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Faecal microbiota transplantation for patients with diabetes type 1 and severe gastrointestinal neuropathy (FADIGAS): a randomised, double-blinded, placebo-controlled trial

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Summary

Background Diabetic gastroenteropathy is associated with nausea, vomiting, bloating, pain, constipation, and diarrhoea. Current therapies are scarce. We tested faecal microbiota transplantation (FMT) for patients with type 1 diabetes and gastroenteropathy.

Methods In a randomised, double-blinded, placebo-controlled pilot trial, adults with type 1 diabetes and moderate-to-severe gastrointestinal symptoms were randomised (1:1) to encapsulated FMT or placebo. Each patient received around 25 capsules containing 50 g of faeces, administered in a single dose. The placebo capsules contained glycerol, saline and food colouring. All patients received FMT as a second intervention. The primary endpoint was number of adverse events of severity grade 2 or more assessed by the Common Terminology Criteria for Adverse Events during the week following the first intervention. Secondary endpoints included gastrointestinal symptoms and quality of life assessed four weeks after treatment. Public trial registration, ClinicalTrials.gov NCT04749030.

Findings We randomised 20 patients to FMT or placebo. Following this intervention, 26 adverse events of grade 2 or more occurred. Four patients in the FMT group reported seven adverse events, and five patients in the placebo group reported 19, with no differences between the groups. The most frequent adverse events were diarrhoea, bloating, and abdominal pain. No serious adverse events were related to the treatment. Patients who received FMT reduced their median Gastrointestinal Symptom Rating Scale—Irritable Bowel Syndrome score from 58 (IQR 54–65) to 35 (32–48), whereas patients receiving placebo reduced their score from 64 (55–70) to 56 (50–77) ($p = 0.01$). The Irritable Bowel Syndrome Impact Scale score improved from 108 (101–123) to 140 (124–161) with FMT and 77 (53–129) to 92 (54–142) with placebo ($p = 0.02$). The Patient Assessment of Gastrointestinal Symptom Severity Index declined from a median of 42 (28–47) to 25 (14–31) after FMT and 47 (31–69) to 41 (36–64) after placebo ($p = 0.03$).

Interpretation FMT was safe and improved clinical outcomes for patients with type 1 diabetes suffering from bowel symptoms.

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Abbreviations: COMPASS31, Composite autonomic symptoms score; CTCAE, Common terminology criteria for adverse events version 5.0; FMT, Faecal microbiota transplantation; GSRS-IBS, Gastrointestinal symptom rating scale, Irritable bowel syndrome; IBS-IS, Irritable bowel syndrome impact scale; PAGI-SYM, Patient assessment of gastrointestinal symptom severity index

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Keywords: Diabetes; Fecal microbiota transplantations; Diarrhea; Randomized controlled trial

Research in context

Evidence before this study

Effective therapeutic interventions for alleviating symptoms of diabetic gastroenteropathy are limited due to insufficient evidence and safety apprehensions. FMT, as a means of restoring the intestinal microbiota and relieving bowel symptoms in patients with type 1 diabetes, has never been applied before. We searched PubMed, Embase, and Scopus from database inception until May 10, 2024, with no language restriction using the search terms "Diabetes" and "Faecal/Fecal microbiota transplantation/installation". We found no trials investigating the efficacy of FMT for alleviating symptoms of diabetic gastroenteropathy.

Added value of this study

This is the first randomised, double-blind, placebo-controlled trial using FMT to improve clinical outcomes for patients with type 1 diabetes and debilitating bowel symptoms. We included patients with moderate to severe bowel symptoms, and we found that capsule-based FMT is safe as there were no differences in adverse events between the FMT group and the placebo group. Bowel symptoms were significantly reduced, and quality of life was improved in the FMT group compared to the placebo group.

Implications of all the available evidence

Changing the intestinal microbiota in patients with diabetes type 1 and bowel symptoms using FMT is a novel and unprecedented approach with promising clinical perspectives. To our knowledge, the present study represents the most encouraging clinical effect of FMT beyond the established use for *Clostridioides difficile* infection. It is our firm expectation that the present study will have a major international impact on the future use of FMT while contributing to the advancement of knowledge in the field of diabetes and gut dysfunction.

Introduction

Diabetic gastroenteropathy often presents with vomiting, intense nausea, bloating, abdominal pain, constipation, diarrhoea, and faecal incontinence.[1] These symptoms are common and major causes of morbidity and reduced quality of life.[2] Autonomic neuropathy, dysfunction of the Cajal cells, and reduced contractility of the intestinal smooth muscle cells contribute to diabetic gastroenteropathy.[3,4] This can lead to prolonged panenteric transit times and faecal accumulation, especially in the caecum and proximal colon.[5] Prolonged colonic transit time may cause colonic dysbiosis, resulting in increased fermentation and gas production, contributing to these symptoms.[6] There are intricate, autonomic-regulated communications between the brain, gut and microbiota that influence the peripheral and central neurotransmitter release via the neuro-immuno-endocrine mediators. Dysbiosis leads to systemic inflammation, including neuro-inflammation mediated via cytokines. This results in altered pathways and neurotransmission. Therefore, dysbiosis may cause increased neuronal activity, potentially leading to amplified perception of pain.

Treatment of diabetic gastroenteropathy traditionally targets gastroparesis, whereas fewer treatment options exist for the remaining part of the gastrointestinal tract. Treating this disease can involve challenges, which are often compounded by limited availability of therapies. This scarcity is frequently attributed to insufficient evidence for their effectiveness or concerns about long-term safety profile.[7] This leaves patients with few alternatives besides general dietary advice, broad-spectrum antibiotics, or prokinetic laxatives.

