WHAT IS "FMT"?

F Microbiota Transplant

Found Effective in Curing:

Rheumatoid Arthritis - Lupus - Multiple sclerosis - Clostridium - Dificile - Thrombocytopenia - Inflammatory Bowel Disease - Crohn's - Parkinson's - Chronic Fatigue Syndrome and Others

FMT Cures C. Diff and Is CURING Lupus and Rheumatoid Arthritis

THIS WILL SOON HAVE MAJOR IMPLICATIONS FOR MANY OF MY PATIENTS WITH CHRONIC ITCHY SKIN, AUTOIMMUNE DISEASES LIKE INFLAMMATORY BOWEL DISEASE, CHRONIC DIARRHEA & GASTRITIS. IT IS A QUANTUM SHIFT CURRENTLY IN HUMAN MEDICINE.

GOOGLE: #microbiota #transplantation #autoimmune #fecaltransplant

For decades, scientists thought there were hundreds of bacteria; like Staph, MERSA, Salmonella, you've read about all of those germs. If we can grow it, it exists. **If it doesn't grow, it doesn't exist**. Or so we thought.

Fifteen years ago, they found out how to find DNA fragments ("signatures") from bacteria in tissues. Bacteria THEY COULD NOT GROW IN MEDIA / PETRI-DISHES. The realization was made that **WE CANNOT GROW 99% OF THE WORLDS' BACTERIA!**

Who cares if we can't grow special bacteria?

Well, scientists found out that your intestinal bacteria (especially some un-growable ones) have MANY functions, including acting as HORMONES, NEUROTRANSMITTERS and IMMUNE SYSTEM MODIFIERS. The problem they're having is; they can't grow most of these magic bacteria. But they can find their DNA signatures.

What makes people with Lupus and Rheumatoid Arthritis different from regular healthy people? They asked. The absence of ONE bacterial "signature". *People with Lupus and Rheumatoid arthritis are missing ONE intestinal bacteria*. And when you replace that particular bacteria in the intestine, the patients recover. Now they're looking back at a lot of Lupus and RA cases and discovering that the disease showed up after sufferers had taken long (or intense) courses of antibiotics. Logically, the "mystery bacteria" were killed. But can be replaced in the intestine by "transplantation" of healthy poop (feces); or "FMT". The bacteria come from the intestines of any healthy young donor. The poop is purified, checked for all diseases, and then given as an enema in a cleaned-out bowel. A study showed that even frozen/thawed FMT is equally effective. You don't have to take it orally but at one time they did make capsules and put them through oral intubation.

It's called FMT. "Fecal Microbiota Transplant". It is literally **CURATIVE** for C. Diff an infection which kills a ga-jillion old people every year. And it's reversing cases of Lupus and Rheumatoid Arthritis.

You wanna know what kills off those "good mystery-function-ungrowable-bacteria" that so many sick people are missing?

- Drugs
- Preservatives and What You Eat
- Antibiotics
- Genetics

I SAID ALL THAT TO SAY THIS: Transplanting healthy poop into dogs with chronic bowel and GI issues and even dogs with chronic immune system disorders like ITCHY SKIN may be helpful if not curative. At least it is in people.

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Fecal microbiota transplantation broadening its application beyond intestinal disorders

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Abstract

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Intestinal dysbiosis is now known to be a complication in a myriad of diseases. Fecal microbiota transplantation (FMT), as a microbiota-target therapy, is arguably very effective for curing *Clostridium difficile* infection and has good outcomes in other intestinal diseases. New insights have raised an interest in FMT for the management of extra-intestinal disorders associated with gut microbiota. This review shows that it is an exciting time in the burgeoning science of FMT application in previously unexpected areas, including metabolic diseases, neuropsychiatric disorders, autoimmune diseases, allergic disorders, and tumors. A randomized controlled trial was conducted on FMT in metabolic syndrome by infusing microbiota from lean donors or from self-collected feces, with the resultant findings showing that the lean donor feces group displayed increased insulin sensitivity, along with increased levels of butyrate-producing intestinal microbiota. Case reports of FMT have also shown favorable outcomes in Parkinson's disease, multiple sclerosis, myoclonus dystonia, chronic fatigue syndrome, and idiopathic thrombocytopenic purpura. FMT is a promising approach in the manipulation of the intestinal microbiota and has potential applications in a variety of extra-intestinal conditions associated with intestinal dysbiosis.

Keywords: Fecal microbiota transplantation, Intestinal microbiota, Dysbiosis, Extra-intestinal disorders, Therapy

Core tip: Fecal microbiota transplantation (FMT) achieved a successful cure rate in recurrent *Clostridium difficile* infection. Although there is a deficiency of randomized controlled trials, the present review reveals that FMT could be a promising rescue therapy in extra-intestinal disorders associated with gut microbiota, including metabolic diseases, neuropsychiatric disorders, autoimmune diseases, allergic disorders, and tumors.

