Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Fecal Microbiota Transplantation: A Prospective Treatment for Type 2 Diabetes Mellitus

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Purpose of Review: The aim of this review is to summarize the role of gastrointestinal microbiome (GM) in the development of type 2 diabetes mellitus (T2DM). Besides, we discuss the feasibility of applying FMT in the treatment of T2DM and propose a series of processes to refine the use of FMT in the treatment of T2DM.

Recent Findings: T2DM is a metabolic disease which is connected with the GM. According to many researches, GM can produce a variety of metabolites such as bile acid, short chain fatty acids, lipopolysaccharides and trimethylamine oxide which play an important role in metabolism. FMT is a method to regulate GM and has been observed to be effective in the treatment of metabolic diseases such as T2DM in some mouse models and people. However, there is still a lack of direct evidence for the use of FMT in the treatment of T2DM, and the process of FMT is not standardized.

Summary: Dysregulation of GM is closely related to the development of T2DM. Promoting the conversion of GM in T2DM patients to normal population through FMT can reduce insulin resistance and lower their blood glucose level, which is an optional treatment for T2DM patients in the future. At present, the feasibility and limitations of applying FMT to the treatment of T2DM need to be further studied.

Keywords: fecal microbiota transplantation, type 2 diabetes mellitus, gastrointestinal microbiome, treatment

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia, which progressively involves systemic micro- and macro-vasculature, leading to disease of the aorta, retina, kidneys and peripheral nerves and an increased risk of cardiovascular and cerebrovascular complications.[1] According to IDF Diabetes Atlas, 537 million adults are living with diabetes worldwide, and this number is predicted to rise to 643 million by 2030 and 783 million by 2045. In addition, 541 million adults have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes.[2] The pathogenesis of T2DM is based on insulin resistance and defective insulin secretion. Studies have shown that adipose tissue dysfunction, chronic inflammation of the intestinal tract, abnormal mitochondrial function and dysregulation of the hypothalamic-pituitary-adrenal axis are directly or indirectly involved in these processes.[1,3] In recent years, a new direction of research has been observed: gastrointestinal microbiome (GM).[4] GM is one of the important regulators of energy metabolism and substrate metabolism in the human body.[5–7] Disturbances in GM may lead to metabolic imbalances in the body, which can lead to a variety of metabolic disorders such as chronic inflammation, insulin resistance, and obesity.[8–10] GM is similarly regulated by signaling molecules from the body, which can contribute to the development of T2DM.[11,12] Thus, disturbances in GM have been recognized as a potential contributor to the increased prevalence of diabetes.[13]

According to some studies, GM can participate in the control of bile acid (BA) metabolism, and its metabolites such as short chain fatty acids (SCFAs), lipopolysaccharides (LPS) and trimethylamine oxide (TMAO) also play a significant function in human metabolism, which can be a new target for the treatment of T2DM.[14–17] Therefore, regulating the composition of the GM in patients with T2DM may suggest a new therapeutic idea.[18] The use of a variety of prebiotic

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and probiotic strains in patients with T2DM appears to reverse ecological dysregulation and restore the functional integrity of the gut.[19] In other words, it is important to maintain bacterial diversity and abundance, rather than stimulating only one bacterial genus.[20]

Fecal microbiota transplantation (FMT) has been used in the treatment of colitis due to recurrent Clostridium Difficile Infection (rCDI) initially. It processes feces from healthy donors and transports them to the recipient via endoscopy, enemas and capsules, relying on the transplanted GM to compete with Clostridium difficile for the dominant strain, changing the abundance of the GM composition and thus restoring the diversity of the GM.[21] Studies in people with metabolic syndrome have found that transplantation of feces from donors leads to a closer composition of GM in the recipient to the donor and an improvement in insulin resistance.[22–24] An FMT test was performed on a T2DM mouse model, and the results showed that the feces of mice after FMT showed an increase in Bifidobacterium, and Prevotella, with a significant decrease in Sulfate-reducing bacteria (SRB), Bilophila, and Desulfovibrio after treatment.[25] Wang et al[26] found that T2DM mice treated with FMT had a decrease in HbA1c levels with time, a decrease in IL-6 and TNF-α inflammatory factors, and a significant increase in the number and size of islets, as well as an increase in insulin sensitivity.

