Encapsulated Faecal Microbiota Transplantation to Preserve Residual Beta Cell Function in Patients with Recently-Diagnosed Type 1 Diabetes Mellitus

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In this study we will confirm that a microbial intervention based on capsules containing autologous (own) lyophilized faecal matter (LFMT), taken daily for 3 month has beneficial effects on residual beta cell function (C-peptide secretion upon MMT)...

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

Summary

ID

NL-OMON50429

Source
ToetsingOnline

Brief title
The ENCAPSULATE-DM1 study

Condition

- Diabetic complications

Synonym
Juveline diabetes, type 1 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: EFSD (systems biology grant 100k)

Intervention

Keyword: -fecal microbiota transplantation, -Microbiome, -Residual beta cell function, -Type 1 diabetes mellitus

Outcome measures

Primary outcome

Preservation of residual beta cell function (insulin secretion capacity)

Residual beta cell function will be determined as stimulated C-peptide release during two hours (AUC0-120min) upon an MMT. The MMT will be performed during every visit at -3, 0, 3 and 6 months. C-peptide concentrations will be presented as pmol/ml.

Secondary outcome

Glycaemic control

To investigate overt effects of the intervention on glycaemic control we will collect fasting blood for determination of glucose, HbA1c, lipid spectrum, liver and kidney function (eGFR). Albumin will be measured in urine (microalbuminuria). In addition, we will read-out participants continuous glucose monitoring device (Freestyle Libre) for their time in range and hyper- and hypo glycaemic episodes and we will record the exogenous insulin dose use. Above measurements will be performed during every visit at -3, 0, 3 and 6 months.

Intestinal microbiota composition

We will determine changes in faecal gut microbiota composition at -3, 0, 3 and 6 months as well as changes in small intestinal microbiota composition at 0 and 3 months. The faecal gut microbiota composition will be determined from faecal samples, collected by the participants at home. The small intestinal microbiota composition will be determined from duodenal biopsies obtained via gastroscopy. DNA will be extracted from duodenal biopsies and faecal samples, which will be shotgun sequenced on an Illumina platform.

Intestinal microbiota metabolites

We will determine changes in (microbial) metabolite composition from fasting plasma samples obtained during the MMT and from 24h urine samples collected at -3, 0, 3 and 6 months. Metabolites will be measured by liquid chromatography-mass spectrometry for metabolomics.

Questionnaires and dietary intake

At each study visit questionnaires will be completed determine changes in:

- Diabetic complications, hypoglycaemic episodes, insulin dosages and medication changes
- Hypo-awareness
- Gastro-intestinal complaints
- Dietary intake 3 days prior to visit

Autoimmunity markers

As we found that baseline immune status predicts response to FMT, detailed

multicolour flow cytometry is performed at the first study visit 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.

Study description

Background summary

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterized by a progressive beta cell destruction and subsequent insulin dependence in the first 2-3 decades of life. In the last thirty years, the incidence of T1D has tripled, leading to a lifelong increase of considerable morbidity and mortality in those affected compared to healthy subjects. In fact, T1D diagnosed in childhood leads to an almost 20 year loss of life-expectancy, which is more than most childhood cancers. Notwithstanding decades of intensive research in animals, the environmental 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 factors including altered diet, antibiotic use as well as mode of birth have been suggested to play a role, and these factors have invariably been linked to changes in the gut microbiome. Indeed, an altered composition of the faecal microbiota composition has been observed in adolescent T1D patients. Moreover, an increased amount of pathogenic bacterial species has been identified in faecal samples of T1D patients at the time of diagnosis. Interestingly, this altered faecal microbiota is already present before the clinical onset of T1D and is related to islet autoantibodies.

Non-obese diabetic (NOD) mouse studies suggest that interaction of intestinal microbes with the innate immune system is a critical factor in developing T1DM, most likely by inducing an altered T-helper cell type 17 (Th17) population in the small intestinal lamina propria. One of the current hypotheses linking the gut microbiome to immunological tone is production of microbial metabolites such as the short-chain fatty acids (SCFAs). Production of these compounds is indeed altered in T1D, and butyrate (one of the best known SCFA) is known to stabilize T-cell function in mice. Furthermore, irritation of the pancreatic duct by microbiota in the proximal gut may contribute to beta cell

inflammation. By introducing beneficial intestinal microbiota to the proximal gut, the organisms or their metabolites that alter immunological tone and irritate the pancreatic duct may be attenuated, resulting in improved beta cell function and restoration.