Several studies have described an association between diabetes and a disturbed gut microbiota. Patients with type 1 diabetes have reduced microbial diversity and an abnormally high prevalence of pathogenic and opportunistic gram-negative species at the expense of commensal bacteria.[8] This may contribute to the pathogenesis of gastrointestinal symptoms. Specifically, patients with type 1 diabetes have an abundance of Bacteroidetes (Bacteroidota), decreased levels of Firmicutes (Bacillota), and a decrease in butyrate-producing bacteria, which negatively influences gut permeability.[9] Increased gut permeability may result in translocation of microbes and microbial metabolites. This, in turn, has the potential to activate the immune cells and send signals to the brain.[10] In recent years, therapies based on microbiota have demonstrated encouraging results in slowing down or preventing the progression of new-onset type 1 diabetes.[11] Furthermore, it has been suggested that FMT may improve insulin sensitivity and modulate autoimmunity, potentially altering the disease course.[9]

FMT is the transfer of minimally processed faeces containing whole microbial communities from a healthy donor to a recipient, leading to prompt engraftment of a donor-like microbiota in the recipient.[12] Recently, capsule-based FMT has been introduced as an easy, safe, and well-tolerated administration option for treating *Clostridioides difficile* infection. Emerging evidence suggests that FMT may be used to treat other medical conditions resulting from dysbiosis, but results have

been conflicting.[13] Until now, FMT has not been explored as a treatment option for diabetic gastroenteropathy. We hypothesised that capsule-based oral FMT is safe and feasible and reduces symptoms of diabetic gastroenteropathy.

The primary aim of the present study was to evaluate the safety of FMT in patients with type 1 diabetes and severe symptoms of gastroenteropathy. The secondary aim was to provide pilot data on the clinical efficacy of such treatment.

Methods

Study design

FADIGAS, an investigator-initiated clinical pilot trial exploring the safety and effects of FMT in patients with type 1 diabetes and severe symptoms of gastroenteropathy, was conducted between June 2021 and May 2023 at Aarhus University Hospital, Denmark. The trial was double-blinded and placebo-controlled and adhered to the principles of good clinical practice and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Throughout the trial, an independent committee monitored its safety and validity. The patients initially received either FMT or placebo blindly, followed by open-label FMT for all patients. The trial protocol was approved by the Central Denmark Region Ethics Committee (R.no. 1–10–72–345–20) and the Regional Data Protection Agency (R.no. 1–16–02–38–21). The study was preregistered with ClinicalTrials.gov (NCT04749030), and the full study protocol is available online.

Patients

We included adult patients who had been diagnosed with type 1 diabetes for more than five years and had a Gastrointestinal Symptom Rating Scale–Irritable Bowel Syndrome (GSRS-IBS) questionnaire score of 40 or more.[14] All patients provided written informed consent before their inclusion in the study.

Exclusion criteria were pregnancy, severe renal insufficiency (estimated glomerular filtration rate (eGFR) < 20 ml/min), cardiac pacemaker *in situ*, recent changes in medication affecting the gastrointestinal tract, dysregulated thyroid disease, ongoing infection with *C. difficile*, other pathogenic intestinal bacteria or parasites, chronic disease affecting gastrointestinal function, or previous major abdominal surgery. Patients who had taken morphine or used antibiotics within the preceding four weeks were also excluded. The severity of autonomic neuropathy was evaluated using the validated Composite Autonomic Symptoms Score (COMPASS 31) questionnaire.[15]

Randomisation and masking

Patients were randomly assigned 1:1 to receive either encapsulated FMT or placebo. Patients, investigators, and study personnel with patient contact were blinded to the assigned treatment. A computerised randomisation procedure was used to generate the allocation table to guarantee impartial allocation of subjects into the two treatment groups. The study investigators used an online electronic form to enrol and randomly assign patients, and they remained blinded to the allocation sequence. Independent unblinded personnel prepared and released the study treatment in sequentially labelled containers according to the generated randomisation list. For each study treatment, a detailed documentation log was kept. Blinded study personnel evaluated the safety and effect outcomes. The FMT and placebo capsules were identical in appearance. To ensure accurate masking, the investigators and patients had to declare which study treatment they believed was provided.

Procedures

Participation in the trial lasted for three months and comprised eight outpatient visits. During the first visit, baseline investigations were conducted. This was followed by the first intervention of the allocated study treatment with encapsulated FMT or placebo. Four weeks after the first intervention, all patients underwent reassessment for clinical outcomes and safety, after which they received the second intervention with open-label treatment with FMT capsules. Patients were assessed again for clinical outcomes and safety four weeks after the second intervention (Supplementary Figure S1).

The patients provided stool samples at baseline and again 4 weeks after each intervention. Before each treatment, patients were required to fast for at least 6 h for solid food and 2 h for liquids. They were instructed to take 10 mg oral metoclopramide 10 min before ingesting the capsules, which were swallowed with low-pH and sugar-free beverages. After receiving the study treatment, the patients were monitored for 30 min at the hospital outpatient clinic.

Encapsulated FMT was prepared by trained personnel at the public Blood Centre at Aarhus University Hospital using 50 g of crude faeces from eight carefully screened healthy blood donors, according to international guidelines.[16] Each patient received FMT from a single donor. The crude stool was mixed with 85% glycerol and homogenised in sterile saline. After centrifugation, a highly dense concentrate was obtained, mixed with glycerol at a 1:0.1 ratio, and suspended in acid-resistant, double-coated enterocapsules (Capsugel Vcaps capsules; Lonza, Colmar, France) of size 0. On average, 25 capsules (range 12–30) were produced. The concentrate for the encapsulated placebo capsules was prepared as a mixture of 49.5% glycerol, 49.5% sterile saline, and 1% food colouring. The placebo concentrate was divided into capsules identical to those used for FMT. The total number of capsules produced matched the varying number of FMT capsules. All capsules were

sealed and stored at –80 °C until use. Treatment with FMT followed international guidelines and the National Danish Tissue Act.[17,18] Safety samples from all faecal donations were stored.

Outcomes

The primary outcome was safety determined by the number of adverse events of severity grade 2 or more assessed by the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5)[19] during the week after the first intervention. All safety data were prospectively collected throughout the study, and the patients were instructed to keep a daily diary recording all possible adverse events in the week following treatment. Any serious adverse reactions or suspected unexpected severe adverse reactions were reported to the relevant authorities. Adverse events were categorised based on their time of occurrence into immediate complications during administration, events occurring within the first 24 h, and events happening more than 24 h after administration. Patients were instructed to document all adverse events in a dedicated diary, and treatment physicians evaluated these events prospectively.