Recently, several studies started to observe the effects of FMT in patients with T2DM. Ng et al[27] found that FMT in obese patients with T2DM acquired ≥20% of lean-associated microbiota at week 24. Another prospective study also showed that GM in T2DM patients is reorganized by FMT and there is a significant decrease in glucose, glycosylated hemoglobin, uric acid and an increase in postprandial C-peptide.[28] However, in this case, they also found that donors with higher levels of the family Rikenellaceae and the genus Anaerotruncus (family Ruminococcaceae) were beneficial in improving the success of FMT.[28] Therefore, increasing beneficial strains of bacteria through FMT and changing the composition of GM in T2DM patients may regulate metabolism.[29] In order to better understand the fundamentals of the therapy, we herein review the role of GM on the pathogenesis of T2DM and the feasibility of FMT in T2DM. Moreover, we discuss the relevant problems in the application of FMT.

Dysbiosis of Gastrointestinal Microbiome is an Important Part of T2DM Pathogenesis

GM is a hot research spot in recent years. Animal experiments and clinical studies have shown that the GM plays a vital function in the pathogenesis of T2DM, which is mainly involved in regulating the metabolic process of the body indirectly or directly through the production of various metabolites.[30,31] In particular, SCFAs, LPS, and TMAO play a key role in the pathogenesis of T2DM, as shown in Figure 1.[32]

SCFAs are the products of dietary fiber fermented by GM, mainly including acetate, propionate and butyrate. Recent studies have found that SCFAs are involved in maintaining the integrity of the intestinal barrier and can prevent the inflammation in the intestine effectively.[33] Meanwhile, SCFAs also have a regulatory differentiation effect on immune cells such as macrophages, perhaps by influencing the secretion of some cytokines such as interleukin-12(IL-12), IL-6, CO.[34] In terms of energy metabolism, both propionate and butyrate can increase intestinal glucose production.[35] Propionate mainly affects glucose and lipogenesis in liver indirectly, while butyrate can directly upregulate intestinal glucogenesis genes.[36] In addition, SCFAs also participate in the gut-brain axis to affect the production of hormones to regulate metabolic activity.[37] In particular, they induce the secretion of hormones such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) by interacting with G protein-coupled receptors (GPCRs) on colonic cells, and subsequently send indirect signals to the brain to influence the appetite of the body.[38,39] SCFAs are also involved in the regulation of insulin and ghrelin.[40,41] Acetate produced by the GM can activate the parasympathetic nervous system to promote the secretion of glucose-stimulated insulin and ghrelin, which leads to obesity, hyperphagia, and insulin resistance.[42] Besides, a significant decrease of butyric acid producing bacteria can be observed in the T2DM patients.[43] Currently, it has been shown in mice that oral supplementation with butyrate prevents the development of insulin resistance and obesity, and an increase in adaptive thermogenesis and fatty acid oxidation.[44]

Metabolic endotoxemia and other chronic low-grade inflammation are also an important part of the pathology of T2DM, and several studies suggest that the release of LPS and some inflammatory cytokines are strongly associated with GM.[45] LPS is a major component of the cytoderm of Gram-negative bacteria and is a common endotoxin in the intestine.

