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Case Report

Fecal microbiota transplantation treatment for type 1 diabetes mellitus with malnutrition: a case report

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***Abstract*:** Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease. Not only genetics, but the intestinal environment affected by gut microbiota is also the key to pathogenesis. Besides the occurrence of diabetes, gut microbiota dysbiosis may also contribute to the development of diabetes-related complications. Fecal microbiota transplantation (FMT) is an emerging technique that had shown its potential as a treatment for metabolic disease. Here, we report the first case of T1DM with malnutrition and gastrointestinal symptoms treated with FMT. A 24-year-old T1DM patient suffered from poor blood glucose control, recurrent nausea and vomiting, severe malnutrition, and intractable constipation after insulin treatment. The clinical response of the patients after FMT was well, especially nausea and vomiting were significantly relieved. In addition, constipation, nutritional status, and blood glucose control (fasting blood glucose, HbA1c) gradually improved. A degree of similarity was found in gut microbiota composition between the patient and healthy donor after FMT while it was totally different before the treatment. Furthermore, pathway function analysis of MetaCYC database implies that the potential mechanism of the response of FMT may be driven by specific bacteria involved in several metabolic pathways that need further exploration. To sum up, we believe that the reconstruction of intestinal flora by FMT may be a new choice for the treatment of T1DM patients with malnutrition.

Keywords: fecal microbiota transplantation (FMT), gut microbiota, malnutrition, MetaCYC database, metagenomic sequencing, type 1 diabetes mellitus (T1DM)

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Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by T-cell-mediated destruction of β-cells leading to absolute insulin deficiency.[1] Recently, more and more evidence indicated that genetics is not the only factor in the occurrence and development of T1DM.[2] T1DM is driven by genetic, immune, environmental, and other factors.[2,3] The interaction between gut microbiota and the immune system regulating the intestinal environment is one of the key factors. Gut microbiota is not only related to the occurrence of diabetes but also contributes to the development of diabetes-related complications, especially diabetes-related malnutrition. Research had revealed the association between malnutrition and the alteration of the intestinal flora, but the majority of them focused on children or animal experiments.[4] Fecal microbiota transplantation (FMT), a technology of transplanting gut microbiota of healthy people into patients' intestines to restore the normal function of intestinal flora in the treatment of intestinal[5–7] and extra-intestinal diseases,[8,9] is also considered as a special 'organ transplantation'. Its potential for diabetes and malnutrition treatment is worth exploring.

This reported case of T1DM with malnutrition was treated with FMT. And there is a significant improvement shown in blood glucose (Glu) concentration and nutritional status after the FMT treatment.