Gastrointestinal symptoms were evaluated four weeks after each intervention using three validated questionnaires. The GSRS-IBS was used to assess symptoms from the distal gastrointestinal tract. The questionnaire comprises 13 items divided into five symptom categories: pain, bloating, constipation, diarrhoea, and early satiety. Each item is rated on a scale ranging from 1 (no discomfort) to 7 (very severe discomfort).[14] The Patient Assessment of Gastrointestinal Symptom Severity Index (PAGI-SYM) consists of 20 items rated on a scale from 0 (no symptoms) to 5 (very severe symptoms), evaluating symptoms from the proximal gastrointestinal tract on six subscales: heartburn/regurgitation, nausea/vomiting, postprandial fullness/early satiety, bloating, upper abdominal pain, and lower abdominal pain.[20] The Irritable Bowel Syndrome Impact Scale (IBS-IS) questionnaire evaluates the bowel-specific quality of life. It comprises 26 items on five domains: fatigue, impact on daily activities, sleep disturbance, emotional distress, and eating habits.[21]

Segmental and whole-gut gastrointestinal transit times were evaluated at baseline using the wireless motility capsule (SmartPill™, Medtronic, Minneapolis, Minnesota, USA). The data obtained were analysed using complementary software MotiliGI™, version 3.1, also developed by Medtronic. Two independent investigators reviewed and then compared our data with normative data on segmental transit times using the 95th percentile as a cut-off.[22]

Microbiota analysis

DNA was extracted from 118 to 156 mg of each faeces sample using the QASymphony PowerFecal Pro DNA Kit with Bead Beating on a TissueLyser II at 25 Hz for 2 × 10 min. Sequencing libraries were prepared with Twist EF 2.0 using 50 ng input, fragmentation for 5 min at 37 °C and eight cycles of PCR. The resulting metagenome libraries were analysed on an Illumina NovaSeq 6000 using 2*150 base pair paired-end sequencing with an expected depth of ≥10 gigabases per sample. Positive and negative controls were prepared alongside the other samples from DNA extraction onwards. As a positive control, we used the ZymoBIOMICS Microbial Community Standard (D6300) (Supplementary Figure S2). As a negative control, we used no input. Anonymised microbial sequencing data, excluding metadata, have been uploaded to the European Nucleotide Archive (ENA) under the accession number PRJEB82718.

Bioinformatics and statistics

Raw microbiome data were processed to generate taxonomic profiles. Reads were initially processed with KneadData v0.12, using standard options for trimming, and reads mapping to the human genome (T2T-CHM13) were removed. Illumina adapters were removed using Cutadapt v4 and duplicate removal using Clumpify from BBMap v39. The cleaned reads were then taxonomically profiled using MetaPhlAn v4.[23]

Statistical analysis

This is the first explorative study with FMT for patients with type 1 diabetes, and assumptions for formal power calculations were unavailable. A group of 20 patients with type 1 diabetes were expected to be sufficient to determine whether there were any common adverse events and major effects on symptoms after FMT administration. The primary outcome analysis was conducted following the intention-to-treat principle. This analysis included all randomly assigned patients. Adverse events registered during the week following the first intervention were stratified according to the treatment group and summarised using descriptive statistics. The Relative Risk (RR) for per-person reported adverse events between the treatment groups was calculated with a 95% confidence interval (CI).

Secondary outcomes were analysed as the difference in change from baseline to four weeks after the first intervention with FMT or placebo between the two groups. Normality was assessed with Q–Q plots. For normally distributed data, two-sample t-tests were used to compare changes from baseline between treatment groups. For non-normally distributed data, Wilcoxon signed-rank tests were used to compare changes from baseline. Baseline data were reported as medians with interquartile ranges (IQR) or counts with frequencies. All analyses were conducted using STATA (SE 18.0).

Diversity measures were calculated from taxonomic profiles. Aitchison was calculated using transformation and distance calculations. Richness was calculated using

the microbiome package, specifically applying the observed richness index.

To assess the significance of the difference between FMT-treated and placebo-treated patients, we used a t-test extracting t-statistics and CI. The robustness of the results was evaluated by applying more statistical models, including the Wilcoxon Rank–Sum Test, Welch's t-test, and permutation test. Additional information regarding the bioinformatics methods can be found in the Supplementary Materials.

Role of the funding source

The study design, data collection, analysis, interpretation, and report writing were all conducted without any funder involvement.

Results

From June 18, 2021, to May 22, 2023, we consecutively screened 23 patients and included 20 (Fig. 1). The 20 patients were randomly allocated to FMT (n = 10) or placebo (n = 10) as their first intervention. All 20 patients adhered to the study protocol and were included in the intention-to-treat analysis population.

Six men and 14 women with type 1 diabetes and a median age of 46 years (IQR 32–52) were included. Their median type 1 diabetes duration was 31 years (IQR 19–36). The patients had a high degree of neuropathy and many gastrointestinal symptoms, indicated by a median baseline COMPASS-31 score of 49 (IQR 30–55) and a median GSRS-IBS score of 59 (IQR 54–69) at the time of inclusion. Compared to existing normative data, gastric emptying time was prolonged in 10 out of 17 available patient recordings (59%), with a median duration of 17 h and 56 min (IQR 1.47–39.40) (Table 1).

