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Analysis of effectiveness of fecal microbiota transplantation in multiple sclerosis

Srija Reddy Kesireddy [1], Shivani Sureshchandra Thaker [2], Sri Anjali Gorle [3], Shelja Sharma [4], Matanat Mammadova [5], Srijamya [6,*] and Munawar Izhar [7]

[1] *S.V.S Medical College, Yenugonda, Mahabubnagar, Telangana, India,5090012.*
[2] *Odessa National Medical University, Valikhovskiy lane, 2, Odessa, Ukraine, 65000.*
[3] *Andhra Medical College, Andhra Medical College, Maharanipeta, Visakhapatnam, India, 530003.*
[4] *Rajasthan University of health sciences, sector 18, kumbha marg, pratap nagar, Jaipur, Rajasthan, India.*
[5] *Azerbaijan Medical University, Samad Vurgun, Baku, Azerbaijan, AZ1022.*
[6] *Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*
[7] *Chicago Hospitals and collaborative research institute, Chicago, Illinois, United States.*

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Abstract

Multiple Sclerosis is a chronic, autoimmune disorder characterized by demyelination and neuroinflammation affecting 2.3 million people around the world. MS have different types, relapsing and remitting MS being the most prevalent type with unpredicted flare ups with complete or incomplete recovery of the patient. Research suggests the emerging impact of alterations in gut microbiome on various diseases. The dysbiosis of gut flora has been linked to various diseases one of many is central nervous system autoimmune disorders.

The study aims to evaluate the potential role and effectiveness of FMT in treating MS.

The literature and clinical trials focused on gut microbiota, efficacy, Safety, and mechanisms of FMT were analyzed. The major focus of the study is assessing the impact of FMT on MS symptoms and gut microbiota composition and results of the study were concluded based on outcomes.

Primary outcomes noted improvement in MS symptoms both subjectively and objectively including enhanced motor symptoms and improved disability scores like EDSS. Secondary outcomes showed significant improvement in gut microbiota and 55-65% reduction in inflammatory markers like IL 6 and TNF alpha. FMT shows promising outcomes to be considered as a therapeutic intervention in MS by offering symptom relief and halting disease progression.

Keywords: Multiple Sclerosis; Fecal microbiota transplantation; Gut brain axis; Neuroinflammation; Autoimmune disorder

1. Introduction

Multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system (CNS), is characterized by demyelination and neuroinflammation, leading to a wide range of neurological symptoms such as fatigue, motor weakness, sensory disturbances, vision problems, cognitive impairment, and balance and coordination issues. In 2024, the global burden of MS is 2.8 million [1].

* Corresponding author: Srijamya

This complex disease manifests in several distinct types, each with unique patterns of progression and symptoms, including Relapsing-Remitting MS (RRMS), Primary Progressive MS (PPMS), Secondary Progressive MS (SPMS), and Progressive-Relapsing MS (PRMS). RRMS is the most prevalent form of the disease, characterized by unpredictable episodes of worsening neurological function due to nerve inflammation followed by periods of partial or complete recovery [3,4]. The FDA approved treatments for relapsing episodes in RRMS are corticosteroids injections and adrenocorticotrophic hormones in gel forms.

In recent years, there has been growing interest in the potential role of the gut microbiome in the pathogenesis of MS. Alterations in the composition and diversity of the gut microbiota have been observed in individuals with MS, suggesting a potential link between gut dysbiosis and disease pathogenesis [3,4]. Recent research has highlighted the potential role of the gut microbiome in MS pathogenesis. Alterations in gut microbiota composition and diversity have been noted in MS patients, suggesting a link between gut dysbiosis and the disease. Emerging preclinical and clinical studies have investigated the potential of fecal microbiota transplantation (FMT) as a novel therapeutic strategy to modulate the gut microbiome and impact disease activity in RRMS patients [3,4].

The study aims to provide a comprehensive overview of the current literature and clinical trials on FMT in MS, examining its underlying mechanisms, preclinical and clinical evidence supporting its efficacy, safety considerations, and future research directions in this evolving field.

2. Gut-brain axis: Bidirectional Communication Network

Intestinal microbiomes are essential for proper functioning of human physiology [5]. They play a crucial role in maintaining immune function, avoiding serious infections, and promoting homeostasis. The gut-brain axis is a complex bidirectional communication network that connects the enteric nervous system (ENS) of the gastrointestinal (GI) tract to CNS. This bidirectional communication is continuous and dynamic interacting at multiple levels and affecting a wide range of physiologic processes and behaviors [6].

