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Clinical efficacy of fecal microbiota transplantation based on syndrome element differentiation principle in the treatment of type 2 diabetes mellitus

Ruiting CHAI[a, b], Jinwen SHI[b], Fangzhen WU[c], Zhaoyang YANG[b], Candong LI[a, b*]

a. School of Basic Medical Sciences, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, 510006, China

b. School of Traditional Chinese Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, 350122, China

c. Department of Rheumatology and Endocrinology, The Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, 350001, China

ARTICLE INFO

Article history
Received 25 June 2025
Accepted 27 August 2025
Available online 25 September 2025

Keywords
Type 2 diabetes mellitus
Fecal microbiota transplantation
Syndrome element differentiation
Precision treatment
Efficacy evaluation

ABSTRACT

Objective To investigate the therapeutic efficacy and potential mechanisms of fecal microbiota transplantation (FMT) in patients with type 2 diabetes mellitus (T2DM), and to preliminarily identify the traditional Chinese medicine (TCM) syndrome element characteristics of FMT in the treatment of T2DM.

Methods Between March 25, 2023 and September 30, 2024, T2DM patients who met the inclusion and exclusion criteria were enrolled at the Department of Rheumatology and Endocrinology of the Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine. Participants received oral microbiota capsules as an adjunct to metformin therapy. Information obtained by four diagnostic methods of TCM, along with clinical and laboratory parameters, was collected before and after the intervention. Metagenomic sequencing was employed to analyze the gut microbiota, and Spearman correlation analysis was used to explore the relationship between laboratory indicators and differential bacterial genera. According to the post-treatment reduction in glycosylated hemoglobin (HbA1c), patients were categorized into a response (R) group and a non-response (NR) group. Treatment outcomes, safety indicators, gut microbiota changes, and TCM syndrome element features were compared between the two groups.

Results A total of 53 T2DM patients were included in the final analysis, and 30 patients were assigned to R group and 23 to NR group. After treatment, the R group exhibited significant reductions in HbA1c, fasting plasma glucose (FPG), and 2-hour postprandial glucose (2hPG) ($P < 0.05$ or $P < 0.01$). The NR group also showed significant decreases in HbA1c and FPG levels $P < 0.01$ or $P < 0.05$. Compared with the NR group, after treatment, FPG level in the R group demonstrated significant reductions ($P < 0.01$). As compared with before treatment, pancreatic islet function demonstrated enhancement in the R group, a significant increase in the 2-hour pastprandial C-peptide (2hC-P) levels in R group ($P < 0.05$), whereas no marked change was observed in the NR group. Regarding body composition indicators, the R group showed significantly lower waist-hip ratio (WHR), visceral fat (VF), and subcutaneous fat (SF) levels compared with the NR group ($P < 0.01$). After treatment, the NR group exhibited a significant elevation in aspartate aminotransferase (AST) levels ($P < 0.05$). Other safety-related indicators fluctuated within normal reference ranges, and no other adverse events, such as diarrhea, fever, or nausea, were reported. Metagenomic sequencing showed that FMT improved the diversity and richness of the gut microbiota, remodeling its overall structure. At the phylum

*Corresponding author: Candong LI, E-mail: fjzylcd@126.com.

Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: 10.1016/j.dcmed.2025.09.008

Citation: CHAI RT, SHI JW, WU FZ, et al. Clinical efficacy of fecal microbiota transplantation based on syndrome element differentiation principle in the treatment of type 2 diabetes mellitus. Digital Chinese Medicine, 2025, 8(3): 363-378.

level, the abundance of *p_Firmicutes* decreased significantly ($P < 0.01$), while the abundances of *p_Bacteroidota* and *p_Proteobacteria* increased significantly ($P < 0.01$). At the family level, among the 125 identified taxa, the abundances of *f_Bacteroidaceae*, *f_Lactobacillaceae*, and *f_Sutterellaceae* were significantly elevated, whereas six families, including *f_Lachnospiraceae*, *f_Ruminococcaceae*, and *f_Coriobacteriaceae*, were significantly decreased (all $P < 0.05$). Among the 367 taxa at the genus level, the top 10 differential genera showed significantly increased abundances of *g_Bacteroides* and *g_Sutterella*, and significantly decreased abundances in eight genera, including *g_Faecalibacterium*, *g_Ruminococcus*, *g_Blautia*, and *g_Collinsella* (all $P < 0.05$). Correlation analysis suggested that the phylum *p_Bacillota* was positively correlated with improvements in T2DM laboratory parameters, *g_norank_f_Prevotellaceae* was significantly positively correlated with fasting C-peptide (FC-P) and 2hC-P ($P < 0.05$). HbA1c demonstrated a significantly positive correlation with *g_Blautia* and *g_Gemmiger* ($P < 0.05$) and a significantly negative correlation with *g_Bacteroides* and *g_Collinsella* ($P > 0.05$). Analysis of syndrome element characteristics revealed that the R group was primarily characterized by pathological patterns of dampness, phlegm, and Yang deficiency. Before treatment, statistically significant reductions in syndrome element scores were observed for dampness, Yang deficiency, spleen, phlegm, Qi deficiency, Qi stagnation, and Yin deficiency ($P < 0.01$), as well as for heat and liver ($P < 0.05$). The NR group was mainly featured with Qi deficiency and Yin deficiency. Statistically significant changes in their syndrome element scores after treatment were noted for Qi deficiency ($P < 0.01$), and for spleen, Qi stagnation, liver, and blood deficiency ($P < 0.05$). In this group, the score changes for Yang deficiency, Yin deficiency, heat, and dampness were not statistically significant ($P > 0.05$).

Conclusion The principles of syndrome element differentiation can be effectively applied to predict treatment efficacy and facilitate patient selection for FMT in the treatment of T2DM. Patients with T2DM presented with specific TCM syndrome element characteristics, notably dampness, phlegm, and Yang deficiency, represent a highly responsive population to FMT therapy.

1 Introduction

Type 2 diabetes mellitus (T2DM) represents a considerable public health challenge globally [1], and the current standard treatment approaches often fail to substantially increase patients' quality of life. Recent studies have indicated that fecal microbiota transplantation (FMT) may offer promising therapeutic benefits for a range of diseases, including T2DM. For example, previous research [2] has shown that fecal FMT can significantly enhance the homeostatic model assessment of insulin resistance (HOMA-IR) and body mass index (BMI) in patients with T2DM. Furthermore, research conducted by NG et al. [3] has indicated that the combined application of FMT and lifestyle interventions can significantly optimize the recipient's microbiota composition. Nevertheless, considerable variability remains in the effectiveness of FMT, which is largely attributed to differences in the baseline characteristics of the recipients [4]. Evidence suggests that patients with lower abundances of intestinal flora may experience more pronounced therapeutic outcomes, indicating that the individual characteristics of patients' gut microbiota could be a critical factor influencing the efficacy of FMT [5]. These findings indicate the potential of investigating a precise and personalized approach to microbiota transplantation through various angles.

Syndrome element differentiation is an effective measure of personalized diagnosis and treatment in traditional Chinese medicine (TCM). The proposal of the syndrome element differentiation [6] overcomes the shortcomings of traditional syndrome differentiation methods in objectivity, measurability, and evaluability to a certain extent. From the perspective of diagnosis, the syndrome element differentiation can be used as a classification tool, which is beneficial to quantitatively evaluate the priority of "disease syndrome"; from the perspective of treatment, syndrome element differentiation can be used as an objective means of efficacy evaluation.

This study employed the syndrome element differentiation as a classification tool to describe and analyze the syndrome element characteristics of the receptor baseline. By delineating the pathological characteristics of patients, the research preliminarily identified the appropriate syndrome element characteristics for patients receiving FMT in the treatment of T2DM. This study provides both theoretical and empirical support for the advancement of personalized and precise FMT treatment strategies.

2 Materials and methods

2.1 Participants

This study recruited patients with T2DM from the Department of Rheumatology and Endocrinology of the Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine, spanning from March 25, 2023 to September 30, 2024.

2.1.1 Diagnostic criteria Diagnostic criteria follow the Clinical Guidelines for Prevention and Treatment of Type 2 Diabetes Mellitus in the Elderly in China (2022 edition) [7].