During the first intervention, 26 adverse events with severity grade 2 or more assessed by CTCEA v5 were registered (Table 2). Four patients who received FMT reported seven adverse events, whereas five patients receiving placebo reported 19 adverse events. RR for per-person reported adverse events between the FMT and placebo groups was 0.80 (95% CI 0.30–2.13). The most frequent adverse events were aggravated

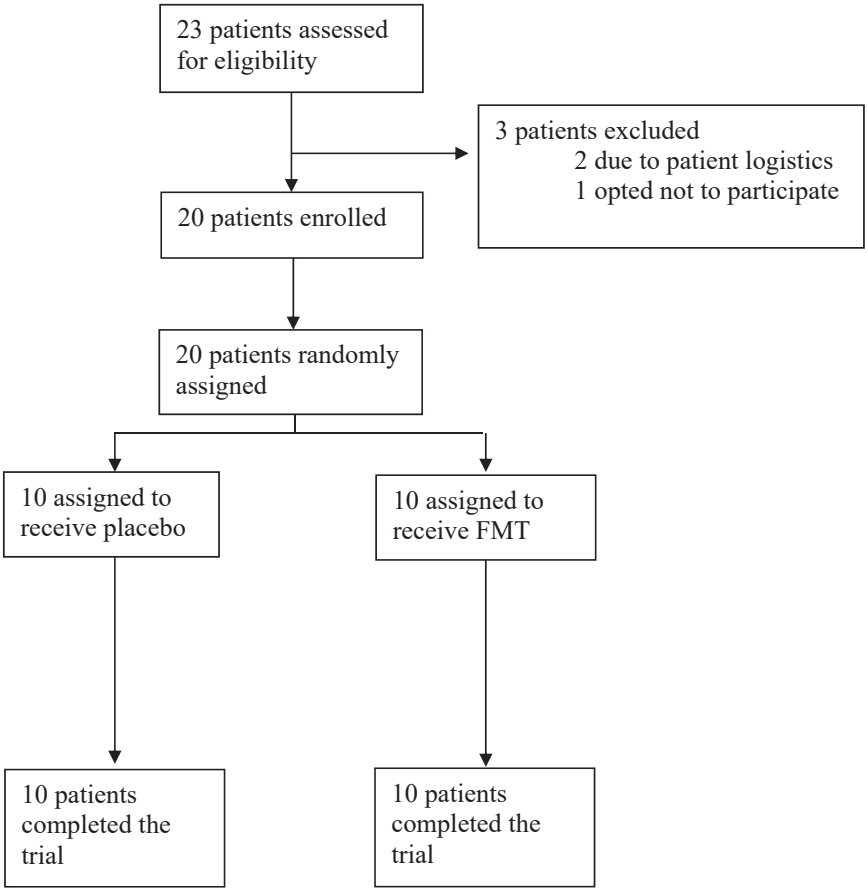

Fig. 1: Trial profile.

	FMT (n = 10)	Placebo (n = 10)
Demographic characteristics		
Age, years, median (IQR)	45 (31–52)	46 (33–54)
Sex		
Male, n (%)	3 (30)	3 (30)
Female, n (%)	7 (70)	7 (70)
Current smoking		
Yes, n (%)	2 (20)	2 (20)
No, n (%)	8 (80)	8 (80)
BMI, kg/m^2, median (IQR)	25 (22–28)	22 (20–27)
Clinical characteristics		
Diabetes duration, years, median (IQR)	21 (9–33)	33 (23–42)
HbA1c, mmol/mol, median (IQR)	65 (53–76)	60 (55–73)
Diabetes-related complication at the latest eye examination[a]		
Yes, n (%)	5 (50)	7 (70)
No, n (%)	5 (50)	3 (30)
Diabetes-related complication at the latest kidney examination[a]		
Yes, n (%)	1 (10)	4 (40)
No, n (%)	9 (90)	6 (60)
Admitted to the hospital in the past year due to high or low blood glucose[a]		
Yes, n (%)	1 (10)	2 (20)
No, n (%)	9 (90)	8 (80)
Active (walking or moving around) less than 1 h per day[a]		
Yes, n (%)	5 (50)	1 (10)
No, n (%)	5 (50)	9 (90)
Continuous glucose monitoring		
Yes, n (%)	8 (80)	7 (70)
No, n (%)	2 (20)	3 (30)
Blood glucose[b]		
Blood glucose in target area, (3.9–10 mmol/L), % (IQR).	67 (50–70)	44 (27–73)
Blood glucose above 10 mmol/L, % (IQR)	27 (13–45)	45 (25–65)
Blood glucose below 3.9 mmol/L, % (IQR)	5 (1–14)	4 (0–5)
Gastrointestinal Symptom Rating Scale—IBS version, median (IQR)	58 (54–66)	66 (53–71)
Autonomic characteristics		
COMPASS-31, median (IQR)[c]	47 (26–55)	51 (34–57)
COMPASS-31 > 16, n (%)	10 (100)	10 (100)
Transit times from Wireless motility capsule[d]		
GET, median (IQR), hours:minutes	8:22 (0:40–33:18)	25:02 (3:17–43:05)
GET >4:58 (female) or > 4:53 (male), n (%)	4 (50)	6 (67)
SBTT, median (IQR) hours:minutes	4:00 (3:04–5:35)	3:55 (3:07–4:34)
SBTT >8:42 (female) or > 5:45 (male), n (%)	3 (38)	3 (43)
CTT, median (IQR), hours:minutes	18:07 (13:04–40:12)	43:29 (21:24–78:41)
CTT >49:37 (female) or > 50:32 (male), n (%)	1 (14)	3 (38)
WGTT, median (IQR), hours:minutes	43:28 (23:23–67:01)	99:22 (50:15–122:36)
WGTT >72:40 (female) or > 65:28 (male), n (%)	3 (38)	5 (56)

Data are n (%) or median (IQR). BMI, Body Mass Index. COMPASS-31, Composite Autonomic Symptoms Score; CTT, colonic transit time; FMT, faecal microbiota transplantation; GET, gastric emptying time; SBTT, small bowel transit time; WGTT, whole gut transit time. [a]Patient-reported measures. [b]Only data from patients with continuous glucose monitoring and reported by patients. Target area measured during the past 14 days. [c]In COMPASS-31, a score >16 indicated autonomic neuropathy. [d]Data on transit times were collected at baseline. The 95 percentile of gender-specific transit times in a large cohort of healthy participants were used as cut-off values.

