part the efficacy of this procedure. Factors that determine gut microbiota diversity and engraftment after FMT and subsequent effects on glucose metabolism are largely unexplored. Bacteriophages (phages) are viruses that exclusively infect and eliminate bacteria. There is substantial evidence for a role of phages in shaping microbial communities in many ecosystems. However, insight in and attention for the role of phages in the human gut microbial community is limited. The effect of interventions that have significant consequences for both bacteria and phage communities, such as FMT, have never been assessed. Since one gram of feces contains ~109 phage-containing particles and ~109 bacterial cells, a vast number of phages are co-transplanted during FMT. The contribution of phages to FMT success (improved glucose metabolism) might therefore be quite substantial but has thus far never been studied. We therefore here propose a study in which we will transfer fecal bacteriophages from lean, healthy subjects to the gut of obese, insulin resistant subjects and assess the effect on engraftment and glucose metabolism.

Hypothesis: We speculate that the virome composition of the lean donor and the subsequent interaction between phages and bacteria in the recipients are crucial determinants of stability and diversity of gut bacterial composition and glucose metabolism in humans after FMT. We hypothesize that lean donor phage transplantation will increase gut microbial diversity and improves glucose handling in insulin resistant recipients at risk to develop T2DM.

Study objective

Primary objective: to assess and compare the effect of lean-donor phage transplantation with placebo treatment (PBS) on glucose tolerance in obese,

insulin resistant subjects at risk to develop diabetes.
Secondary objective: to assess and compare changes in gut microbiota and phage composition following phage transplantation and placebo.

Study design

Prospective, double-blinded, randomised, single-center intervention study.
N=24 metabolic syndrome subjects will be randomised in the placebo arm (N=12) or the phage arm (N=12) of the study.

Healthy lean males will be phage donors

Intervention

Twelve MetSyn subjects will receive PBS (placebo) whereas another group of twelve MetSyn subjects will receive a fecal filtrate transplant (FFT), which lacks bacteria and mainly consists of phages.

1. morning stool sample is collected by recipient and donor
2. randomisation of participant in placebo or phage arm of the study
3. gastroduodenoscopy will be performed to place the duodenal tube. A abdominal Xray will be performed to check for correct placement of the tube.
4. Bowel lavage (2-3liters of KleanPrep) will be performed to Ensure bowel lavage (2-3hrs)
5. Phage or placebo transplant will be prepared and administered through the duodenal tube (500ml).

Study burden and risks

Duration of the study is 7weks during which participants will visit the AMC three times. Participants will spend 12hours in total during this time and around 180ml of blood will be drawn.

Oral glucose tolerance test: no risk
Intravenous cannula: there is a low risk of flebitis at the intravenous injection sites, this is unpleasant, but not harmful, of temporary nature and self-limiting
Abdominal Xray: participants will undergo radiation exposure of 0.7mSv. This has negligible risk.
Phage transplantation: phages are present in the fecal microbiota transplant as we perform them regularly. The risk associated with phage transplantation is therefore considered similar and minimal due to extensive donor screening. In the past decade, around 600 fecal transplant have been performed and no short- or long-term complications were obeserved.
Gastroscopy: the risk of bleeding of perforation during gastroscopy is

considered small. The placing of the duodenal tube can unpleasant but there are no risks involved.
Discomfort: placing of cannula, blood draw and placing of nasoduodenal tube can be experienced as uncomfortable.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Participants:
• Caucasian male/female
• Age: >=18 years old
• BMI: >=25 kg/m2
• At least 3 of the following criteria:
o Fasting plasma glucose >=5.6 mmol/L OR HOMA-IR index >=2.5

o Waist-circumference >=102 cm
o HDL cholesterol <=1.02 mmol/L
o Blood pressure >=130/85 mmHg
o Triglycerides >=1.7 mmol/L
• Subjects should be able to give informed consent

Donors:
• Caucasian male/female
• Age: >18 years old
• BMI: 18-25 kg/m2
• Subjects should be able to give informed consent