2.1.2 Inclusion criteria (i) Participants must meet the established diagnostic criteria. (ii) A diagnosis of T2DM for two years or more, without the presence of other significant underlying medical conditions. (iii) A stable hypoglycemic regimen has been maintained for the past three months, with no use of antibiotics or probiotics in the preceding month.

2.1.3 Exclusion criteria (i) Individuals with type I diabetes mellitus (T1DM), gestational diabetes mellitus, secondary hyperlipidemia, obesity, cardiovascular and cerebrovascular diseases, malignant tumors, or a history of chronic infections. (ii) Individuals exhibiting marked abnormalities in blood glucose levels, blood lipid levels, complete blood count, or liver and kidney function. (iii) Pregnant or lactating women, individuals with substance abuse, or those with binge eating, fasting, eating disorders, or dysphagia. (iv) Participants who are currently enrolled in other clinical trials, have participated in other clinical trials within three months, or have taken oral probiotics, prebiotics, antibiotics, or proton pump inhibitors (PPIs) within the past two weeks.

This study was reviewed and approved by the Medical Ethics Committee of the Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine (SPHFJP-T2023006-02). Furthermore, it has been registered on the China Clinical Trial Registry platform (Chi CTR230077946).

2.2 Intervention protocol

Based on the administration of metformin tablets (0.5 g per tablet, consumed three times daily with meals), participants received oral microbiota capsules. Before ingestion, a fasting period of 4 h was required. The transplantation regimen consisted of nine sessions, with the frequency of transplantation occurring three times, at 2-d intervals, for a total of three sessions. The subsequent four sessions were spaced 14 d apart, culminating in a total of six sessions. Each oral microbiota capsule contained 40 g of bacterial content, with a viable bacterial count exceeding 2.5×10^{12} CFU. Participants were instructed to consume five capsules orally every 15 min, amounting to a total of 40 capsules per session.

2.3 Preparation and formulation of microbiota transplantation capsules

2.3.1 Donor screening Following ethical principles and guidelines, fecal donors aged between 18 and 40 years old, with a BMI ranging from 18.5 to 28.0 kg/m^2, were selected through a comprehensive screening process. This process included online assessments, clinical evaluations, and both stool and blood testing. Potential donors underwent initial screening four weeks before donation, with regular laboratory screenings conducted thereafter to ensure continued suitability [8].

2.3.2 Capsule preparation and precise matching of donor and recipient An automated anaerobic intestinal bacteria extraction system was employed to collect the intestinal microbiota, which were then encapsulated and stored at – 80 °C. High-throughput sequencing techniques were used to analyze its structure. A donor-recipient matching model was developed using machine learning, deep learning, and other advanced algorithms. This model was established based on various indicators, including microbial diversity, characteristic flora, the composition of beneficial and harmful bacteria, metabolic capacity, and gender [9].

2.4 Metagenomic sequencing

2.4.1 DNA extraction and quality assessment Fecal samples were collected before treatment and one month after treatment, subsequently stored in a fecal microbial genome preservation solution at ambient temperature. A 0.25 g aliquot of feces was adopted for the extraction of microbial genomic DNA in line with the protocol outlined in the QIAamp fast DNA stool mini kit. DNA samples that met quality standards were employed for subsequent experimental procedures.

2.4.2 Library construction and quality assessment DNA was randomly fragmented into approximately 350 base pairs (bp) segments using an ultrasonic disruptor, following the protocol outlined in the NEBNext® Ultra™ II DNA library prep kit. The library preparation process involved end repair, A-tailing, adaptor ligation, purification, and polymerase chain reaction (PCR) enrichment, in accordance with the manufacturer's instructions for the DNA library prep kit for Illumina.

2.4.3 Sequencing Following the construction of the libraries, initial quantification was conducted using Qubit 3.0. The libraries were subsequently diluted to a concentration of 1 ng/μL. The insert size of the libraries was then assessed using an Agilent 2100 Bioanalyzer. Upon passing quality inspection, paired-end 150 bp (PE150) sequencing was carried out on the Illumina NovaSeq 6000 sequencing platform.

2.4.4 Bioinformatics analysis Kraken2 was employed for taxonomic classification. Leveraging the results from this classification, the relative abundance of species at various taxonomic levels (such as phylum, class, order, family, genus, and species) was calculated for each sample. The software Mothur was employed to compute alpha diversity indices, and the Wilcoxon rank-sum test was conducted to examine inter-group differences in alpha diversity. Specifically, the Sobs, Chao1, and abundance-based coverage estimator (ACE) indices were used to assess the richness of the microbial community within a

sample, indicating the total number of observed species or the estimated number of species present. The Shannon index was employed to characterize the diversity and evenness of the microbial community, while the Simpson index was used to evaluate the dominance of prevalent species within the sample. Principal coordinates analysis (PCoA), based on the Bray-Curtis distance algorithm, was conducted to assess the similarity of microbial community structures across samples. Furthermore, the permutational multivariate analysis of variance nonparametric test was applied to determine whether significant differences are found in microbial community composition.

2.5 Extraction of TCM syndrome elements

The symptoms and signs collected through the four diagnostic methods of TCM are processed using the Health State Identification System of Traditional Chinese Medicine, a system independently developed by Fujian University of Traditional Chinese Medicine. The syndrome element differentiation method was employed to standardize the information derived from these diagnostic methods. This process involves extracting syndrome elements related to the disease's nature and location, and assigning Stomachghts to each element in accordance with the Clinic Terminology of Traditional Chinese Medical Diagnosis and Treatment—Part 2: Syndromes/Patterns [10], as well as the syndrome element differentiation methodology [11]. The severity of each symptom is assessed as moderate by default; however, if a symptom is severe, its quantitative diagnostic value is adjusted by a factor of 1.5, whereas if a symptom is mild, the value is adjusted by a factor of 0.7. A general threshold of 100 was set for diagnosing and confirming each syndrome element. A syndrome element could be diagnosed if the sum of the contribution degrees of individual symptoms to that specific syndrome element reached or exceeded 100.

2.6 Observation indicators

(i) Efficacy indicators: fasting blood glucose (FPG), 2-hour postprandial blood glucose (2hPG), glycated hemoglobin (HbA1c), fasting C-peptide (FC-P), 2-hour postprandial C-peptide (2hC-P), 2hC-P/FC-P; BMI, waist-hip ratio (WHR), visceral fat (VF), and subcutaneous fat (SF).

(ii) TCM syndrome elements: data on disease-related symptoms and signs are collected using a standardized four-diagnostic information collection form. These data are entered into the TCM Health Status Evaluation System to directly obtain syndrome element results.

(iii) Safety indicators: creatinine (CR), urea (UR), uric acid (UA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), diastolic blood pressure (DBP), and systolic blood pressure (SBP). Other adverse reactions are categorized as follows: (a) gastrointestinal discomfort, including nausea, abdominal pain, abdominal distension, and mild diarrhea; (b) fever; (c) skin-related issues, such as rash and itching.

2.7 Evaluation of efficacy

According to the guidelines from the American Diabetes Association (ADA) [12] and the International Diabetes Federation (IDF) [13], and in alignment with the objectives of this study, participants were classified into the intestinal flora transplantation response (R) group if they met any of the specified conditions. Conversely, those who do not meet these conditions are classified into the intestinal flora transplantation non-response (NR) group.

(i) HbA1c decreased by 1.5% – 3.5% after treatment.

(ii) HbA1c $\geqslant$ 6.5% before treatment and $\leqslant$ 7% after treatment.

(iii) HbA1c $\geqslant$ 8.5% before treatment and < 8.5% after treatment.

2.8 Statistical analysis

The baseline data were evaluated for equilibrium, and the continuous variables were assessed for normality. If the data conforms to a normal distribution and exhibits homogeneity of variance, the numerical variables are expressed as the mean ± standard deviation (SD). Conversely, if the data do not conform to a normal distribution or display heterogeneity of variance, the variables are represented by the median and interquartile range (M [P25, P75]). The data in this study pertain to paired samples. When the difference (d) between groups adheres to a normal distribution, a paired samples t test is employed. If the difference (d) does not conform to a normal distribution, a paired sample rank sum test and a nonparametric test are applied, with a significance level set at $\alpha = 0.05$ for two-sided tests. All P values reported in this study were derived from single tests between two groups; therefore, no correction for multiple comparisons was applied. $P < 0.05$ was considered statistically significant.