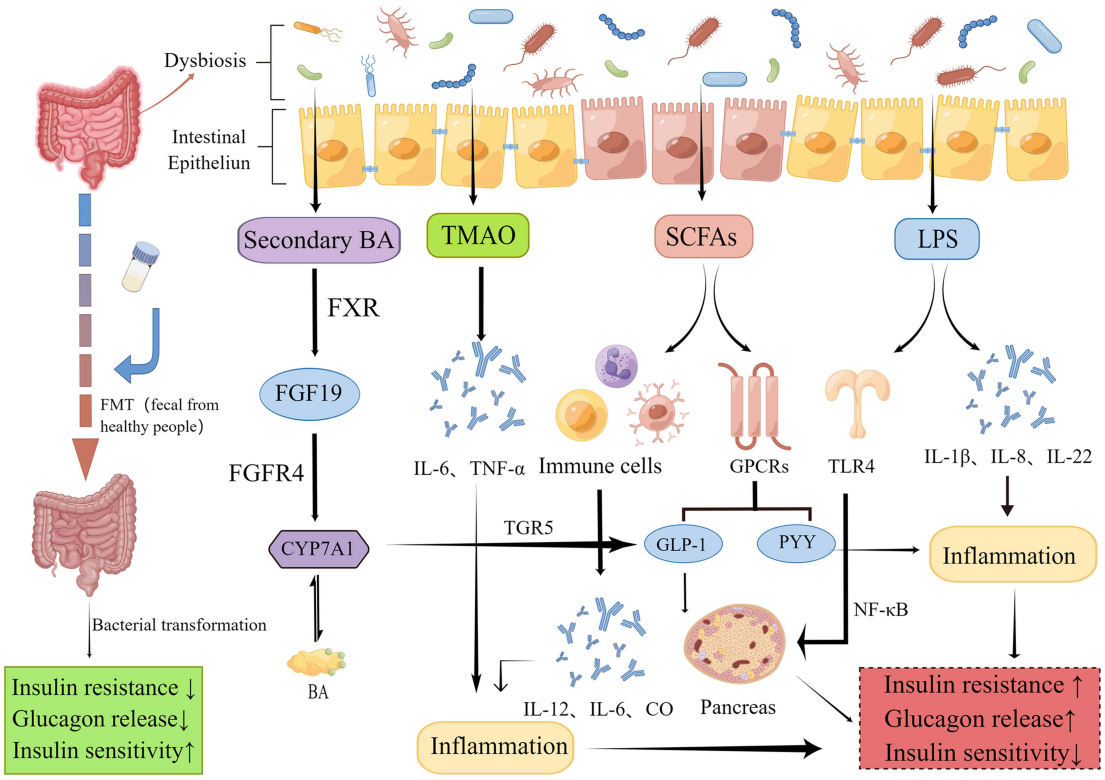

Figure 1 How gastrointestinal microbiome regulates the human's metabolism (Created by Figdraw).

When the intestinal barrier is disrupted, LPS can enter the blood circulation through the intestinal epithelium leading to the development of metabolic endotoxemia and subsequently cause the development of obesity, insulin resistance and T2DM.[8,46] Gomes et al[47] showed that the concentrations of LPS and lipopolysaccharide-binding protein(LBP) were significantly higher in T2DM patients than in healthy ones after systematic evaluation, and affected glucose metabolism. Amyot et al[48] demonstrated that LPS inhibit beta-cell gene expression in a Toll-Like Receptor4(TLR4)-dependent manner and via nuclear factor kappa-B (NF-κB) signaling in pancreatic islets. Tian et al[49] identified a positive correlation between LPS and the levels of cytokines IL-1β and IL-8. IL-1β is involved in the immune response and β-cell injury in islets, while IL-8 recruits neutrophils, macrophages and lymphocytes to the inflammatory sites.[50,51] Both of them involve in the development of metabolic endotoxins and T2DM. The anti-inflammatory cytokine IL-22 plays an important role in stimulating immunity and maintaining the integrity of the intestinal mucosal barrier.[52] It can be increased by GM and has demonstrated that lacking IL-22 receptors has a higher risk of metabolic disorders in a high-fat diet, and giving exogenous IL-22 can reverse the condition of hyperglycemia and insulin resistance in mice.[4,53] In a mouse model, it is possible to decrease some inflammatory factors such as tumor necrosis factor-α (TNF-α) and IL-6 by supplementing with some beneficial intestinal strains such as L. paracasei, Lactobacillus casei CCFM419, and A. muciniphila.[54–56]