A stressor to the immune system can disrupt the finely balanced harmony that exists between microbiota and the host. One of the main stressors in MS development is oxidative stress [8]. It contributes to chronic inflammation, demyelination, and neurodegeneration.

Cellular breakdown, due to this dysbiosis, triggers messages to the brain. This cellular deterioration may speed up the progression of neurodegenerative disorders [10]. Complicating the pro-inflammatory disease process of MS, dysbiosis greatly amplifies oxidative stress. One key component of the dysbiosis-MS relationship is the production of reactive oxygen species (ROS) by the gut bacteria, activating the inflammation process. The release of pro-inflammatory cytokines by this inflammatory cascade and ROS possesses a significant role in the pathogenesis of MS [8]. Table 1 shows different gut bacteria, their actions, and their growth rate in MS.

Table 1 Major Gut Microbes and their properties and effect in MS

Bacteria	**Mechanism of Action**	**Pro/Anti inflammatory**	**Increase/ Decrease in MS**
Methanobrevibacter	Recruitment of inflammatory cells and dendritic cells; associated with inflammatory bowel diseases	pro-inflammatory.	Increase
Akkermansia	Transformation of mucin into short-chain fatty acids mediating immune-regulatory effects; pro-inflammatory activity leading to damage of intestinal barrier and increased antigen exposure	pro-inflammatory.	Increase
Butyricimonas	Production of butyrate, inducing regulatory T cells; reduction disrupts barrier function and promotes inflammation	anti-inflammatory.	Decrease

Clostridium (Clostridia cluster XIV and IV)	Production of short-chain fatty acids inducing regulatory T cells and anti-inflammatory cytokines	anti-inflammatory.	Decrease
Firmicutes (e.g., Blautia, Dorea)	Higher presence associated with MS; some genera associated with anti-inflammatory effects	anti-inflammatory.	Increase
Bacteroidetes (e.g., Parabacteroides, Bacteroides, Prevotella)	Lower presence associated with MS; some genera responsible for production of Lipid 654, involved in immune regulation		Decrease
Prevotella	Reduction linked to expansion of Th17 cells and disease activity; produces anti-inflammatory metabolite propionate	anti-inflammatory.	Decrease
Streptococcus mitis (S. mitis)	Induces differentiation of Th17 cells, involved in cell-mediated tissue damage of autoimmunity	pro-inflammatory.	Increase
Streptococcus oralis	_		Increase
Adlercreutzia	Reduction linked to decrease in anti-inflammatory responses due to phytoestrogen metabolism	pro-inflammatory.	Decrease
Parabacteroides distasonis	Reduction observed in RR-MS patients compared with healthy controls; suggested to play a protective role in RR-MS	anti-inflammatory.	Decrease

3. Fecal Microbiota Transplantation

FMT is a therapeutic intervention aimed at transplanting distal fecal intact and healthy microbiota from donors to dysbiotic recipients via colonoscopy, retention enema, capsule, gastroenteric tube, upper endoscopy, sigmoidoscopy, and the novel technique including frozen-dried stool capsules for oral administration [11,12,16]. In a systematic review and meta-analysis conducted on 1150 subjects showed the highest efficacy (98%) for colonoscopy with multiple FMT infusions [23].

Donor selection is a very crucial step in FMT. Despite the obscurity of evidence-based guidelines from FDA, donor selection is usually carried out by conducting a preliminary interview to assess risk factors of the donor, clinical examination, stool examination to detect the presence of Clostridium Difficile, Salmonella, Shigella, Campylobacter, Escherichia coli, Giardia, and helminths. Hematological screening is also performed to detect Cytomegalovirus, Ebstein barr virus, and Hepatitis A, B, and C. Complete blood count, C reactive protein, liver function tests and renal function tests are also analyzed. General exclusion criteria include infectious diseases risk factors, chronic diseases, recent antibiotic usage, newly appeared GI symptoms, recent ingestion of harmful substances and unable to donate frequently, pregnant women, lactating mothers, and smokers [14,15,18]. Autologous FMT (processed and reintroduced to self-gut microbes) is also found to be effective in restoring gut microbiota [19].