Exclusion criteria

Participants:
• A history of cardiovascular event (cerebrovascular accident (CVA), myocardial infarction (MI)) or pacemaker implantation
• Use of any medication including proton pump inhibitors, antibiotics and pro-/prebiotics in the past three months or during the study period
• (Expected) prolonged compromised immunity (due to recent cytotoxic chemotherapy or human immunodeficiency viruses (HIV) infection with a CD4 count < 240/mm3)
• Presence of overt type 1 diabetes mellitus (T1DM) or T2D
• History of chronic diarrhoea (>=3 stools/day for >4 weeks), chronic obstipation (<2 defecations/week for >3 months), Irritable Bowel Syndrome (IBS) (according to Rome IV criteria) or Inflammatory Bowel Disease (IBD).
• Smoking or illicit drug use (MDMA/amphetamine/cocaine/heroin/GHB) in the past three months or use during the study period
• Use of >5 units of alcohol daily on average in the past three months or use of >2 units of alcohol during the study period
• History of cholecystectomy

Donors:
• Use of any medication including proton pump inhibitors, antibiotics and pro-/prebiotics in the past three months or during the study period
• History of, or known exposure to HIV, hepatitis B (HBV) or C virus (HCV), syphilis, human T-lymphotropic virus (HTLV) I and II, malaria, trypanosomiasis, tuberculosis
• Known systemic infection not controlled at the time of donation
• Smoking or illicit drug use (MDMA/amphetamine/cocaine/heroin/GHB) in the past three months or use during the study period
• Use of >5 units of alcohol daily on average in the past three months or use of >2 units of alcohol during the study period
• Risky sexual behaviour (anonymous sexual contacts; sexual contacts with prostitutes, drug addicts, individuals with HIV, viral hepatitis, syphilis;

work as prostitute; history of sexually transmittable disease)
• Previous reception of tissue/organ transplant
• Previous (<12 months) reception of blood products
• Recent (<6 months) needle stick accident
• Recent (<6 months) body tattoo, piercing, earring, acupuncture
• Recent medical treatment in poorly hygienic conditions
• Risk of transmission of diseases caused by prions
• Recent parasitosis or infection from rotavirus, Giardia lamblia and other microbes with GI involvement
• Recent (<6 months) travel in tropical countries, countries at high risk of communicable diseases or traveller's diarrhoea
• Recent (<6 months) history of vaccination with a live attenuated virus, if there is a possible risk of transmission
• Healthcare providers having frequent patient contact (to exclude the risk of transmission of multidrug-resistant organisms)
• Individual working with animals (to exclude the risk of transmission of zoonotic infections)
• History of IBS (according to Rome IV criteria), IBD, functional chronic constipation, coeliac disease, other chronic GI disorders
• History of chronic, systemic autoimmune disorders with GI involvement
• History of, or high risk for, GI cancer or polyposis
• Recent appearance of diarrhoea (>=3 stools/day), hematochezia
• History of neurological/neurodegenerative disorders
• History of psychiatric conditions
• Presence of chronic low grade inflammation or metabolic syndrome (NCEP criteria)
• Presence of T1DM, T2DM or hypertension
• History of cholecystectomy
• Positive serologic test for HIV 1/2, hepatitis A virus (HAV), HBV, HCV, hepatitis E virus (HEV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV), strongyloides or lues
• Presence of faecal bacterial pathogens Salmonella spp., Shigella spp., Campylobacter spp., Yersinia spp., C. difficile, H. pylori, shigatoxigenic Escherichia coli (STEC), Aeromonas spp. or Pleisiomonas Shigelloides in faeces.
• Positive Dual Faeces Test (DFT) for Giardia Lamblia, Dientamoeb fragilis, Entamoeba histolytica, Microsporidium spp., Cryptosporidium spp., Cyclospora, Isospora or Blastocystis Hominis. Positive microscopic exam for eggs, cysts and larves (e.g. helminth eggs)
• Presence of extended spectrum beta-lactamase (ESBL) producers, carbapenemase-producing Enterobacteriaceae (CPE), vancomycin-resistant enterococci (VRE) or methicillin-resistant Staphylococcus aureus (MRSA) in faeces
• Presence of Rotavirus, Norovirus I/II, Enterovirus, Parechovirus, Astrovirus, Sapovirus or Adenovirus in faeces
• Abnormal liver or renal function (creatinine >110 µmol/l, ureum >8,2 mmol/l, ASAT >40 U/L, ALAT >45 U/L, AF >120 U/L, GGT >60 U/L, bilirubin >17µmol/L) or impaired immunity (CRP >5 mg/L, haemoglobin <8,5 mmol/L, MCV 80-100 fL,

leukocytes 4,0-10,5 x109/L, thrombocytes 150-400 x109/L).

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):	31-07-2019
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO Date:	26-10-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2020
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	NL67136.018.18