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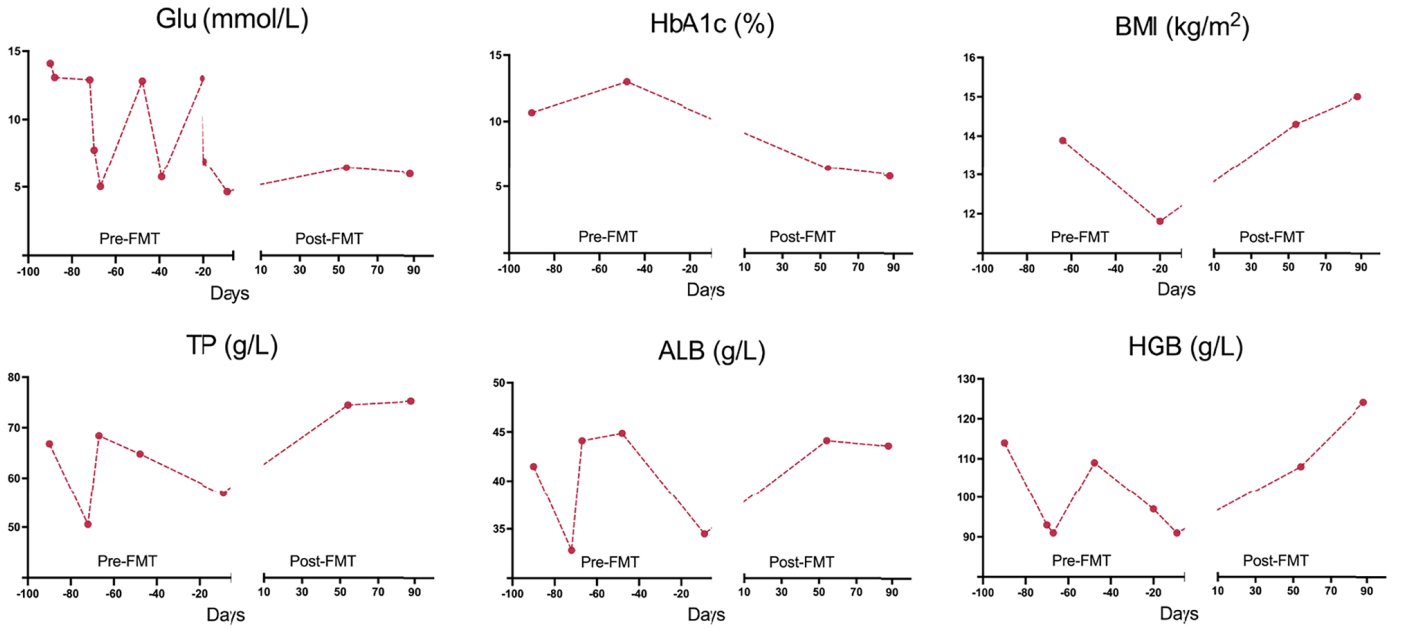

Figure 1. Dynamic curves of Glu, HbA1c, BMI, TP, ALB, and HGB.

Case report

A 24-year-old patient was diagnosed with T1DM 1 year ago and the patient's fasting Glu concentration was not well controlled after a subcutaneous injection of insulin. Since February 2021, the patient repeatedly visited hospitals because of some symptoms of diabetic ketoacidosis, such as abdominal pain, nausea, and vomiting. These symptoms continued after the relevant treatment, and the case was hospitalized in the endocrinology department, on August 14. Then, the patient was transferred to our department on August 27 with a weight of 25.5 kg and a body mass index (BMI) of 11.8 kg/m^2 and was diagnosed with type 1 diabetic ketosis with severe malnutrition after the Nutritional Risk Screening (NRS2002) with a score of 4/13. Besides, the patient had a history of depressive disorder and was treated with drugs.

Obvious gastrointestinal symptoms accompanied by intractable constipation are still repeated after conventional treatment, including proton pump inhibitors (PPIs), mosapride, Oryz-Aspergillus enzyme and pancreatin tablet, metoclopramide, and enteral nutrition. Therefore, we decided to treat the patient with FMT with informed consent. A routine examination was conducted to ensure that there are no contraindications of FMT. In order to enhance enteral nutrition supplement and digestive tract therapy in FMT, we performed nasojejunal tube implantation for the patients. The stool came from a 29-year-old healthy donor. The preparation of fecal microbial suspensions is carried out in accordance with the instructions of the automatic microfiltration system (GenFMTer; FMT Medical, Nanjing, China). The screening of healthy donor and the preparation and transplantation of microbial suspensions followed the Nanjing consensus[10] (Supplementary 1). The prepared fecal microbial suspension was stored at a low temperature of −80°C. Then rewarmed and allocated to 200 ml for injection through nasojejunal tube. This process was executed once on the 3rd and 6th of September, respectively. There were no adverse reactions during the FMT treatment.