After the donor selection, the stool samples are collected in not more than one month's time frame and cryopreserved at a temperature of -80 degree Celsius to -196 degree Celsius in liquid nitrogen. Successful FMT procedure needs minimum 30 to 60 grams of stool samples. Assessment of quality of microbiota in stool takes place. Before administration, frozen FMT is thawed for about 2-4 hours in an ice bath and then transferred to the recipient via any of the above-mentioned routes [18]. Figure 1 shows the process of FMT.

Generally, FMT is considered safe but common adverse events noted are nausea, vomiting, diarrhea, bloating, and abdominal pain. Serious adverse events include hepatic encephalopathy, sepsis, worsening colitis, and rectal abscess 17].

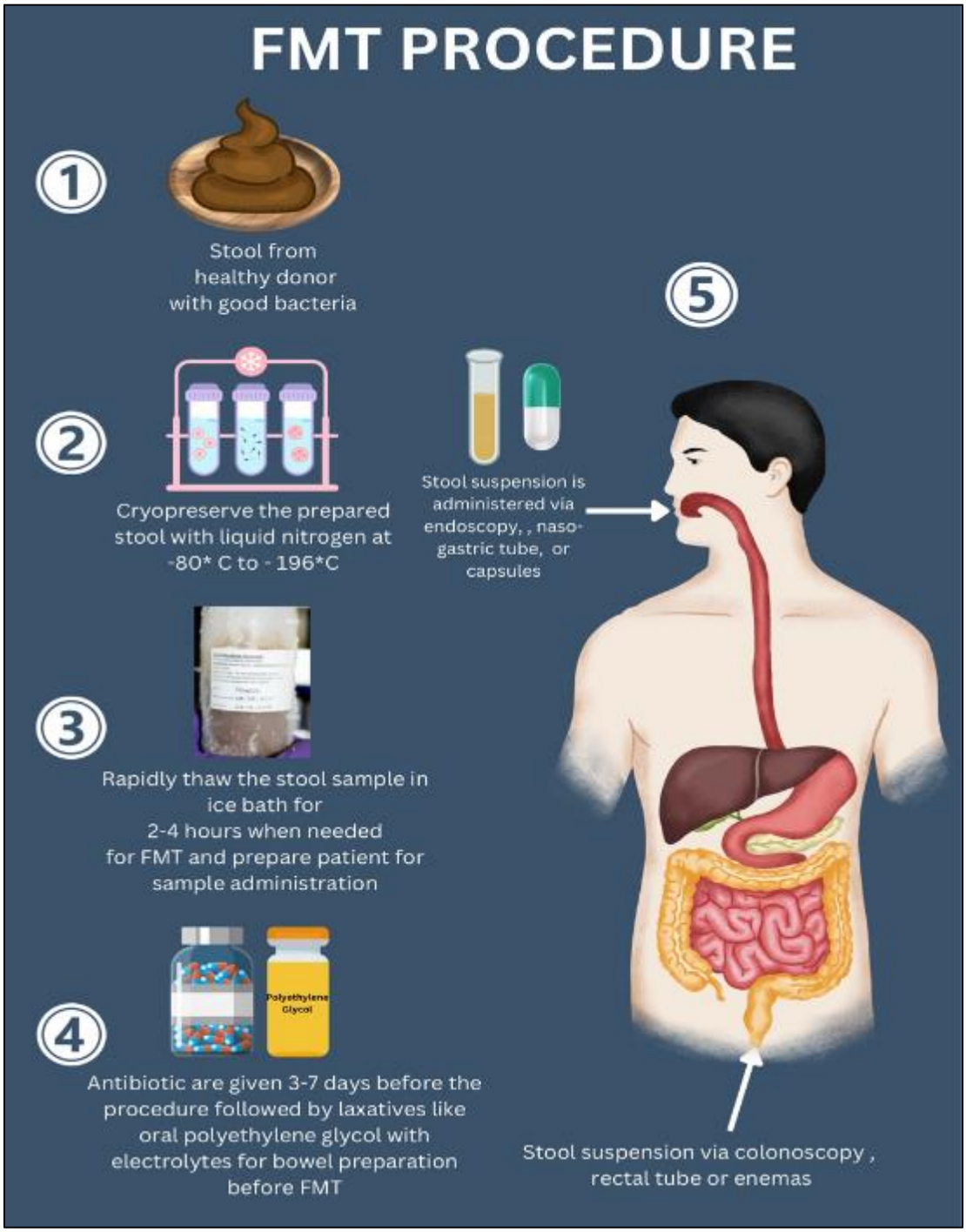

Figure 1 FMT Procedure

4. Fecal Microbiota Transplantation in Multiple Sclerosis:

FMT is a procedure where the gut bacteria from a healthy donor's stool are transferred to a recipient's intestines to help restore a healthy balance of gut bacteria. While there is limited research on FMT in MS, some studies suggest it might improve symptoms. One study found improvements in constipation and neurological symptoms in MS patients who underwent FMT [14].

Analysis of studies on effectiveness of FMT on MS highlights promising results indicating 55-65% reduction of neuroinflammatory markers like Interleukin 6, Tumor Necrosis Factor (TNF) Alpha, Interleukin 1 Beta, Transforming

Growth Factor Beta. FMT is also shown to be effective in restoring deranged gut microbiota with a success rate of 70-80% which contributes to enhanced immune regulation hindering MS progression [20].

The study done on mice showed intestinal bacteria affected a communication pathway that involved a protein CCR9 and a chemical called CCL25 which helps develop specific immune cells in the intestines [10]. The CD4+ T cells expressing CCR9 were lacking in mice that lacked any gut bacteria, but when these mice were treated with antibiotics to alter their gut bacteria, the numbers of CD4+ T cells went up. Additional testing of the effect of gut microbiota alteration in mice with an MS-like disease showed the amelioration of the disease and increased numbers of CD4+ T cells expressing CCR9 [9,10].

Case study observations on three patients of MS treated with FMT showed disease stability for over ten years following FMT [22]. The study conducted by Makkawi et al. provided insights into the post-transplant effects in the subject by studying Expanded Disability Status Scale (EDSS) which was 50% higher one year before FMT remained stable after FMT [21]. A study done for 6 months revealed 40% of subjects had achieved normal intestinal permeability [20]. The study by Philip A Engen et al,observed an increase specific bacteria like increased Faecalibacterium prausnitzii and Prevotelaceae-Bacteroidaceae after FMT. This study also revealed a 92.5% increase in the Brain Derived Neurotrophic Factor (BDNF) levels from baseline.[13]