GM also affects the body's glucose metabolism by participating in bile acid metabolism.[57] BA is mainly produced by cholesterol metabolism in the liver and then excreted by the gallbladder into the intestine and participate in the enterohepatic cycle, while GM can modify bile acids after they enter the intestine, such as deconjugation, dehydrogenation, dehydroxylation, and epimerization.[58] It has been suggested that the GM not only regulates secondary bile acid metabolism, but also restrains the inhibition of Farnesoid X receptor(FXR) in the ileum to reduce bile acid synthesis in the liver.[59,60] We know that the ileal FXR induces the expression of fibroblast growth factor19(FGF19), which combines with FGF receptor 4 (FGFR4) in the liver to inhibit the expression of cholesterol 7α-hydroxylase (CYP7A1), ultimately playing a negative feedback regulatory role on bile acids.[61] However, when ileal FXR is inhibited, GLP-1 gene expression and secretion can be increased to lower body glucose.[62] Takeda G protein-coupled receptor 5(TGR5), a GPCRs, is another bile acid receptor that can increase energy expenditure in brown adipose tissue and muscle and

promote GLP-1 release from intestinal L cells to control glucose homeostasis.[63] Pathak et al[64] found that when intestinal FXR was activated, Acetatifactor and Bacteroides increased in the intestine, which led to the induction of TGR5 to stimulate GLP-1 secretion and improve hepatic glucose and insulin sensitivity. Bacteroides acidifaciens has been shown to regulate glucose metabolism, lipid metabolism and energy homeostasis through signaling factors such as FXR and TGR5.[65,66]

TMAO is one of GM products as well. It is produced from foods rich in phosphatidylcholine and L-carnitine by the effect of intestinal microbial enzymes to produce trimethylamine (TMA), which is subsequently oxidized in the liver by flavin monooxygenase (FMO).[67] Currently, studies have shown that TMAO promotes atherosclerosis and there is a positive dose-dependent association between circulating TMAO levels and increased risk of diabetes.[68,69] TMAO can also promote the release of pro-inflammatory factors such as IL-6 and TNF-α in vivo by activating NF-κB, increasing the possibility of vascular r-associated inflammation.[70] A study conducted in patients with T2DM and Chronic Kidney Disease(CKD) found that TMAO levels in serum were significantly increased and that TMAO-producing bacteria such as Clostridium, Escherichia, Enterobacter, Acinetobacter, Proteus were significantly increased in proportion, while the LPS and Zonulin protein associated with intestinal permeability were also positively correlated with TMAO levels.[15] A Mendelian randomization by Jia et al[71] showed that both T2DM and kidney disease increased TMAO levels in vivo. A case-control study by Shan et al[72] found that higher plasma TMAO was associated with increased odds of T2DM in a linear dose-response fashion and was not modified by FMO polymorphism. However, the exact association between TMAO and T2DM is not defined yet and needs to be further investigated.

Fecal Microbiota Transplantation May Be Used in Treatment for T2DM

FMT is a method of transporting healthy donor fecal microbiota to the patient via nasogastric tube, colonoscope, enema, capsule, or a combination of these to restore a normal GM.[21] FMT was first reported in 1958 and is now widely used in the treatment of recurrent Clostridium difficile infections.[73–75] As FMT can significantly change the composition of GM in diseased patients in a short period of time and bring it closer to that of healthy donors, it can be extended to the treatment of metabolic diseases associated with changes in GM.[76]

Several studies have shown significant differences in the composition of the GM in T2DM patients. Chen[77] found that there are large numbers of Bacteriodetes and Escherichia coli and low numbers of Clostridum and Roseburia and Fecalibacteria in gut dysbiosis in T2DM patients. Another study found a reduced bacterial diversity in mesenteric adipose tissue (MAT) of patients with T2DM, and a more pronounced deposition of Escherichia–Shigella and Serratia as well as a higher presence of Neisseriaceae than people without diabetes.[78] Sedighi et al[79] found a significantly higher level of Lactobacillus and a significantly lower level of Bifidobacterium in patients with T2DM. Prevotella and Fusobacterium groups also showed insignificantly higher levels in diabetic patients.[79] Gurung et al[4] concluded that the genera of Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia and Roseburia were negatively associated with T2DM, while the genera of Ruminococcus, Fusobacterium, and Blautia were positively associated with T2DM. In conclusion, there is a need to reshape the gut microbiota in T2DM therapy.