INTRODUCTION

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The human intestinal tract is home to up to 10^{14} microbes, outnumbering human cells within our bodies by tenfold[1,2]. The number and diversity of bacteria differ according to the different anatomical areas, ranging from the proximal to the distal gastrointestinal tract, with the colon harboring most of the intestinal microbiota[3]. Such an environment developed by host-bacteria associations is termed as being mutualistic. Four predominant bacterial phyla are identified in the human intestine: *Bacteroidetes, Firmicutes, Actinobacteria*, and *Proteobacteria*[4].

Rather than simply occupying space in our bodies, the intestinal microbiota is essential to nutrient metabolism, opportunistic pathogens defense[5], immune system development, and intestinal-barrier function regulation[3,6,7]. The specific balance of intestinal microbial diversity differs by individual according to variations (such as sanitation, social behaviors, and genetics)[8,9]. The beneficial balance of the intestinal microbial ecosystem can be disrupted by a series of factors, which includes antimicrobial drugs, vaccination, and dietary shifts[3]. Previous studies have suggested that intestinal microbiota alterations have been implicated in many gastrointestinal diseases and even systemic illnesses, such as metabolic diseases[10,11], neuropsychiatric conditions[12], autoimmune diseases[13], allergic disorders[14], and tumors[15].

Fecal microbiota transplantation (FMT) is a technique in which intestinal microbiota are transferred from a healthy donor to the patient, with the goal being to introduce or restore a stable microbial community in the gut. The first use of feces in such a manner was described, according to the Handbook of Emergency Medicine, approximately 1700 years ago by a Chinese medical scientist named Ge Hong[16]. It was first published in the English language by Eiseman et al[17] in 1958, when he reported a prompt response in patients with antibiotic-associated diarrhea treated with fecal enemas. Nevertheless, this practice was not well recognized until 1978, when investigators recognized *Clostridium difficile* infection (CDI) was the etiology of antibiotic-associated pseudomembranous colitis[18,19]. In the past few decades, the use of FMT for managing the increasing burdens of CDI has demonstrated it to be an effective therapeutic strategy for CDI[20-23]. In 2012, Borody et al[24] reported that more than 1200 cases have been treated in several centers. A total of 583 CDI patients treated with FMT produced a cumulative cure rate of more than 90% in 36 publications[25]. In addition, standardized frozen donor fecal bacterial preparations used in the treatment of recurrent CDI showed equal cure rates to fresh fecal samples[26]. 2013 guidelines for CDI have recommended that FMT should be considered if there is a third recurrence after a pulsed vancomycin regimen[27].

Although there are still many areas of uncertainty concerning this emerging technology, including transmission of infectious organisms, long-term sequelae, and even cost-effective evaluation, the United States Food and Drugs Administration have recently paid critical attention to FMT protocol in clinical applications. Borody et al[24] regarded the flora in feces as a special organ, and therefore considered the technique of FMT as a particular type of organ transplantation, regardless of the issue of immunological rejection. FMT has hence emerged as an important therapeutic modality in the manipulation of altered intestinal microbiota, with the indications of FMT possibly being expanded to even extra-intestinal conditions.

RATIONALE FOR FMT

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The exact mechanisms by which intestinal dysbiosis becomes involved in disease development are not completely elucidated. Alteration of metabolic activities induced by perturbed intestinal bacterial species leads to weakened defense of the gastrointestinal mucosa, which in turn leads to increasing intestinal permeability and toxic substances being absorbed into the systemic circulation. Prior work has observed disruption of the intestinal microbiota being evident at the phylum level, with marked depletion in levels of probiotics and a relative increase in the numbers of pathogens leading to

complications in intestinal conditions[27]. The alteration of microbial communities in both inflammatory bowel disease (IBD) and CDI patients was characterized by a reduction in two phyla of bacteria, *Firmicutes* and *Bacteroidetes*, which are prominent in healthy controls[28,29]. Moreover, an increase in *Proteobacteria* such as *Enterobacteriaceae* is also found in individuals with IBD[30]. *Bacteroides fragilis*, the prominent human gut commensal, can prevent and cure inflammatory disease *via* the effect of its symbiosis factor (polysaccharide A, an immunomodulatory bacterial molecule) on the activation of the Toll-like receptor 2 pathway, inducing regulatory T cells and interleukin-10 production[31]. Dextran sodium sulfate-induced colitis in a mouse model demonstrated that spore-forming *Firmicutes* in clostridial clusters IV and XIVa reduced intestinal inflammation through regulatory T cells induction[32].

These studies highlight the role of microbiota-target therapy for reinstalling the depleted bacterial species associated with the disease. Probiotics somehow alter the metabolism of the indigenous gut flora, although the effect is largely restricted to limited bacterial species, and have a transient inhabitation effect on the intestine. Nevertheless, the satisfactory outcome of treatment with FMT suggests that feces contain a superior combination of intestinal bacterial strains and is more favorable for repairing disrupted native microbiota by introducing a complete, stable community of intestinal micro-organisms. Feces also harbors additional substances (proteins, bile acids, and vitamins) which might contribute to the recovery of gut function[20].

