Effect of duodenal infusion of Eubacterium Hallii on gene expression, postprandial metabolites and glucose metabolism in males with metabolic syndrome

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In this randomised, double-blind, placebo-controlled cross-over single centre study we propose to study the effect of duodenal infusion of single E. Hallii treatment of 10 ml 10E9/ml in 10% glycerol or 10ml 10 % glycerol (administered via duodenal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON48576

Source
ToetsingOnline

Brief title
EDIE trial

Condition

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

Synonym
metabool syndroom

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: E Hallii, Glucose metabolism metabolic syndrome, gut microbiome

Outcome measures

Primary outcome

The primary endpoint is efficacy (changes in duodenal E. Hallii levels and gene expression (including FXR) 6 hours following single duodenal infusion of 10 ml E. Hallii.

Secondary outcome

Secondary endpoints are (short/longterm) effects of E hallii on glucose metabolism/insulin sensitivity using either 2 uur MMT (Nutridrink) or 7 days continuous glucose measurement (Free Style libre glucose sensor) in relation to changes of E. Hallii and other microbiota in fecal samples collected at baseline, during week 1 and week 4. Dietary intake will be monitored during the course of the study.

Study description

Background summary

Also see page 5, 6, 7, 8 of the protocol.
Due to recently developed high-throughput metagenomic sequencing by 16S rRNA , more knowlegde has been acquired on the role of the (small) intestinal microbiota in the pathofysiologie of metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM) . Based on our earlier lean donor fecal transplantation studies (Vrieze Gastroenterology 2012) , we found that E. hallii bacteria were increased in the small intestine of insulin resistant

subjects which was associated with an improvement in insulin sensitivity (Rd) as determined by clamp. Eubacterium hallii type stam L2-7 was thus HACCP produced at NIZO for human use as it is unique in its capacity to produce butyrate from lactate (which is 10 fold increased in the gut of T2D patients) In our recent pilot study we studied the effect of different E. hallii doses on insulin sensitivity in 27 patients with metabolic syndrome (DIME study, METC 2014_285). We found that daily oral treatment during 4 wks with E hallii was safe and had no side effects. However, the effect on Rd/insulin sensitivity was differential, and although we saw no overall significant effect in all groups, we found that subgroups of patiënts upon E. Hallii did show a response (as defined by insulin sensitivity increase Rd>10%), low dose (10e5/ml E hallii per day): 2 out of 9 subjects , middle dose(10e7/ml Ehallii per day): 4 out of 9 subjects and highest dose (10e9/ml Ehallii per day): 5 out of 9 responders. We thus postulate that in some subjects E. Hallii cannot pass the stomach and thus cannot engraft in the (small) intestinal microbiota and thus not improve metabolism. In this study we therefore aim to test the maximal effect of E. Hallii suspension in males with metabolic syndrome by infusing it at the high dosage, which was tested to be safe and most effective in humans in the DIME trial, via a duodenal tube, making sure it passes the stomach unscathed. Following duodenal infusion of E. Hallii we will obtain duodenal biopsies 6h later, as previously described . Furthermore, we will test the efficacy of the E Hallii suspension on short / long term glucose metabolism by subjecting the subjects to a 2h mixed meal test as well as 7 dgn measurement of glucose levels (CMG by Free Style Libre)

Study objective

In this randomised, double-blind, placebo-controlled cross-over single centre study we propose to study the effect of duodenal infusion of single E. Hallii treatment of 10 ml 10E9/ml in 10% glycerol or 10ml 10 % glycerol (administered via duodenal tube) on gene expression, bacterial composition and short/long term glucose metabolism in subjects with metabolic syndrome.

Study design

Subjects will be given duodenal infusion of 10 ml E. Hallii suspension 10E9/ml in 10% glycerol or 10ml 10 % glycerol . After 6 hours duodenal biopsies will be taken via gastroduodenoscopy, followed by a mixed meal test (2h) as well as CGM by free style libre for short/long term monitoring of glucose metaboism/ insulin sensitivity. After 4 weeks the above will be repeated with either E. Hallii suspension or placebo.

Intervention

Subjects will be given duodenal infusion of 10 ml E. Hallii 10E9/ml suspension

in glycerol or placebo (10 ml of glycerol alone).

Study burden and risks

There will be 2 studyvisits. Both will take about 9h. During them a Cortrak procedure is performed for tube placement and 6h later followed by a gastroduodenoscopy with duodenal biopsies, followed by a mixed meal test taking an additional 2h. Then a continuous glucose sensor (Free style libre) will a fixed on the upper arm of the patient for 7 days measurement.A gastroduodenoscopy is performed for small intestinal biopsies; this is a very frequently performed intervention at our department of Gastroenterology clinic with a very low (<0.1%) complication rate.E. Hallii treatment from the same Batch has been given in our previous study, the DIME trial. No adverse events were expected and none did.

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

- Caucasian males
- 21 to 69 years-old
- body mass index (BMI) 25 to 43 kg/m2
- At least 3 out of 5 NCEP metabolic syndrome criteria: fasting plasma glucose >= 5.6 mmol/l and/or HOMA-IR >= 2.5, triglycerides >= 1.6 mmol/l, waist-circumference > 102 cm HDL-cholesterol <= 1.04 mmol/l, blood pressure >= 130/85 mmHg

Exclusion criteria

A history of cardiovascular event (myocardial infarction or pacemaker implantation), smoking, cholecystectomy, use of any medication including proton pump inhibitors (PPI as this influences intestinal microbiota composition see ref 3), oral anticoagulants and/or oral antibiotics in the past three months, (expected) prolonged compromised immunity (e.g. due to recent cytotoxic chemotherapy or HIV-infection with a CD4 count < 240). Subjects are also excluded if they have experienced excessive weightloss of >10% in the last months or have overt untreated GI disease/abnormal bowelhabits; moreover, if their levels of plasma aspartate aminotransferase and alanine aminotransferase are 2.5 times or more the upper limit of the normal range; if they have a history of heavy alcohol use (>12 to 15 g of alcohol per day, or >12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits); or overt Dm2.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-01-2018
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	12-10-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2018
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	NL62312.018.17