Fecal Microbiota Transplantation to Preserve Residual Beta Cell Function In Patients With Newly-Diagnosed Type 1 Diabetes Mellitus: The FMT-Preserve-DM1-trial

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In this study we will investigate whether changes in gutmicrobiota composition induced by fecal transplantation from *preserved* type 1 diabetes mellitus, administered through a small intestinal tube, has beneficial effects on residual beta cell...

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

Summary

ID

NL-OMON54931

Source
ToetsingOnline

Brief title
FMT-Preserve-DM1-trial

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
juveline diabetes, Type 1 diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: De stichting Diabetes Onderzoek Nederland;Diabetes Fonds

Intervention

Keyword: Microbiome, Microbiota transplantation, Type 1 diabetes

Outcome measures

Primary outcome

Residual beta cell function

Residual beta cell function will be measured by stimulated C-peptide response upon mixed-meal tolerance (MMTT) area under thecurve (AUC0-120min) at 0, 2, 6, 9 and 12 months, using a 2 hour (-10, 0, 15, 30, 45, 60, 90, 120 min) mixed meal (MMT) test at 6ml per kg body weight (max 360 ml per MMT of Sustacal Boost Nutritional Drink, Nestle HS, Switzerland: 33% carbohydrates, 57%fat and 15% protein). An AUC0-120 of plasma C-peptide upon the Boost mixed meal tolerance test (MMTT)) is then calculated.

Secondary outcome

Changes in immunologic tone

II Immunologic parameters: In fresh whole blood samples, detailed multicolor flow cytometry is performed to characterize circulating immune cell fractions and specifically measure T-cell exhaustion. This includes monitoring of general leukocyte composition(monocyte/T/B/NK), granulocytes (Neu/Eo/Baso), particularly focusing at changes in the CD4, CD8 T cell and Treg compartments.Naturally occurring (nTreg) and induced regulatory T cells (tTreg) are analysed by surface and intracellular staining (CD25, CD127,CD122, FOXP3,

IL-10, Ki67, CTLA-4, GITR, LAG-3, CD49b, ICOS and CD39). Detailed analyses of T-cell subsets allowquantification of naïve and memory subsets (using CD45RA, CCR7 and CD95), subsets of antigen-experienced T cells such asTh1, Th2, Th17, Tfh or Trm (using CXCR5, CCR4, CCR6, CXCR3 and CD103) and T cell exhaustion (using CD57, PD-1, Tim3 andCD69). This allows definition of more than 100 different cell subsets, approaching the analyzing resolution of the more expensiveand less sensitive mass-spectrometry (CyTOF). Such analyses provide not only important information regarding the therapyinduced changes but also allow comparisons of the results with trials testing other therapeutic approaches. We will collect pax-genetubes to extract mRNA from whole blood. These measurements will be performed at the LUMC lab of Prof Roep, who is an expert inblood T cell tests in autoimmune diseases. Buffy coats will be stored for HLA and/or epigenetic analyses. We will use RNA seq on whole blood stored in a PAX-gene tube to measure expression patterns and we will use a machine learningalgorithm to pinpoint which immune pathways are differentially expressed by FMT.

Effect on intestinal gut microbiota composition upon multiple allogenic fecal infusions

To assess therapy specificity morning stool samples will be collected 0, 6, 9 and 12 months in the study to determine microbiotacomposition. Samples will be taken by collection on toilet paper (by patient him/herself wearing gloves), divided over 3 eppendorfsand directly frozen in fridge at home (-20C). Samples will be transported to AMC on icepacks. At the AMC, all samples will be

storedat -80C. Fecal analysis will be done by 16s microbiota sequencing at AMC microbiota core center.

Effect on intestinal gut microbiota metabolites upon multiple allogenic fecal infusions

To assess the effect of the FMTs on microbial metabolite composition, we will store plasma obtained by vena puncture alsoperformed for the immunological analyses, and we will ask participants to collect second void urine samples in the morning.

Glycemic control and basic biochemistry

To investigate overt effects of the interventions on glycemic control we will collect fasting blood for determination of glucose, HbA1c,lipid spectrum and eGFR. We will also read-out participants continuous glucose monitoring device for their time in range and hyper-and hypo glycemic episodes.