This scenario has in fact been documented in a recent study of FMT in recurrent CDI trying to elucidate the mechanism of action of fecal infusion[33]. The authors assessed the characteristics of fecal microbiota before, after, and during follow-up of FMT and found the intestinal microbiota changed persistently over time, from a less-diverse disease state (pre-FMT) to a more diverse ecosystem virtually resembling that of fecal donors (post-FMT). Such dynamic monitoring of the intestinal microbiota helps us to identify the key groups representing the ecosystem, as well as further illustrating that normalization of the bowel function was accompanied by the engraftment of intestinal micro-organisms from a healthy donor. Currently, there is significant interest in the area of FMT in IBD[34], especially with the evidence of an impressive curable effect in some ulcerative colitis (UC) patients[35,36]. A study was conducted to determine microbiota composition after FMT in 5 patients with UC by monitoring their fecal bacterial communities at multiple time points[37]. The results showed that one patient had a positive response to FMT, which was characterized by the augmentation of donor-derived microbiota, including *Faecalibacterium prausnitzii*, *Rosebura faecis*, and *Bacteroides ovatus*. According to Borody et al[38] Crohn's disease (CD) is less responsive to FMT when compared with UC. Nonetheless, recent case reports have shown the promising future of FMT as a rescue therapy for CD[39-41]. Data on the application of FMT in irritable bowel syndrome (IBS) is limited to a case series of 55 patients which showed that 36% of patients were regarded as curable while 16% had symptoms reduced[42,43]. To better understand the role of the intestinal microbiota in the etiology and effective treatment of IBD and IBS, future controlled trials are necessary.

For this reason, the core mechanism for the efficacy of FMT is likely to be the establishment of intestinal bacterial strains and antimicrobial components (adhesin, immunomodulatory molecules, bacteriocin, *etc*.) produced by these associated strains. Adhesin molecules can compete for sites with pathogens, leading to them being prevented from colonizing in the intestine and rehabilitating the intestinal microbiota[5].

SAFETY OF FMT

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When FMT entered the medical community, it became a relatively hot therapeutic strategy, bringing with it both promise and controversy. According to published articles, transient adverse responses after FMT have been reported, including mild fever, abdominal pain, diarrhea, exhaust, flatulence, and fatigue[36]. However, these adverse effects are self-limiting. De Leon et al[22] reported a UC patient

quiescent for more than 20 years who developed a flare of UC after FMT. This case gives us cautionary information concerning FMT being used to treat CDI with UC. Moreover, a recent paper reported a UC patient who had a cytomegalovirus infection after performing home FMT without donor screening[44]. As extracts of feces are mediators between the donor and recipient, FMT has the potential for transmitting occult infections even when strict donor screening is performed.

FMT FOR EXTRA-INTESTINAL DISORDERS

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It seems to be serendipitous that the CDI epidemic facilitated the application of FMT to many other diseases (Table 1). The pathogenesis of gut microbiota in extra-intestinal diseases was inspired by massive studies in germ-free (GF) animals. Complete construction of the hypothalamic-pituitary-adrenal axis requires the participation of gut microbiota[45]. GF mice exhibit a dysregulation of the axis, thereby resulting in altered brain-derived hormones (*e.g.*, norepinephrine and tryptophan) and increased caloric intake[45]. Aside from the crucial role of intestinal microbiota in central nervous system activity, another concept is emerging which was termed as "bidirectional brain-gut-microbiota axis"[46-48]. The destruction of the axis leads to altered behaviors and various neurologic conditions[49,50]. Identically, ample human studies have provided evidence for the critical role of the gut microbiota in extra-intestinal disorders.

Table 1

Summary of extra-intestinal disorders associated with gut microbiota

Extra-intestinal disorders	Ref.	Publication year	Study type
Metabolic diseases			
Metabolic syndrome	Vrieze et al[61]	2012	RCT[1]
Obesity	Turnbaugh et al[54]	2009	Observational study
	Armougom et al[56]	2009	Observational study
	Schwiertz et al[55]	2010	Observational study
	Greenblum et al[53]	2012	Observational study
	Parks et al[52]	2013	Experimental study
Type 2 diabetes mellitus	Qin et al[59]	2012	Observational study
Cardiovascular diseases	Wang et al[62]	2011	Experimental study
	Tang et al[65]	2013	Experimental study
	Koeth et al[66]	2013	Experimental study
Non-alcoholic fatty liver	Rabot et al[73]	2010	Experimental study
	Le Roy et al[68]	2013	Experimental study[1]
Neuropsychiatric disorders			
Parkinson's disease	Ananthaswamy[74]	2011	Case report[1]
Multiple sclerosis	Borody et al[76]	2011	Case report[1]
Myoclonus dystonia	Borody et al[78]	2011	Case report[1]
Autism	Finegold et al[79]	2002	Observational study
	Song et al[82]	2004	Observational study