3 Results

A total of 53 patients diagnosed with T2DM were included in the analysis, comprising 28 males and 25 females. The age of the participants ranged from 30 to 70 years, with a mean ± SD of 54.88 ± 8.53 years. The duration of the disease was 6 years, with an interquartile range (IQR) of 4 to 10. Based on the efficacy evaluation criteria, the patients were assigned to R group ($n = 30$) and NR group ($n = 23$).

3.1 Baseline of syndrome element characteristics of patients in the two groups

An analysis of the baseline syndrome element characteristics between the patients in the two groups demonstrated that the primary disease location syndrome element

for both groups was the spleen. In R group, the predominant disease types of syndrome elements were dampness, phlegm, and Yang deficiency, whereas in NR group, they were primarily characterized by Qi deficiency and Yin deficiency (Table 1).

Table 1 Distribution characteristics of syndrome elements in the two groups (only count syndrome element scores ⩾ 100 points)

Group	Syndrome element	Frequency/proportion (*n*/%)
R group	Dampness	27/17.3
	Yang deficiency	25/16.0
	Spleen	24/15.4
	Phlegm	21/13.5
	Qi deficiency	18/11.5
	Qi stagnation	14/9.0
	Heat	6/3.8
	Yin deficiency	6/3.8
	Liver	4/2.6
	Food accumulation	4/2.6
	Uterus	1/0.6
	Large intestine	1/0.6
	Lung	1/0.6
	Kidney	1/0.6
	Stomach	1/0.6
	Heart-kidney	1/0.6
	Blood deficiency	1/0.6
NR group	Yang deficiency	16/18.4
	Yin deficiency	13/14.9
	Qi deficiency	12/14.9
	Spleen	9/10.3
	Qi stagnation	7/8.0
	Heat	7/8.0
	Liver	6/6.9
	Dampness	5/5.7
	Blood deficiency	5/5.7
	Uterus	1/1.1
	Large intestine	1/1.1
	Kidney	1/1.1
	Food accumulation	1/1.1
	Small intestine	1/1.1
	Heart-kidney	1/1.1
	Blood stasis	1/1.1

3.2 Effects of FMT on intestinal microbiota in patients with T2DM

3.2.1 Analysis of intestinal microbial diversity The analysis of alpha diversity indices showed that both the Chao1 and ACE indices exhibited significant increases following FMT treatment ($P < 0.05$), whereas the Shannon and Simpson indices did not demonstrate any significant changes ($P > 0.05$, Figure 1A – 1D). This suggests alterations in the dominant species within the microbial community, potentially indicating the presence of previously undetected rare species and suggesting that FMT may facilitate the colonization of a limited number of new species. Furthermore, beta diversity analysis indicated a clear distinction between before and after treatment samples, with FMT exerting a statistically significant impact on the beta diversity of intestinal microbial species in patients ($P = 0.001$). These findings suggest that FMT induces substantial changes in the overall composition of the intestinal microbiota (Figure 1E).

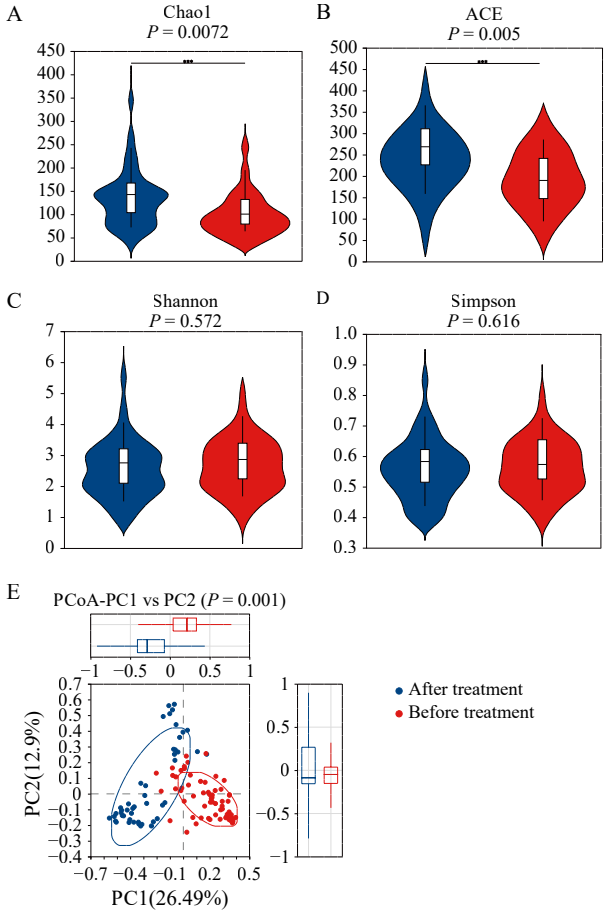

Figure 1 Analysis of alpha diversity and beta diversity of gut microbiota in T2DM patients before and after FMT treatment

A, Chao1 for alpha diversity. B, ACE for alpha diversity. C, Shannon for alpha diversity. D, Simpson for alpha diversity. E, beta diversity.

3.2.2 Analysis of intestinal microbial community structure at different classification levels At the phylum level, a statistically significant reduction in the abundance of *p_Actinobacteriota*, and *p_Firmicutes* was noted following FMT treatment ($P = 0.036$ and $P = 0.001$, respectively). In contrast, the abundances of *p_Bacteroidota* and *p_Proteobacteria* exhibited significant increases after-treatment ($P = 0.001$ and $P = 0.002$, respectively; Table 2).

At the family level, a total of 125 species were identified. After treatment, there were significant increases in

Table 2 Differences in the gut microbial community structure at the phylum level before and after FMT treatment

Substance name	Before treatment	After treatment	*P* value
p_Actinobacteriota	9.127 ± 13.842	4.315 ± 7.931*	0.036
p_Bacteroidota	37.776 ± 28.019	56.870 ± 23.281**	0.001
p_Desulfobacterota	0.442 ± 0.558	0.293 ± 0.393	0.125
p_Firmicutes	43.807 ± 24.906	28.863 ± 17.301**	0.001
p_Fusobacteriota	0.627 ± 2.179	0.933 ± 3.370	0.575
p_Proteobacteria	6.513 ± 6.906	14.132 ± 16.334**	0.002
p_Verrucomicrobiota	0.140 ± 0.526	0.159 ± 0.446	0.847

*$P < 0.05$ and **$P < 0.01$, compared with before FMT treatment.

the abundances of species within the families *f_Bacteroidaceae*, *f_Lactobacillaceae*, and *f_Sutterellaceae*. Additionally, notable decreases were observed in the families *f_Lachnospiraceae*, *f_Ruminococcaceae*, *f_Coriobacteriaceae*, *f_Peptostreptococcaceae*, *f_Erysipelatoclostridiaceae*, and *f_[Eubacterium]_coprostanoligenes_group* (Figure 2).

At the genus level, a total of 367 species were identified. Among these, the 10 species indicating the most significant changes in abundance following FMT treatment were as follows: *g_Faecalibacterium*,*g_Ruminococcus*, *g_Blautia*, *g_[Eubacterium]_coprostanoligenes_group*, *g_Collinsella*, *g_un_f_Ruminococcaceae*, *g_[Ruminococcus]_torques_group*, and *g_Dialister*, all of which showed reductions in abundance. Conversely, *g_Bacteroides* and *g_Sutterella* demonstrated increases in abundance (Figure 3).

3.3 Alterations in the syndrome element scores of patients between the two groups before and after FMT treatment

The findings indicated that R group showed significant reductions in scores for the following syndrome elements: dampness, Yang deficiency, spleen, phlegm, Qi deficiency, Qi stagnation, and Yin deficiency ($P < 0.01$), as well as heat and liver ($P < 0.05$). However, no statistically significant changes were observed in the overall syndrome element scores for Yang deficiency, Yin deficiency, heat, and dampness ($P > 0.05$; Table 3).