Currently, the number of animal and clinical experimental researches on FMT in metabolic diseases is gradually increasing. Ridaura et al[80] found that co-housing mice carrying obese microbiota with mice carrying lean microbiota prevented weight gain and the development of obesity-associated metabolic phenotypes in the obese group of mice, which implied that diet-microbe interactions could be propagated across individuals. In addition, some evidence suggested that infusion of lean donor gastrointestinal microbiota into patients with metabolic syndrome could improve insulin sensitivity, and pre-treatment fecal microbiota characterization might predict treatment efficacy.[22,81,82] Zhang et al[83] suggested that a possible mechanism was that GM and metabolites altered the intestinal structure and improved insulin and leptin resistance through the JAK2 / IRS / Akt pathway, which had a significant improvement in the glycemic-lipid metabolic phenotype. Another study showed that the GM of the T2DM population was significantly different from that of the normal glucose-tolerant population, and transplanting the GM of the normal glucose-tolerant population into mice resulted in a significant decrease in fasting glucose, postprandial glucose, total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol levels, and an increase in high-density lipoprotein (HDL) cholesterol levels.[84] This indicated that GM from normal population might have the potential to improve glycolipid metabolism in T2DM patients through FMT.[84] Wu

et al[85] conducted a randomized controlled prospective study suggested that FMT alone significantly improved clinical indicators such as HOMA-IR and BMI in T2DM, and the donor microbiota effectively colonized in T2DM. Microbial diversity and community were also significantly increased compared to baseline.[85] Despite the fact that most studies showed a significant improvement in metabolism in the receptor group, some studies observed no statistically significant difference in metabolic indices after FMT treatment, which might suggest that FMT alone appeared to be insufficient to treat or prevent metabolic disorders in humans.[23,86] We have summarized the results of current studies applying FMT to the treatment of patients with T2DM, as shown in Table 1.

For safety, several clinical studies on the safety of FMT have shown that no serious adverse reactions have occurred with FMT either by cryo-capsule or endoscopy.[87,88] Occasionally, tolerable gastrointestinal reactions such as bloating, flatulence, belching and abdominal cramps, abdominal discomfort, irregular bowel movements and vomiting have been observed.[23,89,90] Many of the side effects are mild, self-limiting, and gastrointestinal in nature.[91] Very few cases have been reported of death after FMT, but they were mostly due to the patient's comorbidities and not related to the actual FMT procedure itself.[92] Therefore, the use of FMT for T2DM treatment is feasible, but the effect of FMT on GM needs to be further explored, and more clinical trials on how to apply FMT to T2DM are needed.

Problems Faced in the Application of FMT in the Treatment of T2DM

In the 2017 European FMT Conference Consensus, the basic requirements for FMT in C. difficile infection including indications, donor selection, fecal material preparation and transportation, and late clinical management were detailed.[93] However, the norms for the use of FMT in other diseases are still being explored. FMT may be influenced by a variety of factors. For receptor groups, FMT may be more effective in receptors characterized by specific intestinal dysbiosis, while some receptors may not be amenable to FMT. FMT may also be considered in combination with other therapies to improve efficacy. The frequency of FMT and the route of administration are also important. As for donors, the selection criteria of the donor, the treatment of fecal extracts, and the transportation and preservation of the extracts may also affect the efficacy. We will discuss the above issues.

Screening for Specific Receptors

In diabetic patients, the composition of GM is significantly changed. Some bacteria such as Blautia and Faecalibacterium have been shown to be potentially associated with T2DM, and Rikenellaceae and Anaerotruncus may also serve as potential biomarkers for selecting patients with T2DM for FMT.[28,79,94–96] Several species of Lactobacillus are also strongly associated with T2DM, and the Lactobacillus spp correlate positively with fasting glucose and HbA1c levels.[97–99] Studies in different population have also shown that diabetic gut microbiota have lower concentrations of