Extra-intestinal disorders	Ref.	Publication year	Study type
Chronic fatigue syndrome	Borody et al[84]	2012	Cohort study[1]
	Frémont et al[83]	2013	Observational study
Autoimmune disorders			
ITP	Borody et al[85]	2011	Case report[1]
Arthritis	Scher et al[88]	2013	Observational study
	Abdollahi-Roodsaz et al[86]	2014	Experimental study
SS and SLE	Szymula et al[91]	2014	Experimental study
Hashimoto's thyroiditis	Corapçioğlu et al[93]	2002	Observational study
	Strieder et al[92]	2003	Observational study
	Sasso et al[96]	2004	Observational study

Open in a separate window

[1]Fecal microbiota transplantation used in these studies. RCT: Randomized controlled trial; ITP: Idiopathic thrombocytopenic purpura; SS: Sjögren's syndrome; SLE: Systemic lupus erythematosus.

Metabolic diseases

There is compelling evidence that the intestinal microbiota is closely linked to a series of metabolic conditions. Obesity, diabetes mellitus, and metabolic syndrome are epidemic in modern society. There have been extensive investigations concerning microbiota reaction acting as a pivotal role in the pathogenesis of these endocrine diseases in animal models[51,52]. Changes in gut microbiota composition have also been reported in obese humans[53-55], with a shift in the ratio of *Firmicutes* and *Bacteroidetes*[56]. Meanwhile, increased levels of bacteria and their metabolic products were found in the plasma of obese individuals, with one likely mechanism thought to be increased intestinal permeability[57,58]. Recent studies have shown that short chain fatty acid (including butyrate) producing *Clostridiales* strains (*Roseburia* and *Faecalibacterium prausnitzii*) were found to be decreased in patients with type 2 diabetes mellitus, but non-butyrate producing *Clostridiales* and pathogens such as *Clostridium clostridioforme* were increased[59,60]. Vrieze et al[61] conducted a double blind, randomized controlled trial of FMT in 18 male patients with metabolic syndrome. Half of them received fecal microbiota infusion from lean male donors (allogenic group), while the other half received auto-fecal transplants (control group). The results showed that both insulin sensitivity and levels of butyrate-producing intestinal microbiota (*Roseburia intestinalis* and *Eubacterium hallii*) were markedly increased after a six-week infusion of microbiota from lean donors, while no significant changes were found in the control group[61]. In the group following allogenic gut microbiota transfer, the median rate of glucose disappearance increased from 26.2 to 45.3 μmol/kg per minute, while the median endogenous glucose production increased from 51.5% to 61.6%. Hence, it can be speculated that FMT could be developed as a potential therapeutic strategy for increasing insulin sensitivity in humans.

Leaky gut or loss of intestinal integrity may facilitate the development of cardiometabolic disorders due to alterations in composition and diversity of gut microbiota. A close association of microbial translocation with the risk of cardiovascular disease (CVD) have recently been established[62,63], with probiotic bacteria having raised plasma unconjugated bile acid concentrations through modulation of the enterohepatic circulation[64]. It also concomitantly reduced the lipid uptake from the intestine and the plasma cholesterol level, an indirect risk marker of CVD, by means of regulation of a series of

signaling molecules, such as Farnesoid X receptor-α and G-protein-coupled receptors[64]. One study illustrated the negative impact of trimethylamine-*N*-oxide, an atherogenic compound produced by intestinal flora from choline and betaine[65,66], on the morbidity and mortality of cardiovascular events[67]. A variety of data have clearly demonstrated that the intestinal microbiota act as an independent risk factor for CVD, as well as representing a promising therapeutic target for this disease.

An increasing body of published evidence has recently been generated that demonstrates that demonstrates the gut microbiota act as an epigenetic factor driving the progression of non-alcoholic fatty liver disease (NAFLD)[68-70], a metabolic syndrome that manifests in the liver[71]. Intestinal dysbiosis promotes hepatic injury and inflammation through either a breakdown of the intestinal barrier or translocation of microbial products[72]. Abundant studies using GF mice models have illustrated that these special organisms are resistant to steatosis and diet-induced obesity[73]. Le Roy et al[68] performed an animal study to clarify the role of gut microbiota in the development of NAFLD. They divided the conventional mice into two groups (responder and non-responder) according to their response to a high-fat diet (HFD), and found that GF mice receiving FMT from different donors (responder and non-responder) developed comparable results on the HFD. The GF group that received microbiota from the responder group developed steatosis and harbored a larger number of *Barnesiella* and *Roseburia*, whereas *Allobaculum* was higher in the other group[68]. Further evidence has proved that intestinal permeability increased and endotoxemia developed in NAFLD patients. This indicates that microbiota-targeting therapy might be useful in treating NAFLD and obesity.