Results

After the FMT treatment, the clinical response of patients was very well, especially nausea and vomiting were significantly relieved, and constipation gradually improved, so digestive drugs were gradually discontinued. Moreover, the patient's weight and BMI increased gradually (Figure 1). Other clinical indexes, total protein (TP), albumin (ALB), and hemoglobin (HGB) also recovered to a normal level. In terms of glycemic control, Glu and glycosylated hemoglobin (HbA1c) were maintained at a fine level, and the

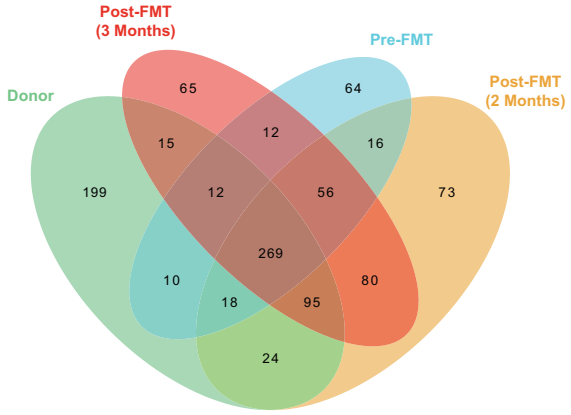

Figure 2. Venn diagram showed all OTUs obtained in fecal samples of donor and receiver (pre- and post-FMT).

dose of insulin was decreased accordingly. Moreover, fasting C-peptide was recovered to 0.12 nmol/l from an extremely low level.

Metagenomic sequencing (Supplementary 2) was performed on fecal samples from the donor and the patient (pre- and post-FMT). The Venn diagram (Figure 2) and principal coordinates analysis (PCoA) analysis (Figure 3) showed the α and β diversity of the gut microbiota among the fecal samples. In contrast to the patient, the fecal microbiota of healthy donor was more abundant in *Bacteroides uniformis*, *Bifidobacterium pseudocatenulatum*, *Escherichia coli*, and *Faecalibacterium prausnitzii* (Figure 4(b)). Significant changes were found in the distribution of the top 20 flora in relative abundances pre- and post-FMT. At the genus level (Figure 4(c)), the relative abundances of *Adlercreutzia*, *Anaerobutyricum*, *Anaerostipes*, *Bacteroides*, *Bifidobacterium*, *Blautia*, *Collinsella*, *Eubacterium siraeum*, *Faecalibacterium*, *Faecalicatena*, *Flavonifractor*, *Mediterraneibacter*, *Phocaeicola*, *Siphoviridae* sp., and *Streptococcus* increased, while those of *Alistipes*, *Escherichia*, *Myoviridae* sp., and *Parabacteroides* decreased post-FMT. At the species level (Figure 4(d)), the relative abundances of *Adlercreutzia equolifaciens*, *Alistipes shahii*, *Anaerobutyricum hallii*, *Bacteroides cellulosilyticus*, *Bacteroides stercoris*, *Bacteroides xylanisolvens*, *Bifidobacterium pseudocatenulatum*, *Blautia* sp. SC05B48, *Faecalibacterium prausnitzii*, *Phocaeicola dorei*, and *Phocaeicola vulgatus* increased, while those of *Alistipes onderdonkii*, *Bacteroides caccae*, *Bacteroides ovatus*, *B. uniformis*, *Escherichia coli*, *Parabacteroides distasonis*, *Parabacteroides merdae*, and *Parabacteroides* sp. CT06 decreased post-FMT.

Additional analysis of pathways and functions on the MetaCYC database was performed (Table 1). A total of 29 pathways associated with 20 functions were found altered post-FMT. They were