3.4 Comparative analysis of physical and chemical indices between the two groups before and After FMT treatment

3.4.1 Comparison of changes in blood glucose-related indicators Before treatment, no significant differences were observed in FPG and 2hPG levels between the two groups ($P > 0.05$). However, the baseline HbA1c level was higher in R group than that in NR group. After treatment, R group exhibited significant reductions in HbA1c, FPG, and 2hPG levels ($P < 0.05$ or $P < 0.01$). Concurrently, NR group demonstrated significant decreases in HbA1c and FPG levels ($P < 0.05$ or $P < 0.01$). Notably, the reduction in FPG levels was significantly more pronounced in R group compared with NR group following treatment ($P < 0.01$; Table 4).

3.4.2 Comparison of islet function changes Before treatment, there were no statistically significant differences in

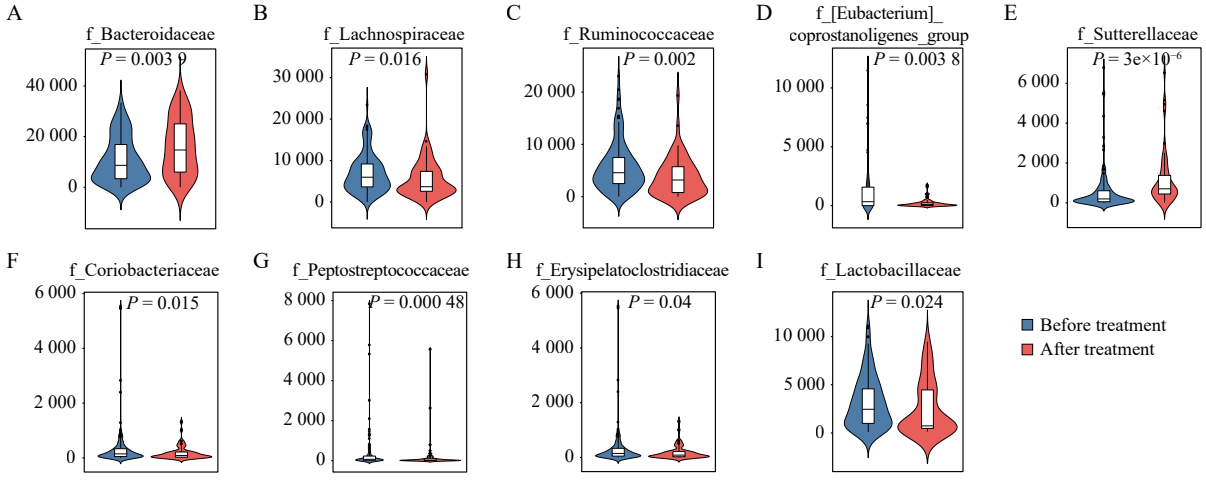

Figure 2 Differences in the gut microbial community structure at the family level before and after FMT treatment

A – I, changes in the relative abundance of *f_Bacteroidaceae*, *f_Lachnospiraceae*, *f_Ruminococcaceae*, *f_[Eubacterium]_coprostanoligenes_group*, *f_Sutterellaceae*, *f_Coriobacteriaceae*, *f_Peptostreptococcaceae*, *f_Erysipelatoclostridiaceae*, and *f_Lactobacillaceae*, respectively.

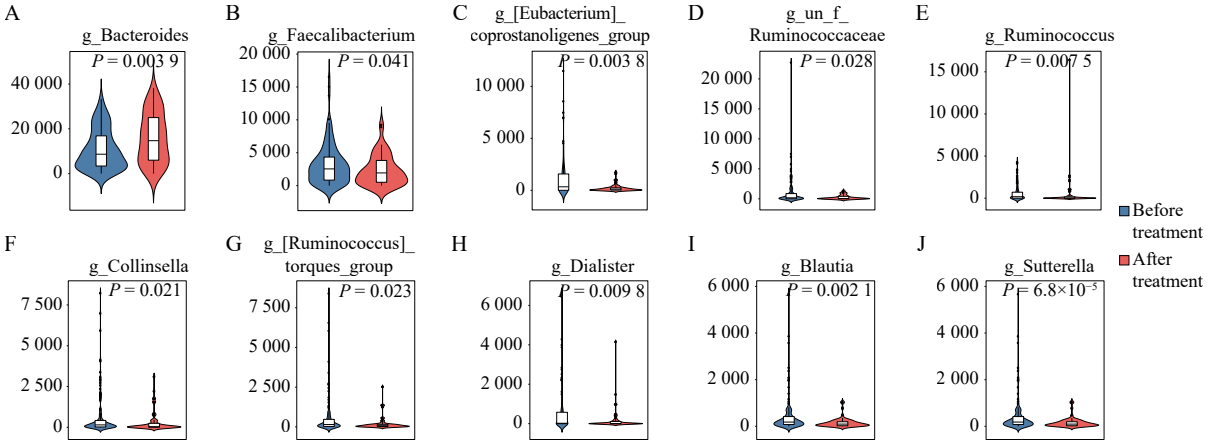

Figure 3 Top 10 differences in the gut microbial community structure at the genus level before and after FMT treatment

A – J, changes in the relative abundance of *g_Bacteroides*, *g_Faecalibacterium*, *g_[Eubacterium]_coprostanoligenes_group*, *g_un_f_Ruminococcaceae*, *g_Ruminococcus*, *g_Collinsella*, *g_[Ruminococcus]_torques_group*, *g_Dialister*, *g_Blautia*, and *g_Sutterella*, respectively.

Table 3 Therapeutic efficacy of FMT on syndrome elements in each group

Group	Syndrome element	Before treatment	After treatment	*t* value	*P* value
R group	Dampness	183.30 ± 63.85	66.62 ± 77.00	7.582**	4.770×10^{-8}
	Yang deficiency	104.30 ± 27.83	– 0.28 ± 34.57	12.430**	6.005×10^{-12}
	Spleen	111.84 ± 24.97	13.78 ± 46.50	10.292**	7.137×10^{-10}
	Phlegm	141.76 ± 38.98	38.43 ± 60.33	6.870**	1×10^{-6}
	Qi deficiency	89.62 ± 13.42	27.67 ± 56.20	5.037**	1×10^{-4}
	Qi stagnation	85.91 ± 16.20	28.06 ± 43.06	4.800**	3.47×10^{-4}
	Heat	92.07 ± 8.41	14.67 ± 43.48	3.980*	1.1×10^{-2}
	Yin deficiency	94.83 ± 13.98	– 11.33 ± 17.74	8.722**	3.28×10^{-8}
	Liver	86.00 ± 8.60	9.75 ± 33.83	5.516*	1.2×10^{-2}
	Food accumulation	74.00 ± 8.00	32.00 ± 48.47	1.749	1.79×10^{-1}
NR group	Yang deficiency	99.06 ± 26.27	72.11 ± 32.74	2.106	5.2×10^{-2}
	Yin deficiency	106.84 ± 20.7	91.38 ± 47.03	1.007	3.34×10^{-2}
	Qi deficiency	115.80 ± 31.46	74.72 ± 29.23	4.656**	1×10^{-3}
	Spleen	104.37 ± 21.67	66.11 ± 27.04	2.774*	2.4×10^{-2}
	Qi stagnation	101.49 ± 28.69	68.69 ± 18.75	3.054*	2.2×10^{-2}
	Heat	84.71 ± 8.10	55.86 ± 41.21	1.771	1.27×10^{-1}
	Liver	85.50 ± 14.49	61.67 ± 20.38	2.845*	3.6×10^{-2}
	Dampness	98.20 ± 26.04	77.20 ± 68.23	0.573	5.97×10^{-1}
	Blood deficiency	88.80 ± 19.64	52.92 ± 39.15	3.451*	2.6×10^{-2}

*$P < 0.05$ and **$P < 0.01$, compared with before FMT treatment.

the FC-P, 2hC-P, and FC-P/2hC-P values between the two groups ($P > 0.05$). After treatment analysis showed a significant increase in the 2hC-P levels in R group ($P < 0.05$), while the changes in the other indicators remained statistically insignificant. There was no statistically significant change in pancreatic islet function-related indicators in NR group after treatment ($P > 0.05$; Table 5).

