Dosefinding trial studying effect of 4 weeks Intervention on safety and efficacy in males with Metabolic syndrome treated with oral Eubacterium hallii

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To investigate different dosages of 4 weeks oral Eubacterium hallii treatment on safety and efficacy parameters.

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

Summary

ID

NL-OMON44478

Source
ToetsingOnline

Brief title
DIME

Condition

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

Synonym
Metabolic syndrome

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 and lipid metabolism, Gut microbiota, liverfat

Outcome measures

Primary outcome

The primary endpoint is safety (plasma biochemistry eg hepatic /inflammatory/cholesterol markers) in relation to efficacy (changes in fecal E. hallii levels and insulin sensitivity as assessed by hyperinsulinemic clamp using [6,6 2H2]-glucose and [1,1,2,3,3]-2H5-glycerol infusion) between baseline and 4 weeks of treatment.

Secondary outcome

Secondary endpoints include daily dietary intake and quality of life and bowel habits (monitored using standardized questionnaires) as well as intestinal microbiota composition (including fecal E. hallii) in fecal samples at 1, 2, 4 weeks after treatment. Moreover, effects on bile acid metabolism in 24h feces and hepatic MRI (for liverfat content) at baseline and after 4 weeks. Finally, washout of fecal E.hallii will be determined after cessation of therapy at 4 weeks by collecting fecal samples at 5 and 6 weeks.

Study description

Background summary

Also see p. 6, 7, 8 in protocol.
Accumulating data from both patients and animal models indicate that imbalances in the composition of the gut microbiota are related to obesity and its associated diseases. We recently published that lean donor gut microbiota

infusion was associated with an increase of E. hallii concentrations in the (small) intestine, with the increase in E. hallii being directly correlated with improvement in (peripheral) insulin sensitivity ($r=0.7$, $p<0.05$). Eubacterium hallii is a butyrate-producing species, but in contrast to other well-known human isolates such as Roseburia and Faecalibacterium spp. that produce butyrate from sugars, E. hallii has the capacity to produce butyrate from lactate in an acid environment (pH 1-2) as found in the small intestine. This makes it very plausible that this bacterial strain can survive stomach passage while being exposed to low pH values. Moreover, E. hallii has the capability to convert a potentially damaging acid (e.g. lactic acid) into other short chain fatty acid butyrate (which is known to exert beneficial effects on glucose metabolism and liverfat.

To further investigate the safety and efficacy of oral E. hallii L2-7 supplementation, we have performed a 4 week daily oral dose finding study in an animal model of insulin resistance with an E. hallii L2-7 strain DSM 17630. We found that increasing dosage of daily E. hallii treatment at 10e6, 10e8 10e10,cells/ml (100ul of each dose) versus placebo (glycerol 10% solution) was safe and did not induce adverse effects (see product dossier). Moreover we observed a dose dependent effect of E. hallii on improved insulin sensitivity (ITT fig 2a) in correspondence with fecal E. hallii levels (fig 2b) and genes of NASH/NAFLD in these mice (see figure 2c, also in IMPD).
While knowledge regarding the relationship between bacterial species and metabolism in rodent models is rapidly increasing, causality about involved strains of gut microbiota in human metabolism is limited. Thus, in this human phase I/II trial we will try to further expand our knowledge by reproducing these animal data in relation to safety and optimal oral daily dosage of E. hallii treatment on various aspects of metabolism in male subjects with metabolic syndrome. As fecal transplantation studies currently performed at our department render important data on the driving causal pathophysiologic mechanisms driving insulin resistance, its nature precludes widespread clinical use. We thus postulate that insulin sensitivity (normalised gluconeogenesis and improved peripheral/muscle insulin sensitivity) as well as lipolysis can be improved by 4 weeks daily oral treatment with E. hallii via altered bile acid metabolism. As a consequence, liver fat content (NAFLD/NASH on liver MRI) will decrease.

Study objective

To investigate different dosages of 4 weeks oral Eubacterium hallii treatment on safety and efficacy parameters.

Study design

This is a phase II single center open randomized controlled trial in which we will perform dose finding study. Patients will be randomized to the following 3

treatment arms:
1.Once daily treatment with Eubacterium hallii 100 ml at concentration of 10e7 cells/vial for 4 weeks (n=9)
2. Once daily treatment with Eubacterium hallii 100 ml at concentration of 10e9 cells/vial for 4 weeks (n=9)
3. Once daily treatment with Eubacterium hallii 100 ml at concentration of 10e11 cells/vial for 4 weeks (n=9)

Intervention

Subjects will be given 100 ml Eubacterium halli suspension per day for 28 days. Increasing dosages of 10e7, 10e9 and 10e11 cells/ vial(dissolved in total volume of 100ml milk) will be tested (n=9 subjects per dosage). The safety of each dosage will be assessed by vital signs, liverfunction tests before introducing the higher dose. Efficacy will be tested by Eubacterium hallii in feces and effects on insulin sensitivity.

Study burden and risks

Total study duration is 6 weeks with a total time per subject of 18 hours. In total 270ml blood will be sampled during 2 hyperinsulinemic clamps and 5 venapunctures, 5 stool samples collected and two MRIs of the liver performed. Risk assessment is moderate:
- During the hyperinsulinemic clamp there is a risk for hypoglycaemia. This is minimised by close monitoring of plasma glucose levels, every 5-10 minutes.
- Eubacterium Hallii: Considering the effects of a short term intervention with E.Hallii in mice it seems unlikely that patients will suffer any side effects. Possible side effects could theoretically consist of temporary flatulence or stomachache.To ensure complete patient safety, we have chosen to use a single blinded dose finding study design, by which the investigators have full access to clinical efficacy and safety data during increasing dosages of E.hallii.

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

otherwise healthy Caucasian obese subjects with metabolic syndrome (males, aged 21 to 69 years-old; body mass index (BMI) 25 to 43 kg/m2, fasting plasma glucose > 5.6 mmol/l and/or HOMA-IR>2.5, fasting triglycerides > 1.6 mmol/l, waist circumference > 102 cm and not on concomitant medication and regular stool pattern.

Exclusion criteria

A history of cardiovascular event (myocardial infarction or pacemaker implantation), smoking,cholecystectomy, use of medication including proton pump inhibitors (PPI as this influences intestinal microbiota composition), 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 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 phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-12-2014
Enrollment:	27
Type:	Actual

Ethics review

Approved WMO Date:	23-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2016
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	NL50612.018.14