Questionares

At each study visit the following questionnaires will be taken

- Intercurrent illnesses, hypoglycemic episodes, insulin dosages, new medication
- Hypo-awareness
- Gastro-intestinal complaints
- Dietary intake lists online (via mijn.voedingscentrum.nl/nl/eetmeter)

Study description

Background summary

The incidence of Type 1 diabetes mellitus (T1D) has tripled in the last thirty years, and T1D is associated with a lifelong increase ofconsiderable morbidity and mortality compared to healthy subjects. In fact, T1D diagnosed in childhood leads to an almost 20 year loss of life-expectancy, more than most childhood cancers. Notwithstanding decades of intensive research in animals, theenvironmental factors driving T1D are still unknown and therapeutic strategies have invariably failed to halt disease progression.

As the increased T1D incidence is primarily observed in subjects who are not genetically predisposed, environmental factorsincluding altered diet, antibiotic use as well as mode of birth have been suggested to play a role, and these factors have invariablybeen linked to changes in the gut microbiome. Indeed, an altered composition of the fecal microbiota composition was observed inadolescent T1D patients. Moreover, an increased amount of pathogenic bacterial species has been observed in fecal samples ofT1D patients at the time of diagnosis. Interestingly, this altered fecal microbiota is already present before the clinical onset of T1D and is related to islet autoantibodies.

Interestingly, non-obese diabetic (NOD) mouse studies suggested that interaction of intestinal microbes with the innate immunesystem is a critical factor in developing T1DM [16], most likely by inducing an altered T-helper cell type 17 (Th17) population in thesmall-intestinal lamina propria. One of the current hypotheses linking the gut microbiome to immunological tone is production ofmicrobial metabolites such as the short-chain fatty acids (SCFAs). Production of these compounds is indeed altered in T1D, and thebest known SCFA butyrate is known to stabilize T-cell function in mice. Furthermore, irritation of the pancreatic duct by microbiota inthe proximal gut may contribute to beta cell inflammation. By introducing beneficial fecal microbiota to the proximal gut, theorganisms that alter immunological tone and irritate the pancreatic duct may be attenuated, resulting in improved beta cell functionand restoration. Thus, intestinal microbiota, their metabolites and their associated gut immune system alterations, may eitherpromote or protect from beta cell autoimmunity. We hypothesize that if one is able to shape the (small) intestinal microbiota withfecal microbiota transplantation (FMT) it may be possible to stabilize or even reverse β-cell destruction, reducing exogenous insulinneeds and subsequently associated complications in T1D.

FMT is a promising treatment for T1D, not only because of potential efficacty, but also because it is a safe procedure, that in our institute has been performed >500 times without any serious adverse events. In short, a fecal microbiota suspension is deliveredthrough a duodenal tube after large bowel lavage. This procedure is usually repeated 3 times with a 2-month interval.

Using anextensive screening protocol for infectious agents in accordance with European guidelines, to date no infections attributable to theprocedure have been recorded in our group. The FMT procedure itself is tasteless and odorless and in general generates few side-effects outside of the discomfort of placing a duodenal tube. Based on this notion, we initiated in 2013 a randomized pilot trial using repetitive donor (healthy donor) vs. autologous (own) FMTon residual β-cell function in new-onset T1D (DIMID trial, publiced in Gut 2020). Newly diagnosed male/female patientswith T1D were included and randomized. Moreover, healthy aged matched males/females were used as donors. Surprisingly, autologous FMT in 10 new onset T1D subjects had a significant ($p<0.01$) effect on preserving residual β-cell functionas determined by Sustacal Boost (Nestle HS) stimulated C-peptide AUC0-120min response after 12 months, whereas donor FMT in10 new onset T1D had a less obvious beneficial effect and showed overall a similar β-cell decline as seen in other trials withplacebo use. We have found several changes induced by both donor and autologous FMT on gut microbiome composition andidentified several bacterial strains and plasma metabolites and T-cell signatures that predicted response to FMT.