Table 1: **Baseline characteristics of included patients (n = 20).**

gastrointestinal symptoms, including diarrhoea, bloating, and abdominal pain.

All patients received FMT as the second intervention. This treatment resulted in 18 adverse events with a severity of grade 2 or more. The adverse events were equally distributed between the two groups as five patients who also received FMT as the first intervention reported nine events, and three patients who received placebo as the first intervention also reported nine adverse events of severity grade 2 or more. RR for per-person reported adverse events between the two groups was 1.66 (95% CI 0.54–5.17) (Table 2).

When including all mild grade 1 adverse events, 91 events were reported during the first intervention and 95 during the second intervention (Table 2). The most frequent adverse events were nausea, abdominal pain, bloating, and fatigue. The number of registered adverse events were distributed equally between the two groups in both interventions, with no statistically significant differences.

Five serious adverse events occurred during the study, but none were deemed related to the study treatment. One serious adverse event was registered after the first intervention as a patient who had received FMT was hospitalised with diabetic ketoacidosis. The admission occurred one month after the study treatment and was related to a defective insulin sensor. Four serious adverse events were registered during the second intervention, during which all patients received FMT. One patient was admitted to the hospital with pneumonia 22 days after receiving the study treatment. Two other patients were hospitalised; one due to pyelonephritis and one due to iron deficiency anaemia and weight loss. Both events occurred approximately two months after the study treatment, and neither were considered related to FMT.

After the first dose of study treatment, the median GSRS-IBS score significantly declined from 58 (IQR 54–65) at baseline to 35 (IQR 32–48) points in the FMT group. In contrast, the placebo group recorded a median change from 64 (IQR 55–70) to 56 (IQR 50–77) points (between-group p = 0.01) (Table 3). In the placebo group, the median GSRS-IBS score at baseline was 64 (IQR 55–70) and changed to 56 (IQR 50–77) after placebo treatment (p = 0.14). Following the treatment with FMT during the second intervention, the score was reduced to 48 (IQR 29–63) (p = 0.04) (Fig. 2a). The subscores for pain and bloating also improved more with FMT than with placebo (Table 3).

The quality of life significantly improved in patients who received FMT. The IBS-IS score increased from 108 (IQR 101–123) to 140 (IQR 124–161) points in the FMT arm compared with patients receiving placebo in whom an increase from 77 (IQR 53–129) to 92 (IQR 54–142) points was recorded, (between-group p = 0.02) (Table 3). In the placebo group, the median IBS-IS score at baseline was 77 (IQR 53–129) and changed to 92 (IQR

54–142) after the placebo treatment (p = 0.39). Following the treatment with FMT, the score increased to 129 (IQR 72–191) (p = 0.13) (Fig. 2b). The observed changes in the sub-scores did not reach statistical significance (Table 3).

Symptoms attributed to the proximal gastrointestinal tract were assessed with the PAGI-SYM. This score improved from a median of 42 (IQR 28–47) points at baseline to 25 (IQR 14–31) after FMT versus 47 (IQR 31–69) points at baseline to 41(IQR 36–64) after placebo (between group p = 0.03) (Fig. 2c) (Table 3). The sub-scores of bloating and upper abdominal pain were also reduced in the FMT compared with the placebo group. No change was found between the two groups in the sub-scores nausea/vomiting, postprandial fullness, or lower abdominal pain.

In the initial intervention, the blinding of both patients and investigators was evaluated while receiving either FMT or placebo treatment. Among 20 treatments, the investigators guessed the correct treatment in 12 cases, whereas patients guessed correctly in 11 cases.

To assess if the microbiome of patients receiving FMT changed from before treatment to four weeks after, we compared the alpha diversity (richness) and beta diversity (Aitchison) between the baseline and the first intervention for each patient. FMT treatment changed the patient microbiome diversity more than placebo. Alpha diversity (richness) was evaluated using a t-test, showing a difference of t = −2.78 (95% CI: −72.65, −9.15). Beta diversity (Aitchison) was also evaluated with a t-test, yielding t = −3.59 (95% CI: −26.15, −6.85) (Fig. 3).

Discussion

In this investigator-initiated clinical trial, we found a highly encouraging safety profile and favourable effects of capsule-based FMT for patients with type 1 diabetes and severe gastroenteropathy symptoms compared with placebo. FMT was safe, significantly reduced bowel symptoms, and improved patients' quality of life. Additionally, FMT led to significant changes in alpha and beta diversities of the gut microbiome compared with placebo, indicating a shift in microbial composition after the first intervention. Patients who received FMT experienced significant relief from their gastrointestinal symptoms and improved quality of life. Although some patients in the placebo group reported reduced symptoms from baseline to the first intervention, when they received placebo, the differences were not statistically significant. Patients who had previously received placebo treatment were given FMT during the second intervention. This resulted in substantial symptom relief and improved quality of life, maintained throughout the patients' participation in the trial. Our findings suggest that FMT may represent a potential new therapeutic option that could fundamentally transform the current

Adverse events ≥2 (CTCAE v5)

	1. Intervention		2. Intervention	
	FMT (n = 10)	Placebo (n = 10)	FMT (n = 10)	FMT (n = 10)
Any adverse event ≥2 (CTCAE v5)	4 (40%)	5 (50%)	3 (30%)	5 (50%)
Total adverse events ≥2 (CTCAE v5)	7	19	9	9
Adverse events ≥2 (CTCAE v5) possibly related to FMT or placebo	6	19	7	7
Adverse events ≥2 (CTCAE v5) not related to FMT or placebo	1	0	2	2
Adverse events reported ≥2 times				
Nausea	8	4	7	4
Abdominal pain	6	7	7	5
Bloating	6	7	7	4
Fatigue	6	6	8	5
Constipation	5	4	4	3
Diarrhoea	1	5	5	5
Decreased appetite	3	3	2	2
Flushing	1	2	1	1
Malaise	2	1	2	2