3.4.3 Comparison of changes in body fat-related indicators No significant differences were noted in baseline body fat-related indicators between the two groups ($P > 0.05$). After treatment analysis showed significant reductions in BMI, VF, and SF within R group ($P < 0.05$ or $P < 0.01$), whereas no significant changes were detected in these indicators within the NR Group ($P > 0.05$). Furthermore, R group exhibited significantly decreased levels of WHR, VF, and SF as compared with NR group ($P < 0.01$; Table 6).

3.4.4 Comparison of changes in safety evaluation indicators The monitoring results of safety-related indicators in both groups, assessed before and after treatment, showed that all safety indicators remained within established medical reference ranges, indicating no significant impairment of liver or kidney function. The only exception was AST in NR group, which exhibited a slight but

Table 4 Comparison of changes in blood glucose-related indicators between two groups before and after FMT treatment

Group	HbA1c				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	7.75 (7.00, 9.40)	6.50 (5.80, 6.80)$^{**\#\#}$	− 0.07 ± 0.99	− 4.784	0.001
NR group	6.90 (6.40, 7.80)$^{\#}$	7.20 (6.75, 8.40)**	− 0.2 (− 0.55, − 0.1)	− 2.824	0.005
t/z	2.496	− 3.288	0.646	—	—
P value	0.013	0.001	0.518	—	—
Group	**FPG**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	7.77 (6.80, 8.91)	7.2 (6.11, 7.97)*	3.76 ± 5.31$^{\#\#}$	− 2.509	0.012
NR group	7.04 (6.35, 8.69)	8.45 ± 1.50*	− 0.65 ± 2.09	− 2.038	0.042
t/z	1.472	− 2.522	− 4.146	—	—
P value	0.141	0.120	0.000	—	—
Group	**2hPG**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	13.20 (11.23, 16.54)	10.58 ± 3.59**	1.35 (0.50, 2.60)	3.878	0.001
NR group	10.31 (9.51, 16.44)	10.61 (8.27, 14.96)	0.75 ± 4.08	0.877	0.390
t/z	1.526	− 0.781	0.485	—	—
P value	0.127	0.435	0.628	—	—

$^{*}P < 0.05$ and $^{**}P < 0.01$, compared with before FMT treatment. $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$, compared with NR group. "—" indicates no statistical significance.

statistically significant increase compared with baseline ($P < 0.05$). Furthermore, no statistically significant differences were observed in the expression levels of various indicators before and after treatment ($P > 0.05$). Additional clinical evaluations, including electrocardiograms (ECGs), did not demonstrate any abnormalities. No adverse reactions, such as diarrhea, fever, or nausea, were reported during the treatment period (Table 7).

Table 5 Comparison of changes in islet function-related indicators between two groups before and after treatment

Group	FC-P				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	2.08 ± 0.95	2.15 ± 0.79	− 1.31 ± 3.27	− 0.373	0.712
NR group	1.91 (1.44, 2.66)	2.27 (1.43,3.09)	0.01 (− 0.32, 0.37)	− 0.289	0.773
t/z	− 0.305	− 0.377	− 1.858	—	—
P value	0.760	0.706	0.063	—	—
Group	**2hC-P**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	5.16 (3.50,6.42)	6.48 ± 2.43*	− 0.19 (− 1.70, 0.39)	− 2.191	0.037
NR group	5.55 ± 2.82	5.66 (3.71, 9.49)	− 0.33 (− 2.90, 1.08)	− 1.460	0.144
t/z	− 0.422	0.233	0.413	—	—
P value	0.673	0.816	0.680	—	—
Group	**2hC-P/ FC-P**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	2.40 (2.00, 3.14)	3.15 (2.19, 4.24)	0.07 (− 0.32, 0.61)	− 1.512	0.131
NR group	2.59 ± 0.93	2.93 ± 0.91	− 0.34 ± 1.12	− 1.460	0.158
t/z	0.099	0.852	1.525	—	—
P value	0.921	0.394	0.127	—	—

$^{*}P < 0.05$, compared with before FMT treatment. "—" indicates no statistical significance.

Table 6 Comparison of changes in body fat-related indices in each group before and after treatment

Group	BMI				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	25.14 ± 3.92	24.28 ± 3.03**	0.575 (– 0.25, 1.79)	3.088	0.004
NR group	26.73 ± 5.63	25.26 (23.18, 27.69)	0.27 ± 1.51	0.866	0.396
t/z	1.214	– 1.310	1.059	—	—
P value	0.230	0.190	0.290	—	—
Group	**WHR**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	0.93 ± 0.06	0.91 ± 0.05	5.00(0, 16.00) ##	– 1.417	0.156
NR group	0.92 ± 0.07	0.93 (0.89, 0.95)	0 ± 0.06	– 0.302	0.765
t/z	– 0.142	– 0.817	2.873	—	—
P value	0.887	0.414	0.004	—	—
Group	**VF**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	92.43 ± 35.57	84.83 ± 33.26*	19.00 (3.00, 44.00)##	– 2.324	0.020
NR group	94.57 ± 36.55	91.00 (77.50, 107.00)	0 (– 2.50,9.50)	– 0.025	0.980
t/z	0.214	– 0.763	3.108	—	—
P value	0.832	0.446	0.002	—	—
Group	**SF**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	194.6 ± 74.68	167.17 ± 64.40**	23.32 (22.00, 24.76)##	– 3.450	0.001
NR group	190.00 (132.50, 221.50)	184.00 (164.00, 211.50)	1.00 (– 8.00, 22.50)	0.486	0.632
t/z	0.368	– 1.571	3.625	—	—
P value	0.713	0.116	0.000	—	—

*$P < 0.05$ and **$P < 0.01$, compared with before FMT treatment. ##$P < 0.01$, compared with NR group. "—" indicates no statistical significance.

3.5 Analysis of correlations between gut flora traits and physicochemical indicators

Spearman correlation analysis was used to observe the key species affecting physical and chemical indicators/disease phenotypes. The results showed that the predominant bacterial phyla involved in FMT for enhancing the physiological and biochemical parameters of patients with T2DM were primarily *p_Bacillota* (Figure 4). Additionally, *p_Actinomycetota*, *p_Bacteroidota*, *p_Pseudomonadota*, and *p_Fusobacteria* were also identified as dominant bacterial groups. This study observed a significant positive correlation of *g_norank_f_Prevotellaceae* with FC-P and 2hC-P. Furthermore, *g_Ruminococcus* was positively correlated with FPG, 2hPG, HbA1c, and other indicators of glucose metabolism, without significant correlations ($P > 0.05$). Simultaneously, HbA1c indicated a significant positive correlation with *g_Blautia*, *g_Gemmiger*, and other bacterial genera ($P < 0.05$), while demonstrating a negative correlation with *g_Bacteroides*, *g_Collinsella*, *g_Fusobacterium,* and additional bacterial genera, without significant correlations ($P > 0.05$). Additionally, 2hC-P/FC-P was positively correlated with *g_Ruminococcus*, *g_Segatella*, and *g_Sutterella*, and negatively correlated with *g_Bacteroides*, *g_Lactobacillus*, and *g_Fusicatenibacter*, and the correlation was not significant ($P > 0.05$).

4 Discussion

4.1 Elicitation of positive therapeutic effects of FMT treatment in T2DM

The pathogenesis of T2DM involves a confluence of factors, among which intestinal dysbiosis has garnered increasing attention [14]. FMT, a therapeutic modality aimed at restoring intestinal microecological balance, has demonstrated considerable potential in managing T2DM [15]. However, its clinical application has been constrained by marked inter-individual variability in therapeutic efficacy. This study, grounded in the principle of Zhengsu Bianzheng (证素辨证, syndrome element differentiation) proposed by Professor Wenfeng ZHU, investigates the correlation between the characteristics of responsive patient populations and their TCM syndrome elements, thereby offering a novel perspective and empirical basis for promoting the precision of FMT efficacy.