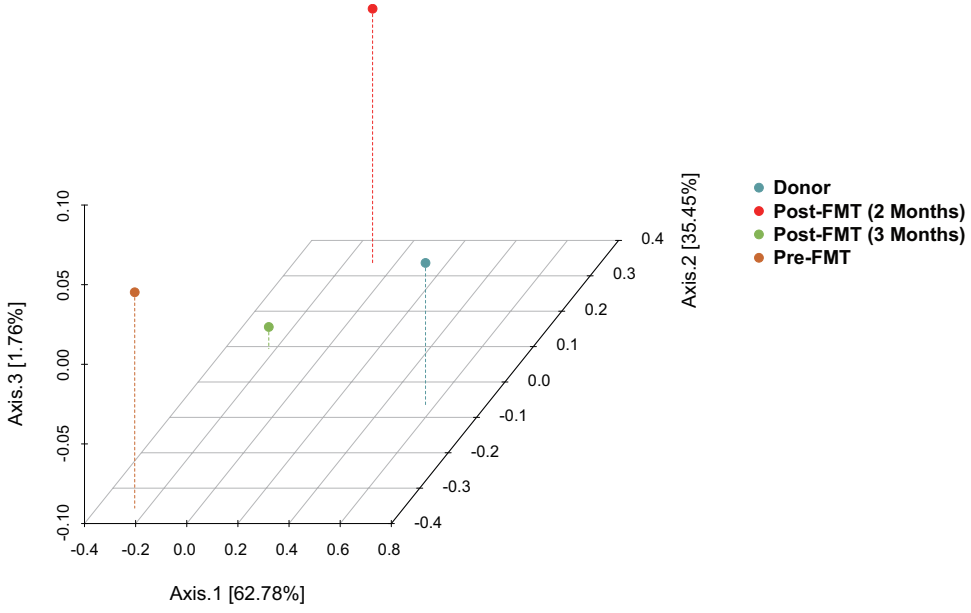

Figure 3. PCoA analysis showed the β diversity among the fecal samples of donor and receiver (pre- and post-FMT).