Table 1 Major Findings from the Studies of FMT in T2DM Patients

Patient Cohort	Type	Groups	Main Observations	References
Obese with T2DM	A 24-week, double-blind, randomised controlled trial	FMT plus LSI, FMT alone, sham FMT plus LSI	A decrease in TC, LDL-C and liver stiffness.	Ng SC et al, 2022[27]
T2DM	A 4-week, randomized, controlled, prospective study	Metformin, FMT, or FMT plus metformin	A decrease in BMI, PBG, HbA1c, and FBG. HOMA-HBCI and HOMA-IR was improved.	Wu Z et al, 2023[85]
T2DM	A 12-week, nonblinded, one-armed intervention trial	FMT	A decrease in HbA1c, FBG and UA, while postprandial C-peptide increased.	Ding D et al, 2022[28]
T2DM	A 90-days, controlled open-label trial	Diet-only, diet-FMT	A decrease in BMI, FBG, HbA1c, and SBP.	Su L et al, 2022[25]

Abbreviations: LSI, lifestyle intervention; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, Body Mass Index; PBG, postprandial blood glucose; HbA1c, glycosylated hemoglobin type A1c; FBG, fasting blood glucose; HOMA-HBCI=20×FINS/(FBG-3.5); HOMA-IR=(FBG×FINS)/22.5; FINS, fasting insulin; UA, uric acid; SBP, systolic blood pressure.

Roseburiaintestinalis and Faecalibacterium prausnitzii (both butyrate-producing bacteria), and higher levels of Lactobacillus gasseri, Streptococcus mutans and Clostridiales members.[100] One study found that an increase in fecal concentrations of Lactobacillus gasseri, Streptococcus mutans, and Escherichia coli could predict the development of insulin resistance.[14] In addition, the genera Ruminococcus, Fusobacterium and Blautia, which are positively correlated with T2DM, and even the reduction of butyrate producing bacteria can be considered as a specific biomarker.[4] Therefore, we propose that the GM of T2DM patients can be pre-tested, focusing on the status of microbiome closely related to T2DM, and if dysbiosis of this microbiome is detected, it can be used as a reference condition for the use of FMT. We recommend that patients have at least one gut bacteria composition measure using the 16S rRNA technique before treatment. 16S rRNA Gene Sequencing can detect bacterial strains with specialized functions in the gut which may have a significant effect on metabolism and body homeostasis.[101] The advantage of this technique is that species are identified by cross-referencing with a database of discovered bacterial species, and identifiable species are limited to the previously sequenced range.[102] Accordingly, we can evaluate the therapeutic effect of FMT by determining if the GM of the recipient is colonized by bacteria from the donor group and whether the structure of the recipient's GM is altered toward the donor composition.[103]

Contraindications for FMT

Not everyone is suitable for treatment with FMT. FMT is not recommended for those with autoimmune deficiency diseases, malignancies, acute complications of T2DM, uncontrolled infections, severe gastrointestinal symptoms such as diarrhea, and serious adverse reactions after receiving FMT. Some studies have shown that adverse events in FMT are mostly related to the severity of the disease itself, rather than FMT itself.[104,105] Therefore, it is necessary to do some evaluation of the patient's condition before deciding to perform FMT. The first step is to determine whether the patient has life-threatening acute complications such as ketoacidosis and hyperglycemic hyperosmolar state, etc. If acute complications are present, the complications will be treated as a priority and the treatment with FMT will be considered after the vital signs are stabilized. Secondly, the adverse effects of transplant flora on the patient should be considered. If the patient is in an abnormal immune status, such as suffering from autoimmune diseases, malignant tumors, or currently existing uncontrolled infection means that after performing FMT may face an increased risk of infection and is not suitable for FMT. This is primarily due to the weak immune system that increases the risk of pathogen transfer and subsequent infection from the donated samples.[91] Finally, the tolerance of the body to FMT should be determined. People who experience a serious gastrointestinal reactions or other adverse reactions after receiving FMT should stop immediately. Currently, the adverse effects regarding the use of FMT in patients with T2DM are unclear and further research is needed.