Outcomes of FMT is assessed by the EDSS, it is an assessment criteria used to quantify disability in multiple sclerosis and monitor changes in disability over a period of time. EDSS score ranges from 0 to 10. Least score indicating no disability and highest score indicates death due to MS. Additionally by subjective assessment, functional system score, modified multiple sclerosis functional composite score, microbiota composition, Alpha diversity metrics by shannon index, BDNF, longitudinal assessment of gait metrics,12 item MS walking scale assessment. Table 2 shows the outcome measures and results of studies done in different periods of time till now.

Table 2 Studies and the results of FMT procedure done on MS patients till date

Study details	**Sample size and patient details**	**Number of FMT**	**Outcome measures**	**Results**
Kait F.Al et al, Randomised Control Trial(10)	n=9	Monthly for 6 months from randomly assigned donor1 and 2	1)Intestinal permeability by measuring lactose, mannitol, and sucrose in urine.	Two of five patients' normal intestinal permeability was achieved.
			2)Microbiota composition.	Increased Muribaculaceae in recipients of donor1 and increased Peptidoglycan synthesis in donor2 recipients. Did not change significantly from baseline.
			3) EDSS	No significant change compared to baseline.
Seraj Makkawi et al Case study(11)	N=1, 61-year-old	Single FMT	1)EDSS	Remained stable, which increased from 3.0 to 6.0 in one year before FMT.
			2)Functional system scores	Minimally improved.
			3)Modified Multiple Sclerosis Functional composite scores.	Minimally improved.

Borody et al(12)	N=3 MS With constipation, Parasthesia, weakness	Five and ten FMT infusions	Subjective assessment	Complete resolution of constipation. Progressively improved MS over 15,3,2 years, respectively. Overall improvement in neurological symptoms.
Phillip A Engen et al Case study(3).	N=1	Two	Alpha diversity metrics by shannon index and species richness. BDNF levels Baseline=2.39ng/ml) Normal (10-25) Longitudinal assessment of Gait metrics 12 Item MS Walking Scale Assessment.	Fermicutes:bacteroidetes and Prevotelaceae-Bacteroidaceae significantly increased. Faecalibacterium prausnitzii has increased. Signficantly higher (mean=32.12ng/ml). Improved walking balance and speed. Improved walking scores.