We hypothesized that if one is able to shape the (small) intestinal microbiota with faecal microbiota transplantation (FMT), it may be possible to stabilize or even reverse β-cell destruction, thereby reducing exogenous insulin needs and subsequently associated complications in T1D. Previously, we showed that an FMT can significantly alter the intestinal microbiota composition for a period of 7-8 weeks. Additionally, it is a safe procedure that has been performed >500 times in our institute without any procedure-related adverse events. Therefore, we initiated in 2013 a randomized pilot trial comparing the efficacy of repetitive allogenic (healthy donor) vs. autologous (own) FMT on residual β-cell function in new-onset T1D (DIMID trial). Newly-diagnosed T1D patients were included and randomized to the allogenic (n=10) or autologous FMT group (n=10). Moreover, healthy age and sex matched donors were used for the allogenic FMT.

Surprisingly, autologous FMT had a significant ($p<0.01$) effect on preserving residual β-cell function as determined by stimulated C-peptide response upon a mixed-meal test after 12 months. Interestingly, the allogenic FMT from a healthy donor had a less obvious beneficial effect and showed overall a similar β-cell decline as seen in other trials with placebo use (see figure 1) [19]. We have found several changes induced by both donor and autologous FMT on gut microbiome composition and identified several bacterial strains and plasma metabolites and T-cell signatures that predicted response to FMT.

The positive impact of the autologous FMT on the beta cell function provides an interesting opportunity to stabilize the beta-cell destruction and extend or even bring back the honeymoon period (wherein individuals with recently diagnosed T1D remain well-regulated with minimal doses of insulin). Especially since the use of autologous FMT comes with even less risks than the use of healthy donor FMT (transmission of potential unknown pathogens). However, the current FMT procedure whereby the faecal suspension is administered through a nasoduodenal tube is quite invasive, time consuming and causes patient discomfort. In contrast, the use of encapsulated autologous FMT is non-invasive, causes no discomfort and can be simply administered in the home setting. If successful, the use of autologous FMT capsules provides a safe and feasible option to treat recently-diagnosed T1D patients on a daily basis to contribute to the preservation of beta cells in recently diagnosed T1D patients.

In the last years we worked on setting up the production of lyophilized FMT (LFMT) capsules at Amsterdam UMC. We optimized the freeze-drying process and determined the viability of the faecal microbes throughout the processing steps and during storage. The lyoprotectant trehalose 10% in combination with maltodextrin 5% appeared to provide the highest bacterial viability and

preserved the microbial composition best during freeze-drying. The optimal freeze-drying time was determined to be 48 hours at -80°C. As expected, during preparation of the LFMT capsules the bacterial viability decreased slightly, especially after freeze-drying and encapsulation. This small decrease in viability after freezing and freeze-drying is a known phenomenon and impossible to avoid. Fortunately, upon restitution of the microbes in the small intestine the viable microbes are able to multiply and engraft, which has been shown in previous studies. Moreover, we found the faecal bacteria in frozen FMT and LFMT capsules were stable during storage in the freezer, without any relevant decreases in bacterial viability.

We thus propose to combine our data from the previous fresh autologous FMT study with our current developments in preparing autologous LFMT capsules to stabilize further beta cell degradation in T1D subjects with residual beta cell function. We will investigate whether the beneficial effect of autologous FMT extents towards recently-diagnosed (0.5-3.5 years) T1D patients, as it is known that beta cell degradation and loss of function is progressive for the first 5-7 years and thereafter stabilises. During this time-period individuals lose their so-called honey-moon period where they become increasingly dependent on intensive insulin use and glucose monitoring. Therefore, it is conceivable that this patient group benefits from beta cell function preserving therapies and makes this application a careful but important step towards a beta-cell preserving therapy in T1D based on modulation of the gut microbiome.

Study objective

In this study we will confirm that a microbial intervention based on capsules containing autologous (own) lyophilized faecal matter (LFMT), taken daily for 3 month has beneficial effects on residual beta cell function (C-peptide secretion upon MMT) in recently diagnosed type 1 diabetes mellitus (0.5-3.5 years). A parallel objective is to assess the impact on glycaemic control and see which small- as well as large intestinal (faecal samples) microbiota are associated with these clinical changes over time.

Study design

Study Design
This is an open label single-arm, single-centre study. During a run-in period of 3 months, stools of the participants will be collected and processed into freeze-dried faecal microbiota capsules. After the run-in period, participants will ingest the autologous FMT capsules daily for 3 months, which will be followed by a follow-up period of 3 months. In total, participants will be followed for 9 months after inclusion.

Study visits
Subjects will visit the AMC 4 times in total. Each visit will take 180 minutes

(maximum of 12 hours over 9 months). A more detailed description of all measurements and procedures can be found in section 7.3 Study procedures.

Visit 1: Screening and run-in visit (-3 months)
Patients will be screened for suitability in the GUTDM1 study (NL73189.018.20, METC_2020_105) and invited to participate. At every visit of the study a MMT will be performed, blood will be drawn for basic biochemistry and patients will hand in the food diaries, questionnaires, 24-hour urine and faeces. In addition, we measure height, weight, blood pressure and calculate BMI. As the faeces is needed to produce the autologous FMT capsules, participants are instructed collect at least 150 grams of fresh faeces. If the fresh faeces is insufficient (<150 g), participants are asked to collect more fresh faeces and bring this to the AMC at a later date (but before the baseline visit).