Neuropsychiatric disorders

A high incidence rate of constipation is found in Parkinson's disease (PD) patients. Constipation can precede the onset of motor symptoms by more than 10 years[50], indicating the disease may start in the intestine. A man suffered from PD and characterized with the motor symptoms of marked pill-rolling hand tremors, micrographia, cogwheel rigidity, and chronic constipation[74]. He received antibiotic therapy (vancomycin, colchicine, and metronidazole) for his constipation and reported an improvement in gastrointestinal symptoms. After consistent therapy for 10 mo, his neurologic symptoms disappeared. This case cured by antibiotics suggests that the gut microbiota are involved in the pathogenesis of PD[74]. The results of symptomatic improvement in PD patients by FMT indicate a new way of thinking for clinicians[75].

Both animal and clinical studies have shown that the pathogenesis of multiple sclerosis (MS) is associated with the intestinal microbiota[76,77]. Three patients with MS who underwent FMT for constipation achieved normal defecation and virtually complete normalization of neurological symptoms, thereby improving their quality of life[76]. Borody et al[78] reported a case of a young female patient with myoclonic dystonia and chronic diarrhea. The symptoms had co-developed since she was 6 years old and progressed in severity to a plateau. FMT resulted in a rapid improvement in diarrhea symptoms, a 90% improvement in her myoclonus dystonia symptoms, and, as a consequence of restoring her fine motor function, improving her ability to perform tasks that require dexterity, such as holding cups and fastening buttons[78].

Autism is another condition in which intestinal microbiota is implicated. The onset of autism is often accompanied by intestinal dysfunction[79-81]. The first description of an association between autism and gastrointestinal syndrome began in 1971, with a report that 6 out of 15 autism patients had changed fecal character and defecation frequency[81]. Finegold et al[79] performed an intestinal flora study in regressive autism. It is compelling to observe that there were higher counts of *Clostridium* and *Ruminococcus spp*. in the stools of autistic children when compared to those in the control group. Nine clostridial species were found in autistic children, while only three were found in healthy children. The authors further observed histologic changes in the gastric and duodenal specimens. Moreover, significant higher numbers of non-spore- forming anaerobes and microaerophilic bacteria were found

in autistic children. Based on the hypothesis that autism involves intestinal microbiota, Song et al[82] characterized *Clostridia* from the feces of autistic and control children. The data indicate that counts of *Clostridium bolteae* and clusters I and XI in autistic group are largely greater than those in control children. There was evidence of autistic symptom remission in two children after FMT[49]. Parallel results were also presented in five children who received daily cultured *Bacteroidetes* and *Clostridia* for several weeks.

Alterations in the intestinal flora have also been observed in patients with chronic fatigue syndrome (CFS)[83]. The proportion of gram-negative *Escherichia coli* was reduced in CFS patients versus that in healthy controls (49% *vs* 92.3%). More recent research examined a larger cohort of 60 CFS patients with gastrointestinal symptoms who had underwent FMT[84]. The results showed that 42/60 (70%) patients responded to treatment and 7/12 (58%) retained complete resolution of symptoms during a 15-20 year follow-up period. These results, suggest that FMT may play a role in the treatment of CFS.

Autoimmune diseases

The incidence of autoimmune diseases has dramatically increased, but the causes of these conditions remain poorly understood. Idiopathic thrombocytopenic purpura (ITP) is caused by the production of autoantibodies against platelet surface antigens. In a patient with ITP who was treated with FMT for UC, prolonged reversal of ITP was reported and the normalization of platelet levels was achieved[85].

The onset of rheumatoid arthritis (RA) is multifactorial and requires both genetic and environmental influential factors, with the commensal intestinal microbiota playing a major role[13,86,87]. Alterations in the intestinal microbiome can have an extended effect on RA through mucosal immune activation. Previous reports have implicated *Prevotella copri* in the pathogenesis of RA[88]. A recent study used the interleukin-1 receptor antagonist deficient (IL-1Ra$^{-/-}$) mouse model, which can spontaneously develop T cell-driven IL-17-dependent autoimmune arthritis[86]. It was shown that IL-1Ra$^{-/-}$ mice had increased Th17 and a reduced proportion of Th1 in small intestinal lamina propria compared with wild-type mice. GF IL-1Ra$^{-/-}$ mice had lower levels of both Th1 and Th17. Interestingly, IL-1Ra$^{-/-}$ mice previously treated by antibiotics was recolonized by segmented filamentous bacteria, a prominent Th17 inducer, leading to full-fledged arthritis. Moreover, elimination of intestinal Gram-negative commensals suppressed the progression of arthritis[86]. Understanding the role of the intestinal microbiota in the onset of RA may provide significant attention to FMT with regards to management of the disease; the potential is therefore worthy of consideration.