5. Discussion

MS is a complex autoimmune neurological disease with various types. Various studies have confirmed the complex relationship between MS and changes in the gut microbiome, suggesting the gut microbiota imbalance is a significant part of its pathophysiology, potentially leading to new treatment strategies involving FMT procedure. According to the literature analysis, dietary changes, intermittent fasting, probiotic supplements, and FMT are the main interventions for MS.

Significantly, this review study shows that FMT helps improve gastrointestinal and neurological symptoms in MS patients, with significant number of patients experiencing benefitting from staying in remission for years.

FMT improves the symptoms of MS patients by restoring a healthy gut microbiota, managing immune reactions, and reducing autoimmune activity against myelin, the nerve fiber protective layer damaged in MS. Additionally, it promotes synthesis of SCFAs like butyrate that maintains blood-brain barrier by decreasing the neuroinflammation. FMT has an ability to decrease the effect of pathogenic bacteria that can worsen MS symptoms by releasing harmful toxins. By changing the gut microbiome, FMT promotes the function of regulatory T-cells (Tregs) that play an essential role in preserving immune tolerance and preventing autoimmune flares, thus improving MS management.

Different clinical trials analysis indicates that FMT decreases neuroinflammatory indicators like IL-6, TNF-α, IL-1β, and TGF-β by 55-65% which are connected with the course and severity of the disease. Additionally, FMT has shown 70-80% of benefit in restoring healthy gut flora in MS patients, thereby slowing the progression of disease. After FMT treatment, some positive changes such as an increase in Faecalibacterium prausnitzii and Prevotellaceae-Bacteroidaceae are notable. Patients treated with FMT have demonstrated stable disease progression, with certain cases reporting illness stability for over ten years after treatment. The Expanded Disability Status Scale (EDSS), used as an indicator for disability in MS, remained steady in patients one year after FMT, indicating a halt in disease progression.

The small sample size, minimal follow-up period, absence of control groups and diverse participants were few of the limitations have been observed in the studies. Regardless of these drawbacks, the studies have shown the benefits of FMT as a therapeutic potential and indicates the importance and need of further research to verify and reaffirm the effects of FMT. In conclusion, the findings of these studies can redefine current MS treatments and introduce new measures by revising the structure of disease management.

6. Results

MS involves the immune system attacking the protective covering of nerve fibres and causing inflammation, leading to various sensory and motor symptoms. FMT procedure is the hope for MS patients as it utilizes micro-organisms, resident to the human gut transplanted from donor to recipient, that plays an essential role in the treatment.

FMT has proven beneficial in multiple ways to reduce relapse in MS evident by as much as 80% restoration of gut microflora that hinders the growth of pro-inflammatory bacteria while it contributes to production of substance like SCFAs that depicted up to 65% reduction in neuro-inflammatory markers in blood. FMT also promotes immune function by increasing the number of CD 4+ cell bearing CCR9 protein in the gut whereas it induces immune regulation by T regulatory cells and helps decrease flare-ups.

Out of the four studies included in the review, one study was focused on safety profile and three were focused on improvement in disease status. These three studies included 5 cases and 80% of them had reported neurological improvement whereas almost 100% cases were relapse free during study and at least one year post-study on follow up. The duration of remaining symptom free and without relapse is noted to be from two to fifteen years in these cases. The favorable effects range from halting of neurological deterioration to complete resolution of symptoms over the course of a few years.

7. Conclusion

MS manifests through debilitating neurological features resulting in great morbidity. With increasing prevalence and lack of understanding of the multiple factorial etiology, FMT has offered a promising treatment modality.

FMT is a multi-faceted approach that has proven to be a viable management for MS. It performs various functions to reverse local GI symptoms and promote neurological recovery. FMT upgrades the immune system and fosters tolerance while aiding in anti-inflammatory function through production of substances like SCFA. Evidence that suggests its usefulness in decreasing EDSS score, maintaining remission and preventing worsening of symptoms is adequate to urge more comprehensive research on the subject matter for superior management strategies and finer understanding of disease process.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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