Effect of oral Eubacterium Hallii on postprandial glucose metabolism in males with type 2 diabetes treated with metformin

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to investigate the effect of 14 days once daily oral Eubacterium hallii (E. hallii) treatment on postprandial glucose levels in relation to SCFA levels in feces in patients with type 2 diabetes treated with metformin.

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

Summary

ID

NL-OMON55732

Source
ToetsingOnline

Brief title
EMDM2 trial

Condition

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

Synonym
type 2 diabetes

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, gut microbiome, type 2 diabetes

Outcome measures

Primary outcome

The primary endpoints are (postprandial) glucose excursions determined by a wearable continuous glucose monitor (CGM) during the 14 days of intervention

Secondary outcome

The secondary endpoint is the effect of oral E. hallii treatment on 4-h mixed meal test (changes in plasma metabolites , glucose and lipids) in relation to changes in fecal microbiota composition and plasma/feces SCFA collected at baseline, week 2 and week 4. Also changes in dietary intake will be monitored

Study description

Background summary

The development of culture-independent approaches, using high-throughput metagenomic sequencing via 16S rRNA3, has drastically increased the knowledge of the gut microbiome, now linking any disturbances in it, both in human and animal models, to the pathophysiology of metabolic diseases such as obesity and type 2 diabetes mellitus (T2DM). Transplantation of lean healthy microbiota in subjects with insulin resistance showed an significantly increased insulin sensitivity and an increased abundance of butyrate-producing bacteria in the gut. In this pilot study we identified a specific increase in the butyrate-producer Eubacterium hallii in small intestinal biopsies of human obese and insulin resistant subjects upon lean donor fecal transplantation.We recently published an animal study in which we studied the effect of E. hallii treatment on metabolism in mice. We found that increasing dosage of daily E. hallii treatment was safe and did not induce adverse effects. Moreover we

observed a dose dependent effect of E. hallii on improved insulin sensitivity in correspondence with fecal E. hallii levels.In the recently finished DIME study (METC 2014_285) we studied safety and optimal dose of daily ingested oral E. hallii L2-7 strain for 4 weeks on insulin resistance/lipid metabolism in 27 male subjects with metabolic syndrome. No side effects were seen on either dosage during the treatment.
In this regard, it is interesting to note that DM2 subjects on metformin treatment have increased levels of lactate in their feces. Since E hallii uses intestinally produced lactate to produce butyrate that is thought to be the beneficial compound driving the effects on insulin sentivity, we hypothesize that adding E hallii to metformin treatment in subjects with DM2 may improve their glycemic control. This as the produced lactate by metformin treatment potentially could be converted by E hallii bacterial strains into the more metabolically beneficial SCFA butyrate. Thus, in the current study we propose to test the effect of daily oral E. hallii treatment in 10e9/ml dose (duration 14 days) in males with type 2 diabetes treated with stable dosages of metformin (3dd 500mg once daily). In order to test the efficacy of 2 weeks oral E. hallii treatment on (postprandial) glucose excursions subjects are asked to wear a subcutaneous continuous glucose monitor (CGM), which measures interstitial fluid glucose on certain time points, during seven days.

Study objective

to investigate the effect of 14 days once daily oral Eubacterium hallii (E. hallii) treatment on postprandial glucose levels in relation to SCFA levels in feces in patients with type 2 diabetes treated with metformin.

Study design

randomized, double-blind, placebo-controlled single center study

Intervention

Subjects will be given oral 10 ml E. hallii suspension with a total concentration of 10e9 cells/ml in 10% glycerol (vial A) or 10ml 10 % glycerol only (Vial D) once daily during 14 days.

Study burden and risks

The total duration of this study is 4 weeks and participants will visit the AMC four (screening, run in, randomization and end of study visit) times. All participants are required to fill out food diaries three days per week and are required to collect 24h urine and feces at baseline, week 2 and week 4 of the study. Furthermore, subjects will undergo a mixed meal test (MMT) before and after the intervention with blood sampling during 2 hours from a placed venflon. Afterwards, subjects are provided with a disposable continuous glucose

sensor (FreeStyle Libre)1, which will be worn for 14 days before and 14 days after the intervention to monitor (postprandial) glucose excursions both short term and long term, with this Free Style glucose sensor no additional blood glucose measurements with finger pricks need to be done. Also, subjects receive an blood pressure monitor to ambulatory measure their blood pressure during 24 hours before and after treatment. In total subjects will spent 6 hours in the AMC (screening visit, 2x 2 hours for the MMT plus CGM at baseline, randomization and after intervention) and we will collect 240 ml blood (at baseline, week 2 and week 4) in total.

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
* type 2 diabetes with the use of metformin on a stable dose (i.e. no changes in the last three months)

Exclusion criteria

* Smoking
* Alcohol abuse (>12 to 15 g of alcohol per day)
* History of cardiovascular event (myocardial infarction or pacemaker implantation)
* Cholecystectomy
* Use of medication other than metformin, including insulin, 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)
* Excessive weight loss of >10% in the last months or have overt untreated GI disease/ abnormal bowel habits.
* Levels of plasma aspartate aminotransferase and alanine aminotransferase 2.5 times or more the upper limit of the normal range

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-11-2018
Enrollment:	24

Type:	Actual

Ethics review

Approved WMO Date:	04-07-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2019
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	NL65951.018.18