Our results demonstrate that FMT significantly enhances glycemic levels, pancreatic function, and adiposity-related indices in a subset of T2DM patients, which

Table 7 Comparison of changes in safety evaluation indicators between the two groups before and after FMT treatment

Group	Cr				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	66.47 ± 15.25	68.50 ± 15.23	0.12 ± 1.45	– 0.866	0.386
NR group	65.35 ± 17.74	63.78 ± 15.23	1.57 ± 8.25	0.910	0.373
t/z	– 0.247	– 1.118	0.946	—	—
P value	0.806	0.269	0.349	—	—
Group	**Ur**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	5.14 ± 0.96	5.00 (4.20, 5.40)	1.50 (– 4.00, 11.00)	0.438	0.665
NR group	5.20 ± 1.16	4.94 ± 1.25	0.26 ± 1.21	1.032	0.313
t/z	0.232	0.359	0.745	—	—
P value	0.817	0.719	0.456	—	—
Group	**UA**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	377.43 ± 95.37	363.13 ± 8 4.08	– 1.00 (– 8.00, 4.00)	0.826	0.416
NR group	382.87 ± 100.07	360.52 ± 88.56	22.35 ± 72.09	1.487	0.151
t/z	0.201	– 0.110	– 1.257	—	—
P value	0.841	0.913	0.209	—	—
Group	**ALT**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	27.50 (18.00, 36.00)	25.00 (17.00, 36.00)	1.00 (– 3.00, 3.00)	1.216	0.234
NR group	25.00 (16.00, 34.50)	33.00 (20.50, 45.00)	– 4.00 (– 9.50, 1.00)	– 1.511	0.131
t/z	0.278	– 1.941	1.798	—	—
P value	0.781	0.052	0.072	—	—
Group	**AST**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	19.00 (16.00, 23.00)	19.00 (18.00, 23.00)	– 0.06 ± 0.37$^{\#\#}$	– 0.249	0.803
NR group	18.00 (15.00, 23.50)	22.00 (19.00, 30.00)**	– 4.00 (– 6.00, – 1.00)	– 2.670	0.008
t/z	0.675	– 1.552	4.284	—	—
P value	0.500	0.121	000	—	—
Group	**DBP**				
	Before treatment	**After treatment**	**d**	**t/z**	***P* value**
R group	82.50 (75.00, 89.00)	80.87 ± 8.25	0 (0, 1.00)	1.269	0.215
NR group	80.96 ± 11.19	80.65 ± 9.38	4.00 (– 11.00, 6.00)	0.259	0.798
t/z	0.422	-0.088	0.090	—	—
P value	0.673	0.930	0.928	—	—
Group	**SBP**				
	Before treatment	**After treatment**	***d***	***t/z***	***P* value**
R group	129.53 ± 17.77	129.50 (117.00, 135.00)	3.75 (0, 6.00)	– 0.597	0.550
NR group	125.30 ± 13.69	125.91 ± 11.92	0 (– 1.00, 0)	– 0.260	0.797
t/z	– 0.946	0.656	– 0.601	—	—
P value	0.349	0.512	0.548	—	—

$^{**}P < 0.01$, compared with before FMT treatment. $^{\#\#}P < 0.01$, compared with NR group. "—" indicates no statistical significance.

aligns with previous research reporting the positive therapeutic efficacy of FMT on T2DM [2]. Crucially, this study identified marked differences in FMT efficacy among patients with distinct TCM syndrome element characteristics, suggesting that not all T2DM patients derive equivalent benefits from this intervention.

To delineate the population that benefits most from FMT, this study employed the Zhengsu Bianzheng framework to systematically analyze the potential correlations between TCM syndrome elements and therapeutic outcomes. The baseline syndrome element characteristics of R group were predominantly pathogenic states of

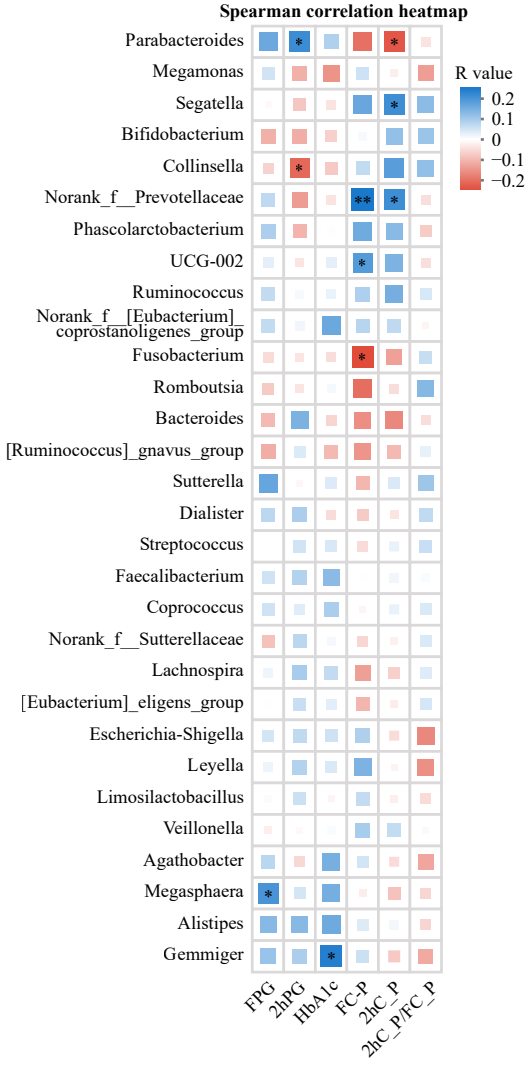

Figure 4 Analysis on the correlation between the relative abundance of bacteria with differences at the genus level and the expression of clinical indicators

The x-axis and y-axis indicate clinical factors and species, respectively. The R value is shown in different colors in the figure, and the legend on the right indicates the color range of different R values. $^{*}P < 0.05$ and $^{**}P < 0.01$.

phlegm, dampness, and Yang deficiency, with the primary disease location identified as the spleen. Following FMT, the scores for dampness, Yang deficiency, spleen, and phlegm syndrome elements in R group were significantly decreased. In contrast, the baseline characteristics of NR group included pathogenic states such as Qi deficiency, Yang deficiency, Yin deficiency, and Qi stagnation, although the disease location was also primarily the spleen. This observation suggests that patients with T2DM whose conditions are localized to the spleen and characterized by the accumulation of pathological products, including dampness and phlegm, or by the dysfunctional state of Yang deficiency, may be more responsive to FMT. This enhanced response is likely attributable to alterations in the gut microbiota that facilitate the clearance of these pathological factors or rectify the corresponding functional imbalances.

According to TCM theory, the spleen governs the transportation and transformation of water and grain essences and is considered the foundation of acquired constitution. Its functions are analogous to the roles of the gut microbiota in aiding digestion and absorption, and regulating metabolic and immune functions [16]. When the spleen's transportation function is impaired due to dietary indiscretion or other factors, the normal distribution and transformation of nutrients are disrupted, causing the internal stagnation of fluids, which generates dampness and coalesces into phlegm, forming a "phlegm-dampness" pathological state. Contemporary research posits that gut microbiota dysbiosis in patients with T2DM constitutes one of the pathological foundations for the spleen deficiency with phlegm-dampness syndrome. This syndrome is often accompanied by elevated levels of pro-inflammatory cytokines, and spleen deficiency itself can exacerbate inflammatory responses. Intestinal dysbiosis is capable of compromising the gut barrier, permitting endotoxin translocation into the bloodstream, which activates an immune response and induces chronic low-grade inflammation—a key mechanism in T2DM pathogenesis [17]. Therefore, the prevalence in R group of dampness and phlegm syndrome elements with disease located in the spleen clinically corroborates the intimate connection between gut dysbiosis and impaired spleen transportation function in T2DM. By transplanting a healthy gut microbiome, FMT helps correct microecological disturbances and restore balance, thereby re-establishing the material basis for the TCM theory of the spleen governing transportation and transformation. This, in turn, promotes fluid metabolism and reduces the formation of pathological products such as phlegm-dampness.