All Adverse events

	1. Intervention		2. Intervention	
	FMT (n = 10)	Placebo (n = 10)	FMT (n = 10)	FMT (n = 10)
Any adverse event	10 (100%)	9 (90%)	10 (100%)	7 (70%)
Total number of adverse events	44	47	54	41
Adverse events possibly related to FMT or placebo	40	46	50	39
Serious adverse events not related to FMT or placebo	1	0	1	3
Serious adverse events possibly related to FMT or placebo	0	0	0	0
Serious unsuspected adverse events possibly related to FMT or placebo	0	0	0	0
Adverse event leading to withdrawal or unmasking	0	0	0	0
Final outcome of adverse events during trial follow-up				
Adverse event leading to death	0	0	0	0
Resolved or improved	42	29	45	30
Resolved with sequelae	0	0	0	0
Not resolved during follow-up or unknown course	2	18	9	11
Adverse events reported ≥2 times				
Nausea	8	4	7	4
Abdominal pain	6	7	7	5
Bloating	6	7	7	4
Fatigue	6	6	8	5
Constipation	5	4	4	3
Diarrhoea	1	5	5	5
Decreased appetite	3	3	2	2
Flushing	1	2	1	1
Malaise	2	1	2	2
Organ-specific and timing of adverse events				
Gastrointestinal adverse events[a]	30	33	37	25
During the administration	1	1	1	3
During follow-up within 24 h	18	24	13	4

(Table 2 continues on next page)

All Adverse events	1. Intervention		2. Intervention	
	FMT (n = 10)	Placebo (n = 10)	FMT (n = 10)	FMT (n = 10)
(Continued from previous page)				
During follow-up >24 h	11	8	23	18
Systemic adverse events[b]	10	13	13	15
During the administration	3	4	1	0
During follow-up within 24 h	5	8	6	2
During follow-up >24 h	2	1	6	13

Data are n (%). CTCAE v5, Common Terminology Criteria for Adverse Events version 5.0; FMT, faecal microbiota transplantation. [a]Gastrointestinal adverse events included nausea, abdominal pain, diarrhoea, bloating, vomiting, constipation, decreased appetite, bowel sounds, faecal incontinence, flatulence, bad breath, and early satiety. [b]Systemic adverse events include fatigue, flushing, malaise headache, change in insulin requirement, oedema, and feeling lightheaded.

Table 2: **Adverse events registered during the first and second intervention.**

approach to treating bowel symptoms in patients with type 1 diabetes. Future long-term studies may determine the persistence of the treatment benefits and based on the current understanding and the observed data from our study, the need for repeated FMT in this indication is an important consideration. While our study provides initial evidence of the benefits of FMT for gastrointestinal symptom alleviation, it is plausible that repeated or ongoing treatments may be necessary to maintain these effects over time.

1. Intervention	FMT (n = 10)		Placebo (n = 10)		
	Baseline	FMT	Baseline	Placebo	p-value
GSRS-IBS	58	35	66	56	0.01
Pain	10	6	10	10	0.002
Bloating	15	9	17	18	0.03
Constipation	8	8	7	6	0.46
Diarrhoea	20	10	21	19	0.08
Early satiety	8	6	11	10	0.86
IBS-IS	108	140	77	92	0.02
Fatigue	22	27	19	18	0.06
Impact on daily activities	34	42	28	32	0.17
Sleep disturbances	12	16	11	11	0.06
Emotional distress	22	28	13	16	0.09
Eating habits	11	16	11	12	0.45
PAGI-SYM	42	25	47	41	0.03
Heartburn/regurgitation	7	3	9	10	0.07
Fullness/early satiety	11	7	13	13	0.25
Nausea/vomiting	5	2	3	4	0.40
Bloating	7	4	8	8	0.01
Upper abdominal pain	6	3	6	6	0.04
Lower abdominal pain	5	3	8	6	0.49

Data are median values. p-values indicate the change in median between the two groups during the first intervention. FMT, faecal microbiota transplantation; GSRS-IBS, Gastrointestinal Symptom Rating Scale–Irritable Bowel Syndrome; IBS-IS, Irritable Bowel Syndrome Impact Scale; PAGI-SYM, Patient Assessment of Gastrointestinal Symptom Severity Index.

Table 3: **Questionnaire scores and sub-scores.**

A complex interplay between the autonomic, central, and enteric nervous systems coordinates gastrointestinal motility. This regulation involves multiple endocrine pathways and interactions with the gut microbiota.[24] How the microbiota affects gut motility remains uncertain. Bacteria produce short-chain fatty acids during fermentation and contribute significantly to the acidity of the gastrointestinal tract. Studies suggest that these acids may play a role in stimulating movements in the lower part of the colon, thereby modifying motility patterns.[25] Recent research has proposed FMT as a potential treatment to mitigate the severity of peripheral diabetic neuropathy.[26] It has also been suggested that the gut microbiota has a causative role in maintaining glucose homeostasis.[27] Whether changes in gut motility are a consequence or a cause of abnormal microbiota remains unclear.

Most current treatment options for diabetic gastroenteropathy focus on alleviating gastroparesis. Effective management of bowel symptoms is limited by inadequate evidence and safety concerns related to available therapies.[7] This leaves patients with few alternatives besides general dietary advice, broad-spectrum antibiotics, or prokinetic laxatives. However, restoring the intestinal microbiota using FMT is an unprecedented approach with promising clinical perspectives.

FMT has become a well-established treatment for recurrent infections with *C. difficile*.[28] Furthermore, evidence is mounting in support of the role of FMT for other indications. However, the transfer of donor faecal constituents may pose a risk of adverse reactions due to the unidentified nature of the transferred material. It is also important to consider that patients with diabetic gastroenteropathy often have prolonged gastric emptying and transit through the small intestine. Additionally, they may have increased gut permeability and reduced infection resistance, which may hamper treatment effect or even predispose to serious side effects.[29] Therefore, comparing benefits against potential risks is necessary before applying FMT for new indications. In the present trial, grade 2 or higher adverse events were comparable in the two groups. The Relative Risk (RR) for adverse events of this severity was estimated at 0.8, but the broad 95% confidence interval (0.30–2.13) indicates a high degree of uncertainty. This interval means that we cannot exclude the possibility of a doubling of the per-person risk in the treatment group. However, it likely reflects the limited statistical power of this pilot study and the close distribution of adverse events between the groups.