In both Sjögren's syndrome (SS) and systemic lupus erythematosus (SLE), Sjögren's syndrome antigen A/Ro60 is one of the main autoantigens. Ro60 reactive autoantibodies are associated with manifestation severity in SS[89] and with photosensitivity in SLE[90]. *Escherichia coli* expresses von Willebrand factor type A domain protein, which can activate Ro60-reactive T cells[91]. Therefore, immune responses to the gut microbiota may play a pivotal role in the initiation of autoimmunity in SLE and SS. This sheds a light on a novel therapeutic strategy for the diseases.

Hashimoto's thyroiditis (HT) is a thyroid autoimmune disorder, and a series of studies have been implemented to explore the link between gut micro-organisms and HT[92-95]. Although no data on gut microbiota composition are available in HT, increased intestinal permeability was detected in patients with HT[96]. The onset of HT is associated with *Yersinia enterocolitica*, though conflicting data has also been presented[92,95]. Further work is required to test the hypothesis that the gut microbiota is an epigenetic factor for triggering HT, and thereby determine whether FMT is favorable for managing the illness.

Allergic disorders

The prevalence of allergic diseases has been increasing in modern society over the past 50 years. To date, there are two hypotheses for the allergy pandemic[97]: the hygiene hypothesis[98] and the microbiota hypothesis[99]. The latter hypothesis suggests that the disruption of intestinal microbiota drives the emergence of allergy. A wealth of studies regarding the relationship between allergic diseases and microbiota has been conducted in both humans and mice. In the model of allergic airway inflammation induced by ovalbumin/alum, GF mice develop more severe allergic disease than conventional mice[100,101]. Moreover, accumulating evidence has suggested early-life antibiotic exposure is involved in the development of atopy, such as allergic asthma and food allergies, with an altered composition of intestinal microbiota possibly being involved[102,103]. Though probiotic strategies have shown some promise in animal models in preventing asthma development[104,105], it has had little success in humans[106,107]. The use of FMT seems promising in restoring immune homeostasis by transferring a complex community of bacteria which is more stable and harbors a greater ability to colonize[97].

POTENTIAL THERAPEUTIC ROLE IN EXTRA-INTESTINAL TUMORS

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A strong association has now been illustrated between the intestinal microbiota (*e.g., Streptococcus bovis, Enterococcus spp*, enterotoxigenic *Bacteroides fragilis*, pathogenic *Escherichia coli*, and *Fusobacterium nucleatum*) and colorectal cancer[108-110]. Recently, incremental data has suggested that the gut flora (namely *Streptococcus bovis* and *Helicobacter hepaticus*) might be involved in extra-intestinal tumors. Gold et al[15] reviewed 8 extraintestinal malignancies [3 pancreatic adenocarcinomas, 1 lung cancer, 1 ovarian cancer, 1 endometrial cancer, 2 non-solid-organ malignancies (1 chronic myelogenous leukemia with blast crisis and 1 chronic lymphocytic leukemia with end-stage liver disease)] in 45 cases with *Streptococcus bovis* bacteremia in a retrospective study, which suggested that extraintestinal malignancy might be warranted in patients with *Streptococcus bovis*. In addition, prior work has shown the gut microbiota is also involved in mammary tumors[111,112]. The authors infected recombination-activating gene 2-deficient multiple intestinal neoplasia ($Apc^{Min/+}$) mice with *Helicobacter hepaticus* and found the gut flora modulated the carcinogenesis of both mammary carcinoma and intestinal adenocarcinoma in females by triggering inflammatory responses. On a similar note, Rao et al[113] emphasized the question as to whether the gut bacteria should be examined in terms of prevention and treatment for mammary cancer.

In addition, Fox et al[114] used a mouse model to examine the hypothesis that specific intestinal bacteria were associated with hepatocarcinogenesis. The progress of hepatocellular carcinoma induced by aflatoxin and hepatitis C transgene was promoted by *Helicobacter hepaticus* colonization in the intestine through activation of the nuclear factor-κB pathway, which was associated with immunity in the intestine and liver. Surprisingly, neither hepatitis nor bacterial translocation to the liver was essential during this course. These results lead us to think of intestinal bacteria as an attractive therapeutic target.

More recently, Yamamoto et al[115] investigated the relationship between the gut microbiota and lymphoma. Using an $Atm^{-/-}$ mouse model (mice with ataxia-telangiectasia, which can eventually developed into lymphoma), the authors compared the incidence of lymphoma in isogenic mice reared in 2 distinct housing conditions, and found that the gut microbiota acted as a potential contributor to lymphoma onset. Meanwhile, *Lactobacillus johnsonii* was identified to be abundant in more cancer-resistant mice and was further tested for its ability to confer reduced systemic inflammation and genotoxicity when re-established by oral transfer. Given that gut microbiota impact lymphoma incidence and latency, FMT holds promise for reducing lymphoma risk in susceptible individuals.

CONCLUSION

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FMT is proven to be a well-established procedure and the most effective therapy for recurrent CDI to date. Case studies suggest that FMT also has potential clinical applications in treating a wide spectrum of other conditions associated with intestinal dysbiosis. However, additional high quality data are urgently needed to further establish the efficacy of FMT. It is expected that the standardization of FMT will be established in the coming years and its indications expanded. For this reason, besides conventional approaches, FMT is promising as an alternative therapy for many extra-intestinal disorders associated with gut microbiota.