Regarding the Yang deficiency syndrome element, this state is characterized by an insufficiency of the body's Yang Qi, leading to a decline in its warming, impelling, and Qi transformation functions. In the context of spleen-stomach Yang deficiency syndrome, the weakened transformative power of spleen Yang more readily leads to dampness and phlegm. Concurrently, an excess of dampness can further suppress Yang Qi, creating a vicious cycle described as dampness flourishing while Yang wanes from *Wenre Lun* (《温热论》, *Warm-Heat Diseases*). Research by OUYANG et al. [18] has revealed correlations between spleen-stomach Yang deficiency and specific alterations in gut microbiota (e.g., changes in *g_Lactobacillus*, *g_Parasutterella*) and metabolic disturbances, particularly in steroid hormone biosynthesis and amino acid metabolism pathways. These changes may cause impaired intestinal energy metabolism, affecting the body's absorption and utilization of nutrients and indirectly weakening Yang Qi. By introducing a functionally robust microbiome, FMT can correct the gut dysbiosis in patients presented with Yang deficiency, restore the

abundance of beneficial bacteria, and consequently influence host energy metabolic efficiency. This improves the intestinal microenvironment and modulates key metabolic pathways, such as steroid hormone synthesis, thereby indirectly exerting a warming effect on spleen Yang and ameliorating the metabolic dysregulation caused by deficient transformation functions. In summary, FMT, by modulating the gut microbiota structure, may alleviate the intertwined pathological states of spleen deficiency, phlegm-dampness, and yang deficiency in patients with T2DM. This modulation mitigates associated chronic inflammation and immune imbalances, leading to more marked clinical improvements in glycemic control, pancreatic function, and body fat metabolism for patients exhibiting phlegm, dampness, Yang deficiency, and spleen-related TCM syndrome elements.

Furthermore, this study showed that R group not only achieved superior glycemic control post-treatment, but also yielded more pronounced improvements in body fat indices such as WHR, VF, and SF, further substantiating the comprehensive regulatory effect of FMT on metabolic disorders in specific patient cohorts.

4.2 Effects of FMT treatment on the intestinal microecology of T2DM patients

Numerous studies have reported the influence of metformin on the gut microbiota in T2DM. A recent systematic review summarizing 13 clinical studies on metformin-induced microbiota changes indicated divergent effects on microbial diversity: eight studies reported no significant effect on alpha diversity, three noted an increase, and two indicated a significant decrease [19]. Concurrently, other research has highlighted the significant effect of FMT on gut microbiota diversity. In patients with metabolic syndrome, FMT from lean donors can shift the gut microbial composition towards a more diverse and beneficial profile [20]. Additionally, FMT can strengthen glycemic homeostasis in patients with T2DM by enhancing the diversity and richness of the gut microbiota [21]. To date, reports on the impact of FMT on gut microbiota diversity are scarcely lacking, and the effects of metformin remain to be fully elucidated. This study, adopting a therapeutic strategy of metformin combined with FMT, demonstrated significant alterations in both alpha and beta diversity after treatment. This suggests that FMT may augment metformin's ability to influence the diversity of the intestinal microecology, though the precise mechanisms warrant further investigation.

This study analyzed the impact of FMT on the gut microbial composition of patients with T2DM at the phylum, family, and genus levels. At the phylum level, post-treatment changes in *p_Actinobacteriota*, *p_Firmicutes*, *p_Bacteroidota*, and *p_Proteobacteria* were statistically significant. Research indicates that FMT can modulate the intestinal microecological composition, increasing the abundance of *p_Bacteroidota* while reducing *p_Firmicutes* [22], which is consistent with our findings. *p_Bacteroidota* are involved in the degradation of complex carbohydrates and play a role in the development of the immune system. Many species within this phylum are known for their abilities to synthesize various capsular polysaccharides, which may help them evade host immune responses [23].

At the family and genus levels, significant elevations in the abundance of *f_Bacteroidaceae*, *g_Bacteroides,* and *f_Sutterellaceae*, and *g_Sutterella* were observed post-FMT. Study has shown that *g_Bacteroides* plays a crucial role in the breakdown of complex polysaccharides and the production of short-chain fatty acids (SCFAs) [24]. The abundance of *g_Bacteroides* is typically lower in patients with T2DM, and its increase following FMT can contribute to improved host metabolic health. By augmenting SCFA production, it is beneficial to ameliorate metabolic disturbances, thereby exerting a glucose-lowering effect [25]. Research on *f_Sutterellaceae* and *g_Sutterella* is comparatively limited. However, a relevant report [26] on the intervention effects of FMT in mice with experimental autoimmune encephalomyelitis found that FMT might enhance intestinal inflammatory responses by increasing the relative abundance of genera including *g_Sutterella*, thereby maintaining intestinal environmental stability. This suggests that an increase in *g_Sutterella* abundance may contribute to improved gut barrier function, although its role in metabolic diseases merits further exploration.

This study also noted an increase in *f_Lactobacillaceae*. Members of this family, such as *g_Lactobacillus*, are widely recognized as probiotics, which are known for their ability to produce lactic acid, maintain an acidic intestinal environment, inhibit the growth of pathogenic bacteria, and modulate the host immune system. For instance, *Lactobacillus plantarum* HF02 has been shown to mitigate fat accumulation and gut microbiota dysbiosis in high-fat diet-induced obese mice, indicating its potential in managing obesity-related metabolic disorders [27]. Similarly, *Lactobacillus fermentum* CECT5716 exhibited anti-obesity effects by modulating gut microbiota dysbiosis and reducing inflammation in a high-fat diet-induced obesity model [28]. Supplementation with *Lactobacillus paracasei* HII01 was found to improve glycemic and inflammatory biomarkers in patients with T2DM, highlighting its role in regulating gut microbiota and reducing endotoxemia [29]. *g_Lactobacillus plantarum* has also been demonstrated to alleviate obesity by altering the composition of the gut microbiota in high-fat diet-fed mice, further supporting its role in promoting metabolic health [30]. Collectively, these findings indicate that *g_Lactobacillus* strains can play a major role in managing metabolic disorders through the modulation of the gut microbiota.

Genera that were considerably reduced in abundance after FMT included *f_Lachnospiraceae* and *g_Blautia*. A study on gut microbiota changes in mice with allergic colitis showed that *f_Lachnospiraceae* was more abundant in the sensitized group [31]. Conversely, other research observed an enrichment of *f_Lachnospiraceae* in the gut following the restoration of the intestinal mucosal barrier by dietary Nobiletin [32]. In a study by LIU et al. [33], oral administration of inulin hydrogel increased the relative abundances of *f_Lachnospiraceae* and *g_Blautia*, as well as SCFA metabolites, in the gut microbiota of mice with colorectal cancer, thereby increasing radiotherapy efficacy and reducing radiation injury. Other research has found that a reduction in *g_Blautia* is a key factor in the therapeutic effect of Alisma decoction on non-alcoholic fatty liver disease in rats [34]. In our study, the relative abundances of both were decreased post-treatment, which may be related to the repair of the intestinal mucosal barrier. Further research on their roles in metabolic diseases is warranted.

Also reduced in abundance post-treatment were *f_Ruminococcaceae* and its subordinate members *g_Ruminococcus*, *g_[Ruminococcus]_torques_group*, and *g_Faecalibacterium*. As a known mucin-degrader, *g_Ruminococcus* is able to break down mucin glycoproteins, which can disrupt the protective mucus barrier of the intestine and increase disease susceptibility. Modulating the gut microbiota, including lowering *g_Ruminococcus*, has been shown in multiple studies to improve metabolic outcomes. For instance, a study on the relationship between gut microbiota and T2DM susceptibility in rats suggested that the enrichment of *g_Ruminococcus* might predispose rats to T2DM [35], indicating that its reduction could be beneficial to T2DM management. *g_Faecalibacterium* can break down dietary fiber to produce SCFAs and possesses anti-inflammatory properties [36]. A study of the impact of FMT on recurrent *g_Clostridioides difficile* infection showed an increased abundance of *g_Faecalibacterium* post-transplantation, suggesting its anti-inflammatory role in the success of FMT [37]. However, other studies have reported a positive correlation between the levels of *g_Faecalibacterium* and elevated blood glucose in patients with T2DM [38]. In summary, *f_Ruminococcaceae* and some of its members appear to function as non-probiotics in T2DM treatment, whereas the role of *g_Faecalibacterium* from the same family merits further research.