Selection of FMT Donors

The selection of FMT donor plays a decisive role in the efficacy of FMT. Some of the risks of FMT can be mitigated by rigorous donor screening.[106] We think that we can refer to the donor screening criteria and process proposed in previous studies.[93,107–110] In addition, Alang and Kelly report an example of a patient who became obese after FMT, so we focus on the requirement that the donor does not have T2DM or other metabolism-related diseases and has normal fasting glucose and insulin levels.[107] A systematic screening of the donor should be conducted before the first four weeks of FMT, focusing on screening for infectious disease-related pathogens, fecal-associated pathogens, glucose tolerance tests, and islet function measurements. In order to improve the efficiency of FMT, we recommend performing selective FMT aimed at selective modulation based on the dysregulated fraction of the patient's GM. A study which compared changes in the composition of the bacterial community before and after FMT showed that key genera required for recolonization and bacterial community resilience were present in donors for FMT and showed an increase in the abundance and diversity of this community after treatment.[111] Donors with relatively abundant strains which is dysregulated in patients can be selected for FMT preferentially. It has been suggested that early intervention with antibiotics or diet should be used to improve clinical outcomes and the intervention option depends on the microbiota status of both donor and recipient.[89] Besides, the concept about super fecal donors was first mentioned in a randomized controlled trial using FMT for ulcerative colitis (UC). One donor in this trial produced feces that were more effective than the control, while patients treated with feces from any of the other donors had similar results to the control.[112] The super fecal donor is probably a desirable donor due to the particularly rich diversity of the microbiota, which can significantly enhance transplantation

after FMT.[113] We suggest that a pre-experiment could be performed after collection of donor stool to see if a super donor is present. If the collected stool is not observed to be different from the placebo in the pre-experiment, then a different donor should be considered, and conversely, if a super stool donor is found to be available, further studies can be conducted on the stool, and it will help us to build a more complete stool donor pool.[114]

Collection, Handling, Transportation and Preservation of Manure in FMT

After searching several clinical trials on the collection and handling of feces, we think that donors should be required to collect feces into clean containers and transport them to the hospital immediately on the day of FMT. To avoid transplanting too few strains, not less than 30g of feces should be used each time, and fresh feces should be processed as soon as possible after collection, usually within 5–6 hours after defecation.[76,93,112] This time has now been reduced to less than one hour in China through a fully automated system.[115] Collected feces must be diluted and homogenized into a form that can be applied.[109] The stool should be filtered using a stirrer or manually suspended in saline to avoid clogging the syringe and tubing. Considering the inconvenience of actual clinical operation and the inability of some patients to perform FMT in time, we need to store the processed stools appropriately. A common method of p reservation is to freeze the processed stool sample, and studies have shown that frozen stool does not affect the final FMT results.[116–118] The samples can generally be added with 10% glycerol and stored at −80°C, and labeled well for use.[86,117,119] On the day of preparing the stool for FMT, the stool suspension should be thawed in warm water (37°C) and transplanted within 5–6 hours, avoiding repeated thawing and freezing as much as possible.

Clinical Operation and Treatment Frequency of FMT

There are several routes to conduct FMT clinically, the typical ones are by endoscopic delivery, naso-intestinal tube delivery, retention enemas, the proximal colon by colonoscopy, and recently the capsule ingestion for FMT has been proposed.[23,76,86,93,120–125] Currently, there is no clear consensus on the optimal route of use, and there is some variability in the populations targeted by each route. Considering the potential for injury during invasive procedures in patients with T2DM, we suggest that for patients who can eat on their own and do not have swallowing difficulties and choking risks, the convenient and non-invasive oral capsule route can be used for transplantation. The oral capsule method is easier and less expensive than other clinical operations, and is conducive to multiple repetitions of FMT. The only thing to be noted is that the capsules need to be refrigerated for preparation and storage.[119] For other patients with T2DM who are unable to use oral capsules there is also the option of FMT by endoscopy or enema. Since the duration of a single FMT is short, we recommend combining exercise and diet therapy with FMT treatment, which can significantly improve the efficiency and duration of effect of FMT.[25,27,113] For patients with T2DM who appear to have impaired fasting glucose or insulin resistance but have insignificant changes in GM at a relatively early stage, single FMT plus diet and exercise therapy can be used to restore islet function and increase beneficial bacteria in the intestine to prevent further progression of the disease. Patients in the terminal stage of T2DM without serious complications can be treated with FMT in multiple intervals to continuously promote the conversion of the patient's GM to the normal microbiome, in order to slow down the progression of complications and improve the patient's quality of life. The frequency of treatment for FMT needs to be followed up further to see if there are other potential risks.