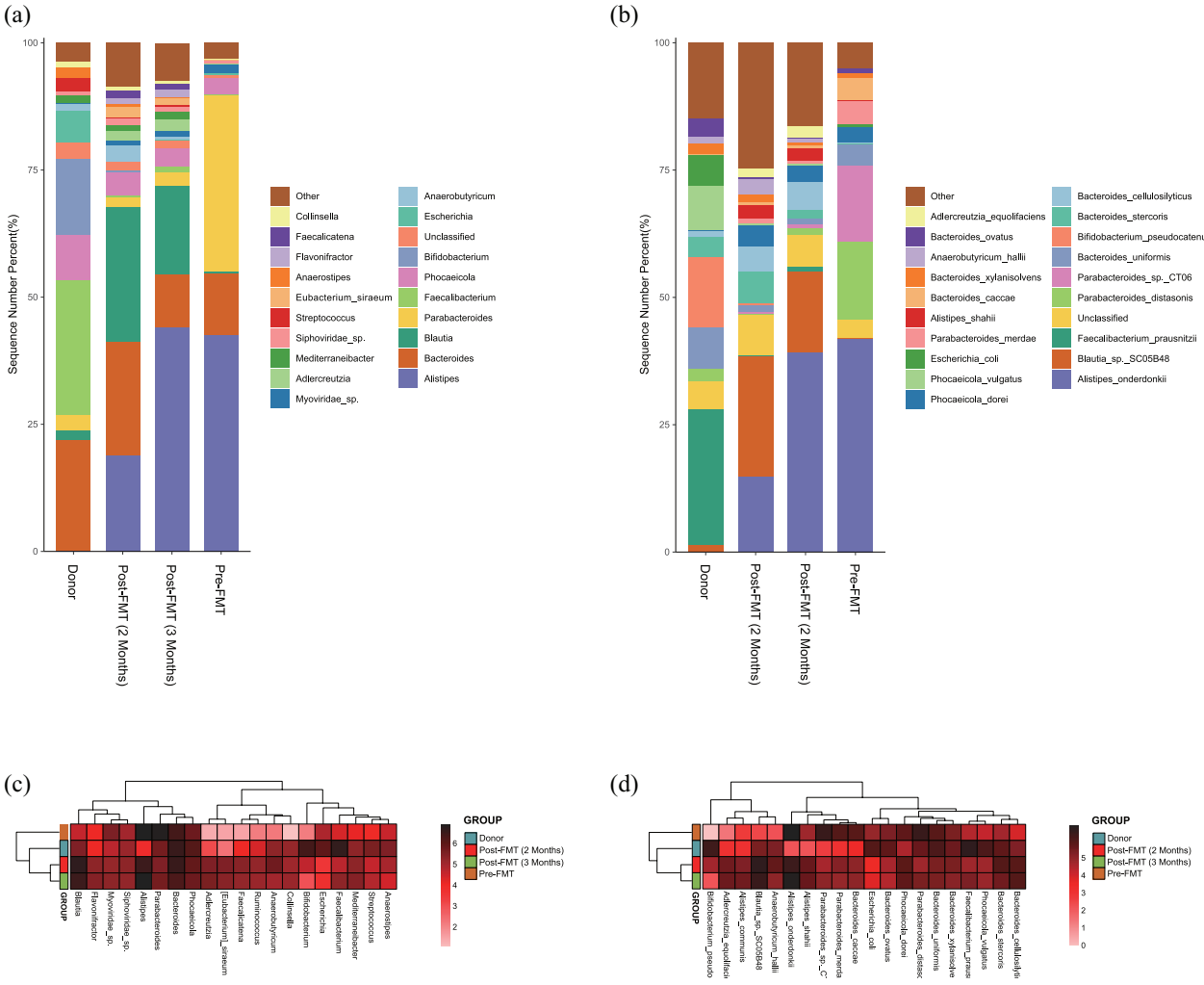

Figure 4. The bar plot showed the distribution of the top 20 flora in relative abundance at the genus (a) and species (b) levels. The heatmap showed the clustering results of the top 20 flora in relative abundance at the genus (c) and species (d) levels.

ANAGLYCOLYSIS-PWY, COA-PWY-1, PEPTIDOGLYCANSYN-PWY, PANTO-PWY, PWY0-1319, PWY-1042, PWY-2942, PWY-3841, PWY5097, PWY-5659, PWY-5667, PWY-5686, PWY-5695, PWY-6121, PWY-6122, PWY-6123, PWY-6124, PWY-6151, PWY-6277, PWY-6385, PWY-6386, PWY-6387, PWY-6609, PWY66-400, PWY-7219, PWY-7220, PWY-7282, PYRIDOXSYN-PWY, and VALSYN-PWY.

Discussion

Gut microbiota plays an important role in human health and disease. Compared with the gut microbiota of healthy people, the abundance of butyric acid-producing anaerobic bacteria and firmicutes/bacteroides ratio of T1DM patients decreased,[11,12] which was consistent with our metagenomics results. De Groot *et al.*[13] have found that FMT treatment can improve Glu control in patients with T1DM and retain the function of residual β cells. The glucose concentration of our patient fluctuated from 4.66 to 14.10 mmol/l before FMT, and it was controlled at an average of 6.23 mmol/l after the treatment. These improvements in glucose metabolism might owe to the alteration in *B. ovatus* which was confirmed over-abundance in T1DM children as compared with healthy controls.[14] Cinek *et al.*[15] have found

Table 1. MetaCYC database pathway function analysis.