Several members of *f_Peptostreptococcaceae* have been linked to compromised gut health. A study investigating the effects of metformin on the gut microbiota in T2DM patients found that metformin treatment ameliorated gut dysbiosis, which included changes in the abundance of specific *f_Peptostreptococcaceae* species [25]. Bacteria in *f_Coriobacteriaceae* (such as *g_Collinsella*) are associated with bile acid and cholesterol metabolism, and their increased abundances are often correlated with insulin resistance and metabolic disorders [39]. This indicates that FMT can induce a decrease in the abundance of non-beneficial bacteria.

4.3 Correlation between gut microbiota characteristics and clinical factors

There is a complex network of associations between the intestinal microecology of T2DM patients and various metabolic indicators. Research has shown that gut microbiota diversity is negatively correlated with HbA1c level, that is, higher diversity is associated with lower HbA1c level [40]. In the present study, we found a significant positive correlation between HbA1c and genera such as *g_Gemmiger*, and a negative correlation with *g_Bacteroides*, suggesting that *g_Gemmiger* is not beneficial for stable glycemic control in T2DM patients, whereas *g_Bacteroides* is beneficial.

Furthermore, FC-P and 2hC-P are indicators of insulin secretion, and their levels are correlated with insulin sensitivity and β-cell function in patients with T2DM. Studies have found that C-peptide levels were correlated with insulin requirements and metrics such as waist circumference, HbA1c, FPG, and 2hPG in these patients [41]. Our study found that the 2hC-P/FC-P ratio was positively correlated with genera such as *g_Ruminococcus*, *g_Segatella*, and *g_Sutterella*, and negatively correlated with *g_Bacteroides*, *g_Lactobacillus*, and *g_Fusicatenibacter*. Although these correlations did not reach statistical significance, potentially due to the small sample size, the observed trends are largely consistent with previous findings.

4.4 Limitations and future prospects

There are several limitations to note: FMT is a new therapy, so the number of cases studied was small. Individual gut microbiota varies widely and is influenced by diet and lifestyle, but these factors weren't statistically considered. The observation period was also short, so while initial conclusions about treatment efficacy can be made, longer follow-up is needed to assess long-term effectiveness. Lastly, the mechanisms behind the identified microbial changes are not yet experimentally confirmed. Our team will investigate these in future studies.

5 Conclusion

This study uses the TCM principle of Zhengsu Bianzheng to predict the success of FMT in T2DM and to identify suitable patients. By examining patients' baseline syndrome elements, factors affecting FMT outcomes were identified, supporting personalized TCM-based FMT therapy. The findings show that FMT improves clinical and biochemical parameters in T2DM patients, particularly those with TCM elements like dampness, phlegm, and Yang deficiency. This research aids in optimizing

FMT's clinical use, selecting responsive patients, and enhancing its effectiveness for T2DM.

Fundings

National Natural Science Foundation of Joint Fund in China (U22A20376).

Competing interests

Candong LI is an editorial board member for *Digital Chinese Medicine* and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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基于证素辨证原理的肠道菌群移植治疗 2 型糖尿病的临床疗效观察

柴瑞婷[a, b], 石锦雯[b], 吴方真[c], 杨朝阳[b], 李灿东[a, b*]

a. 广州中医药大学基础医学院, 广东 广州 510006, 中国
b. 福建中医药大学中医学院, 福建 福州 350122, 中国
c. 福建中医药大学附属第二人民医院风湿内分泌科, 福建 福州 350001, 中国

【摘要】目的 探讨肠道菌群移植（FMT）对 2 型糖尿病（T2DM）的治疗作用及其作用机制，初步识别出 FMT 治疗 T2DM 的适宜患者证素特征。**方法** 于 2023 年 3 月 25 日至 2024 年 9 月 30 日期间在福建中医药大学附属第二人民医院风湿内分泌科纳入符合纳排标准的 T2DM 患者，在二甲双胍片治疗的基础上口服菌群胶囊。分别采集治疗前后患者的中医四诊信息和临床理化指标。采用宏基因测序技术分析肠道菌群，Spearman 相关性分析探索理化指标与差异菌属的相关性。根据治疗后糖化血红蛋白（HbA1c）的降低情况，将患者分为反应（R）组和无反应（NR）组。比较两组的治疗结果、安全性指标、肠道微生物群变化和中医证素特征。**结果** 最终分析共纳入 53 例 T2DM 患者，其中 30 例为 R 组，23 例为 NR 组。治疗后 R 组 HbA1c、空腹血糖（FPG）及餐后 2h 血糖（2hPG）均显著降低（$P < 0.05$ 或 $P < 0.01$），NR 组 HbA1c 与 FPG 水平亦显著降低（$P < 0.01$ 或 $P < 0.05$）。与 NR 组相比，治疗后 R 组 FPG 水平显著降低（$P < 0.01$）。R 组患者胰岛功能水平较治疗前有所恢复，R 组餐后 2 小时 C 肽（2hC-P）水平显著升高（$P < 0.05$），NR 组无明显变化。体脂相关指标方面，与 NR 组相比，R 组腰臀比（WHR）、内脏脂肪（VF）及皮下脂肪（SF）水平显著降低（$P < 0.01$）。治疗后 NR 组天冬氨酸氨基转移酶（AST）水平较治疗前升高（$P < 0.05$），其余安全性相关指标均在医学参考值范围内小幅波动，未出现其他不良反应，如腹泻、发热、恶心等。宏基因测序结果显示，肠道菌群移植可以改善患者肠道菌群物种的多样性，增加物种丰富度，重构整体菌群结构。在门水平，*p_Firmicutes* 丰度显著下降（$P < 0.01$），而 *p_Bacteroidota* 和 *p_Proteobacteria* 丰度显著升高（$P < 0.01$）。科水平共检测出 125 个分类单元，其中 *f_Bacteroidaceae*、*f_Lactobacillaceae* 和 *f_Sutterellaceae* 丰度显著上升，*f_Lachnospieaceae*、*f_Ruminococcacese*、*f_Coriobacteriaceae* 等 6 个科显著下降（均 $P < 0.05$）。属水平 367 个分类单元中，排名前 10 差异菌属显示：*g_Bacteroides* 和 *g_Sutterella* 丰度显著升高，而 *g_Faecalibacterium*、*g_Ruminococcus*、*g_Blautia*、*g_Collinsella* 等 8 个菌属显著降低（均 $P < 0.05$）。相关性分析提示，*p_Bacillota* 与 T2DM 理化指标改善呈正相关，*g_norank_f_Prevotellaceae* 与空腹 C 肽（FC-P）、2hC-P 显著正相关（$P < 0.05$）。HbA1c 与 *g_Blautia*、*g_Gemmiger* 显著正相关（$P < 0.05$），与 *g_Bacteroides*、*g_Collinsella* 呈负相关趋势（$P > 0.05$）。对两组证素特征进行分析发现，R 组以湿、痰、阳虚为主要病理特征，治疗后证素积分降低具有统计学意义的是：湿、阳虚、脾、痰、气虚、气滞、阴虚（$P < 0.01$）及热、肝（$P < 0.05$）；NR 组以气虚、阴虚为主要病理特征，治疗后证素积分变化具有统计学意义的是：气虚（$P < 0.01$）及脾、气滞、肝、血虚（$P < 0.05$）；其中阳虚、阴虚、热、湿的证素积分变化无统计学意义（$P > 0.05$）。**结论** 证素辨证原理可以应用于适宜 FMT 治疗 T2DM 的人群筛选及疗效预测，具有特定中医证素特征如湿、痰、阳虚的 T2DM 患者是 FMT 治疗的敏感人群。

【关键词】2 型糖尿病；肠道菌群移植；证素辨证；精准治疗；疗效评价