The high number of reported adverse events suggests a significant disease burden within this patient population. Moreover, the request for patients to keep a

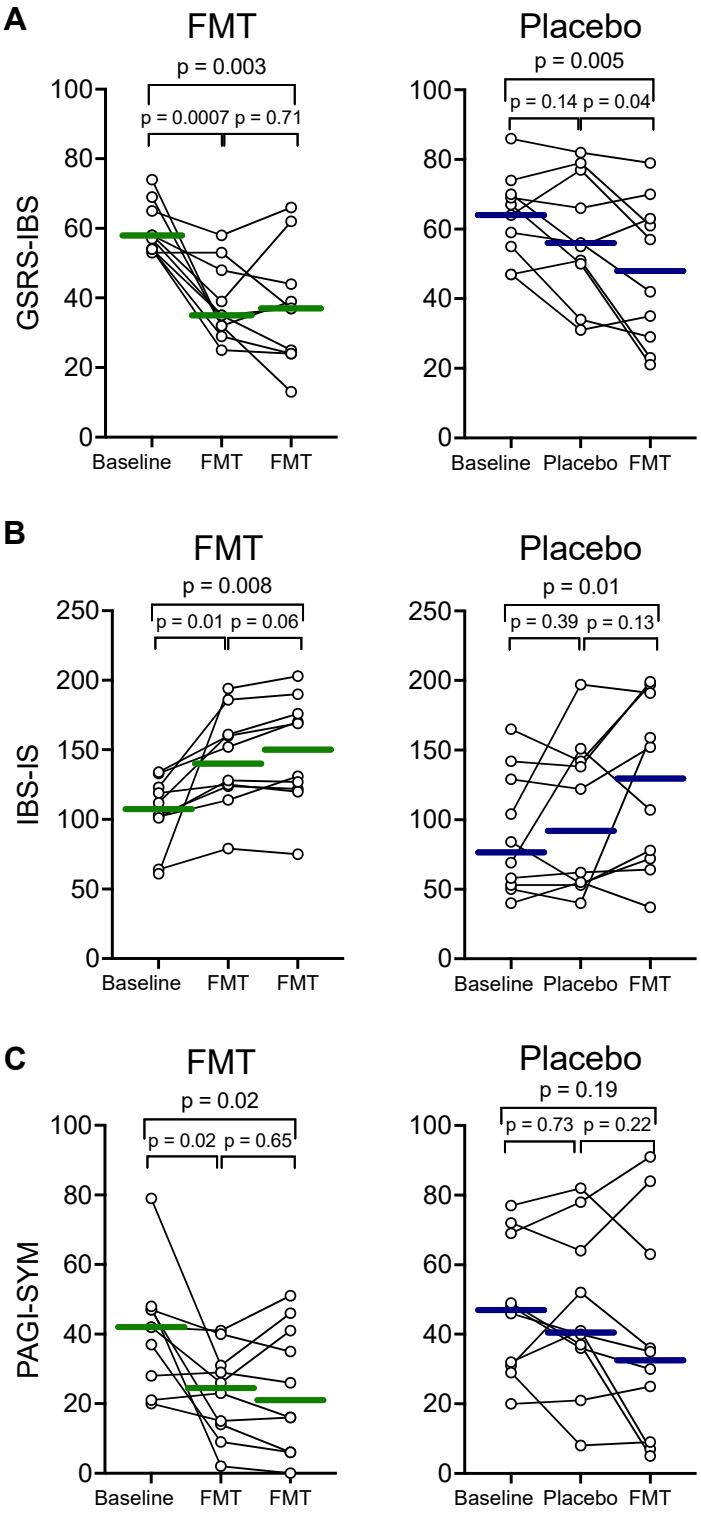

Fig. 2: Mean values for GSRS-IBS (**a**), IBS-IS (**b**) and PAGI-SYM (**c**) at baseline and during the first and second interventions, with ten patients in the FMT group and ten patents in the placebo group. The coloured line represents the mean values for each treatment. p-values indicate within-group comparisons. Assessments were made 4 weeks after each intervention, with 6 weeks between each intervention. FMT, faecal microbiota transplantation; GSRS-IBS, Gastrointestinal Symptom Rating Scale–Irritable Bowel Syndrome; IBS-IS, Irritable Bowel Syndrome Impact Scale; PAGI-SYM, Patient Assessment of Gastrointestinal Symptom Severity Index.