Functions (altered post-FMT)	Pathway IDs	Principal bacteria
4-Amino-2-methyl-5-phosphomethylpyrimidine biosynthesis	PWY-7282	*Bacteroides ovatus/xylanisolvens*
5-Aminoimidazole ribonucleotide biosynthesis	PWY-6121 PWY-6122 PWY-6277	*Alistipes onderdonkii* *Clostridium bolteae* *Eggerthella lenta* *Eubacterium siraeum*
Adenine and adenosine salvage III	PWY-6609	*Alistipes shahii* *Bacteroides caccae/ovatus/xylanisolvens* *Odoribacter splanchnicus* *Ruminococcus gnavus*
Adenosine deoxyribonucleotides de novo biosynthesis II	PWY-7220	*Bacteroides cellulosilyticus*
Adenosine ribonucleotides de novo biosynthesis	PWY-7219	*Alistipes onderdonkii/shahii* *Bacteroides caccae/cellulosilyticus/ovatus/uniformis/vulgatus* *Parabacteroides distasonis/merdae* *Ruminococcus gnavus*
CDP-diacylglycerol biosynthesis	PWY-5667 PWY0-1319	*Bacteroides caccae/ovatus/stercoris/uniformis* *Parabacteroides distasonis/merdae*
Coenzyme A biosynthesis	COA-PWY-1	*Bacteroides caccae/ovatus/uniformis/vulgatus* *Eubacterium siraeum* *Megasphaera elsdenii* *Parabacteroides distasonis*
Folate transformations	PWY-3841	*Bacteroides caccae/ovatus/uniformis/vulgatus* *Parabacteroides distasonis/merdae*
GDP-mannose biosynthesis	PWY-5659	*Alistipes onderdonkii/shahii* *Bacteroides ovatus/xylanisolvens* *Eubacterium siraeum*
Glycolysis	ANAGLYCOLYSIS-PWY PWY-1042 PWY66-400	*Alistipes shahii* *Bacteroides caccae/ovatus* *Odoribacter splanchnicus*
Inosine-5'-phosphate biosynthesis	PWY-6123 PWY-6124	*Bacteroides ovatus*
L-lysine biosynthesis	PWY-2942 PWY5097	*Bacteroides caccae/cellulosilyticus /ovatus/stercoris/uniformis/vulgatus* *Parabacteroides distasonis/merdae*
L-valine biosynthesis	VALSYN-PWY	*Bacteroides caccae/cellulosilyticus/massiliensis/stercoris/vulgatus* *Eubacterium siraeum* *Parabacteroides distasonis*
Peptidoglycan biosynthesis	PEPTIDOGLYCANSYN-PWY PWY-6385	*Alistipes onderdonkii* *Bacteroides ovatus/uniformis/vulgatus* *Parabacteroides distasonis/merdae*

(Continued)

Table 1. (Continued)

Functions (altered post-FMT)	Pathway IDs	Principal bacteria
Phosphopantothenate biosynthesis	PANTO-PWY	*Bacteroides caccae/cellulosilyticus/ovatus / stercoris/uniformis/vulgatus* *Parabacteroides distasonis/merdae*
Pyridoxal 5'-phosphate biosynthesis	PYRIDOXSYN-PWY	*Bacteroides caccae/ovatus/stercoris/uniformis*
S-adenosyl-L-methionine cycle I	PWY-6151	*Bacteroides massiliensis/stercoris/uniformis/ vulgatus* *Eubacterium hallii*
UDP-*N*-acetylmuramoyl-pentapeptide biosynthesis	PWY-6386 PWY-6387	*Alistipes onderdonkii* *Bacteroides ovatus/uniformis/vulgatus* *Parabacteroides distasonis*
UMP biosynthesis	PWY-5686	*Alistipes onderdonkii* *Bacteroides caccae/ovatus/stercoris/uniformis* *Collinsella aerofaciens* *Eubacterium siraeum* *Parabacteroides distasonis/merdae*
Urate biosynthesis/inosine 5'-phosphate degradation	PWY-5695	*Alistipes shahii* *Bacteroides caccae/ovatus/stercoris/vulgatus* *Megasphaera elsdenii* *Parabacteroides distasonis*

that the imbalance within the *Bacteroides* genus might be one of the key factors in T1DM. But some species, such as *B. caccae* and *Bacteroides vulgatus*, were found to increase in T1DM women in pregnancy while they were proved to decrease in islet autoimmunity children and inversely associated with it,[15,16] their roles in T1DM are still ambiguous. The results of our case were in line with the pregnant women study. These three species of *Bacteroides* were involved in 19 functions alteration post-FMT. Among them, pyridoxal 5'-phosphate that could protect islet beta-cell from streptozotocin-induced dysfunction might be the key pathway (PYRIDOXSYN-PWY) that benefits diabetes improvement.[17] But this specific mechanism still needs further exploration to illustrate.