The immunological consequence of flooding the small intestine with large bowel microbiota by FMT may be an importantimmunological event. Based on our pilot data, we therefore formulate a paradigm shift, in which we hypothesize that the molecular mimicry against microbiome-associated antigens that drives T1D can be exhausted by challenging the immune system though FMT administered in the duodenum. Exhausted T-cells are ineffective T-cells that express high levels of the so-called check-pointproteins that inhibit immunological responses. Slow progression of T1D is linked to more exhausted CD8 cells in infiltrated islets[23], while increased circulating exhausted T cells predicted response to anti-CD3 therapy in T1D.

We hypothesize that the beneficial effect of autologous FMT in newly diagnosed T1D individuals can be maximized by using fecal microbiotica from individuals with T1D and a durable highly preserved beta cell fraction, as these individuals likely carry a microbiome with an overrepresentation of the microbiota that dampen the beta cell directed immune response. Our aim is to use FMTs to shift the *permanent honeymoon-phase* from a rare to the default phenotype. This will be, if achieved, a major breakthrough for the treatment of T1D.
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Study objective

In this study we will investigate whether changes in gutmicrobiota composition induced by fecal transplantation from *preserved* type 1 diabetes mellitus, administered through a small intestinal tube, has beneficial effects on residual beta cell function and immune status in newly type 1 diabetes mellitus. A parallel objective is to see which small (duodenal biopsy) and

large intestinal (fecal samples) microbiota predict these clinical changes.

Study design

This is a double blind randomised clinical trial. Patients will be treated with infusion of a placebo or allogenic feces by duodenal tube after bowel lavage. Newly diagnosed type 1 diabetes mellitus patients will be randomized to the following 2 treatment arms:
1. Multiple allogenic Type 1 diabetes donor fecal infusions at 0, 8 and 16 weeks.
2. Multiple placebo infusions at 0, 8 and 16 weeks.

At baseline, 6, 9 and 12 months residual beta cel function, microbial composition, and immune celfunction will be characterised.

Intervention

Patients will be treated with infusion of allogenic feces by duodenal tube after bowel lavage.
Type 1 diabetes mellitus patients will be randomized to the following 2 treatment arms:
1. Multiple allogenic Type 1 diabetes donor fecal infusions at 0, 8 and 16 weeks.
2. Placebo infusions at 0, 8 and 16 weeks.

Study burden and risks

Participant may benefit in terms of helping to further unravel the relation between the gut microbiome and residual beta cell function.The DIMID study was promising, suggesting that manipulation of the gut microbiome may indeed preserve the residual beta cell mass. This study will investigate if FMT is more beneficial when individudal with type 1 diabetes and a highly preserved beta cell mass are used. Participants may benefit from an increased redisual beta cell function, which is associated with a lower risk of diabetic complications and hypoglycemia. In the long therm, the FMT procedure may be refined to a probiotic formation or a combination of potent microbial metabolites andantigens that induce immunotolerance. Therefore, the risks described below outweigh the potential gain from this study.

For the mixed meal test, morning long- and short acting insulin must be withheld. This carries a small risk of hypo- andhyperglycemia. The study participants will be carefully instructed and no major risk is expected in the context of this procedure,especially given the current use of continuous glucose-monitoring technologies. The placing of the intravenous cannula in our studycan be an unpleasant experience for the subjects and may result in (self limiting) bruising.

Gastroscopy is a procedure associated with discomfort, but when participants are well fasted is very safe. The required fasting isassociated with a small risk of hypoglycemia, for which participants will be adequately instructed. In the age of continuous glucosemonitoring this risk is also very low.
In our centre, FMT procedures have not been associated with major adverse events, and donors are extensively screened tomitigate the risk of potential infections by the FMT procedure.

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

Inclusion criteria
• Patients with <6 weeks type 1 diabetes
• Aged 18-65 years

• BMI 18-30 kg/m2
• Male/females
• No concomitant medication except insulin

Exclusion criteria

• Inability to provide written informed consent
• Evidence for absent residual beta cel function (undetectable C-peptide)
• Antibiotics use in the last 3 months and proton-pump inhibitor use
• Evidence for compromised immunity
• Second auto-immune disease (i.e. coeliac disease, hyper- or hypothyroidism, inflammatory bowel disease)

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:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-06-2021
Enrollment:	34
Type:	Actual

Ethics review

Approved WMO

Date:	02-02-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC

Not approved

Date:	11-05-2021
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	NL74995.018.20