Visit 2: baseline visit (0 months)
At this visit, a gastroscopy is performed and 6 duodenal biopsy*s are collected. The MMT will be repeated, blood will be drawn for basic biochemistry and patients will hand in the food diaries, questionnaires, 24-hour urine and faeces. In addition, we measure height, weight, blood pressure and calculate BMI again. Thereafter, the participant will start with the LFMT capsules for 3 months (84 ±6 days). The first capsule is ingested with the investigator present to ensure the participant tolerates the capsules well. After this visit the participant is contacted biweekly to ensure adherence.

Visit 3: follow-up visit (3 months)
During this visit, the gastroscopy is repeated and 6 duodenal biopsy*s are collected. The MMT will be repeated, blood will be drawn for basic biochemistry and patients will hand in the food diaries, questionnaires, 24-hour urine and faeces. In addition, we measure height, weight, blood pressure and calculate BMI again. Participants stop with the LFMT capsules and return any remaining capsules to the investigator.

Visit 4: follow-up visit (6 months)
During this last visit, the MMT will be repeated, blood will be drawn for basic biochemistry and patients will hand in the food diaries, questionnaires, 24-hour urine and faeces. In addition, we measure height, weight, blood pressure and calculate BMI again.

Intervention

After the 3 month run-in phase of the study, patients will be treated on a daily basis with capsules containing lyophilized autologous faecal matter for a period of 3 months. During the run-in phase participants will collect their stool, which will be processed into the autologous LFMT capsules containing approximately 1 gram stool per capsule, and stored at -80°C. Participants store the capsules at home in the freezer and ingest one capsule per day for a period of 3 months (84 ±6 days). Capsules are advised to be ingested with a glass of

water on an empty stomach in the morning, preferably an hour before breakfast (while still fasted).

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 very promising, suggesting that manipulation of the gut microbiome may indeed preserve the residual beta cell mass. Participants may benefit from an increased residual beta cell function, which is associated with a lower risk of diabetic complications and hypoglycaemia. In the long-term, the FMT procedure may be refined to a probiotic formation or a combination of potent microbial metabolites and antigens that induce immune-tolerance.

For the mixed meal test, morning long- and short acting insulin must be withheld. This carries a small risk of hypo- and hyperglycaemia. The study participants will be carefully instructed and no major risk is expected in the context of this procedure. The placing of the intravenous cannula in our study can be an unpleasant experience for the subjects and may result in (self-limiting) bruising. The amount of blood drawn (70 mL) is far below the maximum 500 mL per day; other study procedures (such as faeces collection or dietary diary) are considered harmless and will not cause any physical or physiological discomfort.

Gastroscopy is a procedure associated with discomfort, but when participants are well fasted it is very safe. The required fasting is associated with a small risk of hypoglycaemia, for which participants will be adequately instructed. In the age of continuous glucose monitoring this risk is also very low.

In our centre, FMT procedures have not been associated with major adverse events and only minor gastrointestinal symptoms were reported by recipients. Compared to an allogenic FMT from healthy donors, the autologous FMT approach used in this study comes with no risk for pathogen transmission. In addition, the LFMT capsules are not invasive, cause almost no patient discomfort and can be easily ingested by the patient as compared to the fresh FMT administered.

Contacts

Public
Selecteer

Meibergdreef 9
Amsterdam 1105 AZ

NL
Scientific
Selecteer

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Male or female recently diagnosed (0.5-3.5 years) with type 1 diabetes mellitus.
2. Age: 18-65 years
3. BMI: 18-30 kg/m2
4. Remaining (detectable) residual beta cell function: detectable urinary or plasma C- peptide at inclusion of the study.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. History or symptoms of other autoimmune disease (e.g. hypo- or hyperthyroidism, rheumatoid arthritis).
2. (Expected) prolonged comprised immunity (e.g. due to recent cytotoxic chemotherapy or human immunodeficiency virus (HIV) infection with a CD4 count < 240/mm3).
3. History of a severe disease of the digestive tract, such as celiac disease, 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).
4. Use of antibiotics, antacid drugs or proton pump inhibitors in the past 3 months or during the study period.
5. Use of pro-/prebiotics in the past three months or during the study period.
6. Smoking or illicit drug use (e.g. MDMA/amphetamine/cocaine/heroin/GHB) in the past three months or use during the study period.
7. Use of >21 units of alcohol per week on average in the past three months
8. Pregnancy or breast feeding

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-05-2022
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	31-01-2022
Application type:	First submission
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	NL79666.018.21