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

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26916

Source
Nationaal Trial Register

Brief title
PIMMS

Health condition

Metabolic Syndrome; insulin resistance

Sponsors and support

Primary sponsor: Investigator initiated
Source(s) of monetary or material Support: Diabetes II Breakthrough grant (Diabetes Fonds & ZonMW)

Intervention

Outcome measures

Primary outcome

To assess and compare the effect of lean-donor phage transplantation with placebo treatment (saline) on glucose tolerance (via an OGTT) in obese, insulin resistant subjects at risk to develop diabetes.

Secondary outcome

To assess and compare changes in gut microbiota and phage composition following phage transplantation and placebo:
• An overview of the dynamic changes in gut microbiota and virome population following phage transplantation compared to placebo.
• A comparison between phage composition in individuals at risk to develop T2DM at baseline with phage composition in lean, healthy subjects (donors).

Study description

Background summary

Rationale
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 faecal 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 faeces 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 faecal 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.

Objective
• Primary objective: to assess and compare the effect of lean-donor phage transplantation with placebo treatment (saline) 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.

Study population
Male overweight, metabolic syndrome (MetSyn) subjects (N=24, ≥18 years old, BMI ≥ 25 kg/m2, treatment naive.)

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

Main study parameters/endpoints
• An approximation of the potential of lean-donor phage transplantation to modify gut microbiota composition and improve glucose metabolism in individuals at risk to develop T2DM
• An overview of the dynamic changes in gut microbiota and virome population following phage transplantation compared to placebo.
• A comparison between phage composition in individuals at risk to develop T2DM at baseline with phage composition in lean, healthy subjects (donors).

Study objective

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 design

Visits to the AMC: screening and inclusion, visit 1 (day 0) and visit 2 (day 28);
Collection of fecal samples: day -7, 0, 2, 4, 7, 14, 28, 42

Continuous glucose monitoring: from dag -7 to day 7
Dietary diary: from dag -7 to day 7
OGTT: during visit 1 (day 0) and visit 2 (day 28)
FFT or placebo: during visit 1 (day 0)

Intervention

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

Contacts

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Eligibility criteria

Inclusion criteria

• 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 (HOMA-IR is measured as (fasting insulin (pmol/L) x fasting glucose (mmol/L)) / 135)
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

Exclusion criteria

• 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

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-07-2019
Enrollment:	24
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	15-01-2020
Application type:	First submission

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
NTR-new	NL8289
Other	METC AMC : METC 2018_231, NL67136.018.18

Study results