Besides diabetes, our patient was also complicated with severe malnutrition. The application of FMT treatment in malnutrition was still relatively rare, only one case of weight gain after FMT was reported.[18] In our case, the improvement in the condition of nutrition is markedly reflected in the increase in BMI, TP, ALB, and HGB. The patient also came back from malnutrition-led amenorrhea after FMT. In the gut microbiota changes part, two bacteria came to our notice. *Blautia* is a kind of intestinal flora that had a positive correlation with weight.[19] We observed a significant increase in *Blautia* after FMT. *Parabacteroides*, a probiotic enriched in the patient's flora before FMT and decreased after FMT. Evidence showed that *P. distasonis* improves lipid metabolism and decreases weight gain by elevating the level of succinate.[20] Other research found that succinate-fed mice had a higher basic energy consumption.[21] These implied that the over-abundance of *P. distasonis* might turn it into a pathogenic bacterium, which led to malnutrition in our case.

In addition, the patient had been hospitalized for depressive disorder and had taken duloxetine previously. And our results were surprised to find changes in depression-related flora, such as *A. onderdonkii*, *B. uniformis*, and *P. diatasonis*.[22–25] Fortunately, the depression did not recur during the follow-up.

Conclusion

In summary, FMT treatment was successfully performed in a T1DM patient with malnutrition

in this case. This means a new choice for the treatment of these diseases was now offered. Further research on its mechanism still needs to be done. Despite this being a case report, our results are highly suggestive for exploring the association between gut microbiota and metabolic diseases.

Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the provisions of the Declaration of Helsinki of 1975. The Committee of The First Affiliated Hospital of Shantou University Medical College approved the study (approval no. 2019090). Written informed consent was obtained from the patient for treatment before FMT.

Consent for publication

Written informed consent was obtained from the patient for publication of the case and any accompanying data.

Author contributions

Yan-Chun Xie: Data curation; Formal analysis; Visualization; Writing – original draft.

Xu-Bin Jing: Conceptualization; Resources; Supervision; Writing – review & editing.

Xiang Chen: Formal analysis; Visualization; Writing – review & editing.

Ling-Zi Chen: Methodology; Writing – review & editing.

Shao-Hui Zhang: Methodology; Writing – review & editing.

Xian-Bin Cai: Conceptualization; Funding acquisition; Project administration; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The raw data were available in the NCBI Bioproject database with an ID of PRJNA849709.

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Supplemental material

Supplemental material for this article is available online.

References

1. DiMeglio LA, Evans-Molina C and Oram RA. Type 1 diabetes. *The Lancet* 2018; 391: 2449–2462.
2. Durazzo M, Ferro A and Gruden G. Gastrointestinal microbiota and type 1 diabetes mellitus: the state of art. *J Clin Med* 2019; 8: 1843.
3. Ilonen J, Lempainen J and Veijola R. The heterogeneous pathogenesis of type 1 diabetes mellitus. *Nat Rev Endocrinol* 2019; 15: 635–650.
4. Fluitman KS, De Clercq NC, Keijser BJF, *et al.* The intestinal microbiota, energy balance, and malnutrition: emphasis on the role of short-chain fatty acids. *Expert Rev Endocrinol Metab* 2017; 12: 215–226.
5. Surawicz CM, Brandt LJ, Binion DG, *et al.* Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013; 108: 478–498; quiz 499.
6. Johnsen PH, Hilpüsch F, Cavanagh JP, *et al.* Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol* 2018; 3: 17–24.
7. Costello SP, Hughes PA, Waters O, *et al.* Effect of fecal microbiota transplantation on 8-week

remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA* 2019; 321: 156–164.