Footnotes

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FMT Cures C. Diff and Is CURING Lupus and Rheumatoid Arthritis

THIS WILL SOON HAVE MAJOR IMPLICATIONS FOR MANY OF MY PATIENTS WITH CHRONIC ITCHY SKIN, AUTOIMMUNE DISEASES LIKE INFLAMMATORY BOWEL DISEASE, CHRONIC DIARRHEA & GASTRITIS. IT IS A QUANTUM SHIFT CURRENTLY IN HUMAN MEDICINE.

GOOGLE: #microbiota #transplantation #autoimmune #fecaltransplant

For decades, scientists thought there were hundreds of bacteria; like Staph, MERSA, Salmonella, you've read about all of those germs. If we can grow it, it exists. **If it doesn't grow, it doesn't exist**. Or so we thought.

Fifteen years ago, they found out how to find DNA fragments ("signatures") from bacteria in tissues. Bacteria THEY COULD NOT GROW IN MEDIA / PETRI-DISHES. The realization was made that **WE CANNOT GROW 99% OF THE WORLDS' BACTERIA!**

Who cares if we can't grow special bacteria?

Well, scientists found out that your intestinal bacteria (especially some un-growable ones) have MANY functions, including acting as HORMONES, NEUROTRANSMITTERS and IMMUNE SYSTEM MODIFIERS. The problem they're having is; they can't grow most of these magic bacteria. But they can find their DNA signatures.

What makes people with Lupus and Rheumatoid Arthritis different from regular healthy people? They asked. The absence of ONE bacterial "signature". *People with Lupus and Rheumatoid arthritis are missing ONE intestinal bacteria*. And when you replace that particular bacteria in the intestine, the patients recover. Now they're looking back at a lot of Lupus and RA cases and discovering that the disease showed up after sufferers had taken long (or intense) courses of antibiotics. Logically, the "mystery bacteria" were killed. But can be replaced in the intestine by "transplantation" of healthy poop (feces); or "FMT". The bacteria come from the intestines of any healthy young donor. The poop is purified, checked for all diseases, and then given as an enema in a cleaned-out bowel. A study showed that even frozen/thawed FMT is equally effective. You don't have to take it orally but at one time they did make capsules and put them through oral intubation.

It's called FMT. "Fecal Microbiota Transplant". It is literally **CURATIVE** for C. Diff an infection which kills a ga-jillion old people every year. And it's reversing cases of Lupus and Rheumatoid Arthritis.

You wanna know what kills off those "good mystery-function-ungrowable-bacteria" that so many sick people are missing?

- Drugs
- Preservatives and What You Eat
- Antibiotics
- Genetics

I SAID ALL THAT TO SAY THIS: Transplanting healthy poop into dogs with chronic bowel and GI issues and even dogs with chronic immune system disorders like ITCHY SKIN may be helpful if not curative. At least it is in people.

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Treating Obesity and Metabolic Syndrome with Fecal Microbiota Transplantation

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Abstract

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The worldwide prevalence of metabolic syndrome, which includes obesity and its associated diseases, is rising rapidly. The human gut microbiome is recognized as an independent environmental modulator of host metabolic health and disease. Research in animal models has demonstrated that the gut microbiome has the functional capacity to induce or relieve metabolic syndrome. One way to modify the human gut microbiome is by transplanting fecal matter, which contains an abundance of live microorganisms, from a healthy individual to a diseased one in the hopes of alleviating illness. Here we review recent evidence suggesting efficacy of fecal microbiota transplant (FMT) in animal models and humans for the treatment of obesity and its associated metabolic disorders.

Keywords: Fecal microbiota transplant, metabolic syndrome, obesity

Introduction

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Over the past half-century, the prevalence of obesity and its related metabolic disorders, such as type 2 diabetes (T2D), non-alcoholic fatty liver disease, and hypercholesterolemia, have increased dramatically. Collectively, these diseases cause an undue burden on health care costs and significant morbidity and mortality. While these diseases are linked to human genetics and lifestyle changes, the human gut microbiome, or the microorganisms living in the gut and their collective genomes, is now recognized to play an emerging role in metabolic health and disease [1,2]. Trillions of diverse organisms, including bacteria, fungi, archaea, and viruses, have co-evolved to live in the human gut [3]. These commensal organisms comprise the gut microbiome, and their collective genome, referred to as the metagenome, contains more than a hundred-fold the number of genes than their host does [4]. Certain metagenomic patterns are associated with obesity, as well as other phenotypes [5]. These patterns are responsive to weight change in individuals [6], suggesting that modulating the gut microbiome is dynamically correlated with the human host's metabolic phenotype.