Follow-Up Management of FMT

Close follow-up observation should generally be performed for at least 8 weeks after FMT, focusing on observing patients for significant adverse effects, mainly including abdominal pain, diarrhea, constipation, vomiting, belching, fever, and new infections.[93] Diabetic patients should also closely monitor their fasting and postprandial blood glucose after FMT. A scale of adverse reactions should be set up for follow-up and promptly dealt with when intolerable adverse reactions occurred. We advise a systematic examination at every 4 weeks after FMT, including fecal routine, fecal bacterial determination, pancreatic function and glucose determination, BMI, and metabolism-related biochemical indexes, etc. A method of tracking strains in the report of Smillie et al[126] can also be referred to observe the change of bacteria before and after FMT. 16S rRNA gene deep sequencing can also be applied to compare changes in bacteria before and after FMT.[111] It is important to determine the transplantation efficiency of FMT and to observe any significant

changes in GM and any improvement in the metabolic status of the recipients. After a complete FMT treatment period, the above indicators should be repeated to assess the efficacy of FMT, focusing on the cross-sectional comparison of bacteria and metabolic indicators, and the doctors can decide whether to adjust the donor conditions for FMT based on the composition of the recipients' bacteria. Therefore, to facilitate better follow-up, donor fecal samples should be kept frozen for at least two years.[115]

Of course, the use of FMT does not conflict with the conventional treatment of T2DM, and there should be a synergistic relationship between them. Diet and exercise are fundamental in the treatment of patients with T2DM, and as we previously described, therapies of diet control and exercise enhancement will interact with FMT to maintain the effects of FMT for a long time. Drug therapy is also an important part of T2DM. Metformin is a common drug for T2DM, and it has been found in clinical studies that the GM in patients treated with metformin is altered, mainly with an increase in the bacteria associated with butyrate and propionate production and an increase in the number of Escherichia coli.[127,128] Besides metformin, sitagliptin phosphate was also found to show some transformation of GM after use, but this transformation did not conflict with the trend of altered bacteria after FMT.[129] Roux-en-Y gastric bypass (RYGB) has also been shown to be effective in reversing insulin resistance, and using the people after RYGB as a donor modifies the recipient's GM and reduces insulin resistance.[24] Although no clinical studies have been conducted to compare the efficacy of FMT treatment with the conventional methods, we believe that FMT has the advantage of being more convenient and less invasive in comparison and can be treated as a more preferred modality.

Conclusion

In summary, GM is involved in the pathogenesis of T2DM in several ways and is one of the important targets in the treatment of T2DM. The indications for FMT have expanded from rCDI to other metabolic diseases such as obesity, metabolic syndrome, and T2DM. FMT has great potential to modulate the GM of T2DM patients as well as to improve glucolipid metabolism and reduce weight. In the future, FMT should be optimized and standardized for patients with T2DM, and its long-term safety should be further investigated.

Abbreviations

FMT, fecal microbiota transplantation; T2DM, type 2 diabetes mellitus; GM, gastrointestinal microbiome; IGT, impaired glucose tolerance; BA, bile acid; SCFAs, short chain fatty acids; LPS, lipopolysaccharides; TMAO, trimethylamine oxide; MAT, mesenteric adipose tissue; rCDI, recurrent Clostridium Difficile Infection; SRB, Sulfate-reducing bacteria; GLP-1, glucagon-like peptide 1; PYY, peptide YY; GPCRs, G protein-coupled receptors; LBP, lipopolysaccharide-binding protein; IL, interleukin; TLR4, Toll-Like Receptor4; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-α; FXR, Farnesoid X receptor; FGF19, fibroblast growth factor19; FGFR4, FGF receptor 4; CYP7A1, cholesterol 7α-hydroxylase; TGR5, Takeda G protein-coupled receptor 5; TMA, trimethylamine; FMO, flavin monooxygenase; CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin, type A1c; UC, ulcerative colitis; RYGB, Roux-en-Y gastric bypass.

Data Sharing Statement

The datasets analyzed for this study can be found in the article, further inquiries can be directed to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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