8. Bajaj JS, Kassam Z, Fagan A, *et al*. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. *Hepatology* 2017; 66: 1727–1738.
9. Vendrik KEW, Ooijevaar RE, de Jong PRC, *et al*. Fecal microbiota transplantation in neurological disorders. *Front Cell Infect Microbiol* 2020; 10: 98.
10. Group FMT-S. Nanjing consensus on methodology of washed microbiota transplantation. *Chin Med J* 2020; 133: 2330–2332.
11. Leiva-Gea I, Sanchez-Alcoholado L, Martin-Tejedor B, *et al*. Gut microbiota differs in composition and functionality between children with type 1 diabetes and MODY2 and healthy control subjects: a case-control study. *Diabetes Care* 2018; 41: 2385–2395.
12. Giongo A, Gano KA, Crabb DB, *et al*. Toward defining the autoimmune microbiome for type 1 diabetes. *ISME J* 2011; 5: 82–91.
13. De Groot P, Nikolic T, Pellegrini S, *et al*. Faecal microbiota transplantation halts progression of human new-onset type 1 diabetes in a randomised controlled trial. *Gut* 2021; 70: 92–105.
14. Mokhtari P, Metos J and Anandh Babu PV. Impact of type 1 diabetes on the composition and functional potential of gut microbiome in children and adolescents: possible mechanisms, current knowledge, and challenges. *Gut Microbes* 2021; 13: 1–18.
15. Cinek O, Kramna L, Lin J, *et al*. Imbalance of bacteriome profiles within the Finnish Diabetes Prediction and Prevention study: parallel use of 16S profiling and virome sequencing in stool samples from children with islet autoimmunity and matched controls. *Pediatr Diabetes* 2017; 18: 588–598.
16. Roth-Schulze AJ, Penno MAS, Ngui KM, *et al*. Type 1 diabetes in pregnancy is associated with distinct changes in the composition and function of the gut microbiome. *Microbiome* 2021; 9: 167.
17. Kiran SG, Dorisetty RK, Umrani MR, *et al*. Pyridoxal 5' phosphate protects islets against streptozotocin-induced beta-cell dysfunction – in vitro and in vivo. *Exp Biol Med* 2011; 236: 456–465.
18. Alang N and Kelly CR. Weight gain after fecal microbiota transplantation. *Open Forum Infect Dis* 2015; 2: ofv004.
19. Zhao T, Zhan L, Zhou W, *et al*. The effects of erchen decoction on gut microbiota and lipid metabolism disorders in Zucker diabetic fatty rats. *Front Pharmacol* 2021; 12: 647529.
20. Wang K, Liao M, Zhou N, *et al*. Parabacteroides distasonis alleviates obesity and metabolic dysfunctions via production of succinate and secondary bile acids. *Cell Rep* 2019; 26: 222–235. e225.
21. De Vadder F, Kovatcheva-Datchary P, Zitoun C, *et al*. Microbiota-produced succinate improves glucose homeostasis via intestinal gluconeogenesis. *Cell Metab* 2016; 24: 151–157.
22. Gomez-Nguyen A, Basson AR, Dark-Fleury L, *et al*. Parabacteroides distasonis induces depressive-like behavior in a mouse model of Crohn's disease. *Brain Behav Immun* 2021; 98: 245–250.
23. Zhang Y, Fan Q, Hou Y, *et al*. Bacteroides species differentially modulate depression-like behavior via gut-brain metabolic signaling. *Brain Behav Immun* 2022; 102: 11–22.
24. Strandwitz P, Kim KH, Terekhova D, *et al*. GABA-modulating bacteria of the human gut microbiota. *Nat Microbiol* 2019; 4: 396–403.
25. Parker BJ, Wearsch PA, Veloo ACM, *et al*. The genus *Alistipes*: gut bacteria with emerging implications to inflammation, cancer, and mental health. *Front Immunol* 2020; 11: 906.

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