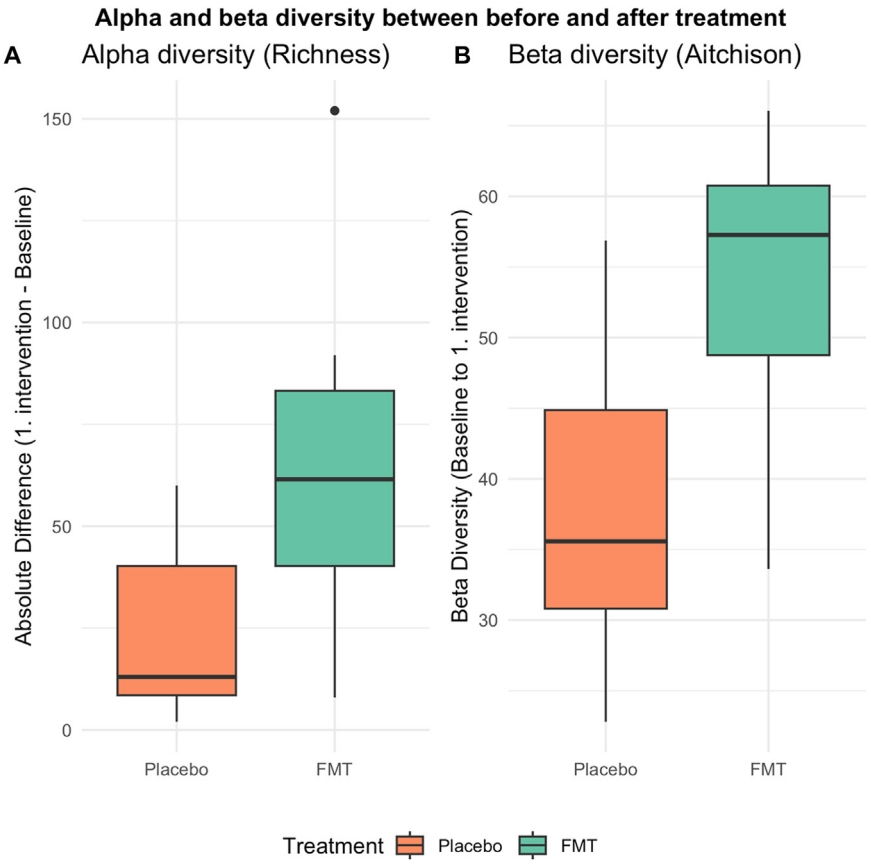

Fig. 3: Alpha and beta diversity changes from baseline to four weeks after treatment with FMT or placebo. (a) Alpha diversity (Richness) shows the absolute difference in diversity in observed richness. The FMT group exhibited a greater change in richness compared to placebo. (b) Beta diversity (Aitchison) represents the change in bacterial composition from baseline to after the first intervention. The FMT group demonstrated a more significant shift in microbial composition compared to the placebo group. Data are presented as box plots, with the middle line indicating the median, the box covering the IQR, the whiskers stretching to the furthest sample within 1.5 times the IQR from the box, and any outliers represented by a dot.

diary of daily symptoms highlights the attention to detail in monitoring their symptoms. The most commonly reported adverse events were transient and self-limiting gastrointestinal symptoms comparable to those experienced in previous FMT trials.[28] A few serious adverse events occurred, but none were considered to be related to the study treatment. The trial has yet to publish long-term follow-up data on safety. However, experiences with FMT for *C. difficile* indicate that the associated risks are low when following strict safety standards in line with those used for blood products and human tissues.[30]

The present study has limitations. It was a pilot study, and the number of patients was low. Furthermore, long-term follow-up data on our patients are pending. Thus, adverse events and clinical recurrences in gastrointestinal symptoms may occur. Most patients had severe gastrointestinal symptoms and significantly prolonged gastric emptying time. Moreover, we have yet to determine if patients with less severe symptoms may also benefit from FMT. No validated questionnaires exist for assessing symptoms of gastroenteropathy among patients with type 1 diabetes. Therefore, we used questionnaires developed for patients with irritable bowel syndrome, a group of patients sharing many of the same symptoms. The use of eight donors for 20 participants is another consideration in this study. While the setup allowed us to evaluate the different effects of specific donors, it also introduced a risk of interdependence in patient outcomes because one donor could provide faeces for more than one patient, which may influence the results. Future studies with larger sample sizes should aim to separately identify donor-specific and patient-specific determinants of effect to understand their distinct contributions to clinical outcomes. Our findings suggest a need to conduct extensive randomised studies with FMT in patients with type 1 diabetes suffering from bowel symptoms. Such studies should evaluate the clinical outcomes of FMT

and explore the underlying mechanisms. Additional randomised studies may also provide unique insights into the role of the gut microbiome in modulating onset and progression of neuropathy, glucose homeostasis, and the effects of the donor/host relationship.

In conclusion, this is the first randomised trial of FMT for patients with type 1 diabetes and symptoms of severe diabetic gastroenteropathy. To our knowledge, this study represents the most promising clinical effect of FMT beyond its established efficacy in treating *C. difficile* infection. FMT was safe, reduced gastrointestinal symptoms, and improved quality of life in a group of patients with few available treatment options. It induces significant changes in the microbiome compared to placebo, specifically in terms of richness and beta diversity. These findings support the idea that FMT drives substantial shifts in gut microbial composition, which could contribute to its therapeutic effects. In this regard, FMT holds promise as an easy-to-perform, well-tolerated, and efficient treatment for a group of patients with very severe symptoms. The results obtained in our study also hold promise for effects in patients with type 2 diabetes and could potentially positively impact the quality of life of a considerable number of patients worldwide.

Contributors

All authors met the International Committee of Medical Journal Editors criteria for authorship, taking responsibility for the integrity of the work. They were all involved in the critical review and drafting of the manuscript and approved the final version. KLH, SMDB, CLH, and KK designed and conceived the study. KK and KLH prepared the first draft with input from SMDB and CLH. KLH and DSK conducted the statistical analysis. LBT conducted the microbiome analysis and bioinformatics. KLH, SMDB, CLH, and KK directly accessed and verified the underlying data reported in the manuscript. KLH, SMDB, CLH, MWK, AMD, KBY, and KK recruited and treated patients. KLH, SMDB, CLH, CE, SM, MSM and KK contributed significant developments required to ensure trial conduct and validity. All authors contributed important intellectual content and data interpretation, had access to the study data, and carried final responsibility for the decision to submit for publication.

Data sharing statement

Data will be made available upon request in anonymised form compliant with the General Data Protection Regulation. Gaining access to pseudonymised participant data requires a formal data access agreement and, if relevant, legal ethics committee approval. Data dictionary forms will be made available following publication. The study protocol and statistical analysis plan are available online. All proposals should be directed to kathoeye@rm.dk.

Declaration of interests

CE received grants from Novo Nordisk and Abbott Diagnostics. AMD received a grant from Shionogi, consulting fees from Coloplast, and served on the advisory board for Coloplast. CH received a grant from Novo Nordisk, honoraria for lectures from Baxter, Janssen-Cilag, BMS, and Tillotts, and served as head of the board for the Danish Society for Clinical Nutrition (unpaid). SMDB received lecture honoraria from Tillotts. The remaining authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103000.

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