There are many ways that the gut microbiota can be altered, including probiotics (non-pathogenic organisms beneficial to the host), prebiotics (chemicals that induce growth and/or activity of commensal organisms), and fecal microbiota transplantation (FMT) [7]. Though beneficial effects of probiotics have been reported in many studies, none show an alteration in fecal microbiota composition [8]. FMT on the other hand, causes significant changes in fecal microbiota composition [9]. FMT as a potential therapeutic has a long history. The successful practice of altering gut microbiota with FMT from a healthy to diseased individual was first recorded in the 4th century for the treatment of severe diarrhea [10]. Recently, randomized controlled clinical trials show astounding successes for recurrent, refractory *Clostridium dificile* infection (CDI). Multiple studies have reported greater than 90 percent efficacy, dramatically more successful than traditional therapy, in resolving recurrent CDI [11]. Recent evidence from animal and human models suggests FMT could also be used as a therapeutic intervention against obesity [12,13]. In this review we will provide a status update on the role of FMT in treating obesity and its associated metabolic disorders.

Gut Microbiota and Host Metabolism

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Whereas inter-individual microbiota composition can vary dramatically, a conserved set of bacterial functional gene profiles are present in all healthy individuals, implying a role for the microbiome in physiological gut functioning [1,14,15]. Alterations of this complex physiological bacterial population associated with negative functional outcomes or disease, known as dysbiosis, can cause low-level inflammation and altered intestinal homeostasis. Dysbiosis is linked to a variety of ailments, including obesity and its associated metabolic disturbances [16].

The mechanism by which dysbiosis leads to metabolic disturbances is not well understood. Leading theories include changes in the microbiome's digestive efficiency and perturbed intestinal signaling through alterations of luminal metabolites, low molecular weight signaling chemicals, released by bacteria in the intestinal lumen such as secondary bile acids (BAs) and short-chain fatty acids (SCFAs) [17]. The gut microbiome is essential for fermenting indigestible foodstuffs into products that can be used by, or modulate, the intestine (e.g. complex carbohydrates into SCFAs) [18]. In murine models, obesity-related microbes are able to harvest greater energy from ingested material [19]. In addition, the microbiome's metabolism of primary BAs to secondary BAs affects host metabolism by modulating activation of the farnesoid X receptor, a master regulator of hepatic triglyceride and glucose homeostasis [20], as well as G-protein coupled BA receptors, which can increase metabolic rate in brown adipose tissue [21-23]. Lastly, diet accounts for 57 percent of structural variation in the mouse gut microbiome [24], which shifts tremendously in response to the host's gender, diet, circadian rhythms, and feeding pattern [25-28], suggesting that it is a malleable system amenable to manipulation for therapeutic advantage.

Fecal Matter Transplant Methodology

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Currently, only recurrent CDI is approved by the FDA for FMT therapy without requiring an investigational new drug (IND) approval. Therefore, the majority of FMT recipients have been treated for severe CDI. These individuals failed repeated treatment with antibiotics and had few therapeutic options left. In addition, FMT has been studied in inflammatory bowel disease (IBD) since the etiology of this disease, at least in part, results from dysbiosis. However, there have been few controlled, randomized trials for IBD patients and there is no evidence that FMT improves clinical outcomes. In all, FMT has been performed in primarily ill individuals who are at high risk for complications. Hence, the potential risks and complications for relatively healthy patients with obesity or metabolic syndrome remain hypothetically lower compared to previous studies performed in patients with refractory, recurrent CDI or IBD.

Though FMT is relatively easy to perform, there is wide inter-institutional variability in methodology. For example, in preparation for FMT, some institutions give their patients multiple doses of doxycycline or vancomycin in an effort to reduce the native, dysbiotic population [29]. In many institutions, immediately prior to FMT, patients are typically given a polyethylene glycol colon preparation to increase the opportunity for the transplanted microbiome to successfully colonize the gut regardless of whether the FMT is introduced in the upper GI tract or through a colonoscopy. However, there is no published evidence suggesting that this preparation improves FMT clinical outcomes [22].

The processing of fecal matter for transplant is not standardized and needs to be experimentally validated for optimal efficacy. The general principal, however, is more or less universal. As outlined in Figure 1, the donated stool is first mixed with saline solution to homogenize it into a liquid sample, and is then filtered to remove any solid feces that may interfere with the transplant. In order to standardize the processing of fecal matter, studies have compared the efficacy of frozen versus fresh stool samples prior to processing and transplantation. These studies have thus far shown no significant difference in primary outcomes [30,31]. While studies have performed 16s rRNA sequencing before and after processing to evaluate sample loss, fecal matter contains 99 percent anaerobic species which may not survive vigorous aerobic blending [32,33]. Furthermore, 16s rRNA sequencing does not discriminate viable from dead cells. Nevertheless, the overwhelming number of positive results obtained from FMT in treating CDI patients suggests that either the viability of the cells is relatively unimportant, or that a small proportion of survived cells is sufficient to induce a change in the recipient's microbiome and a therapeutic effect.

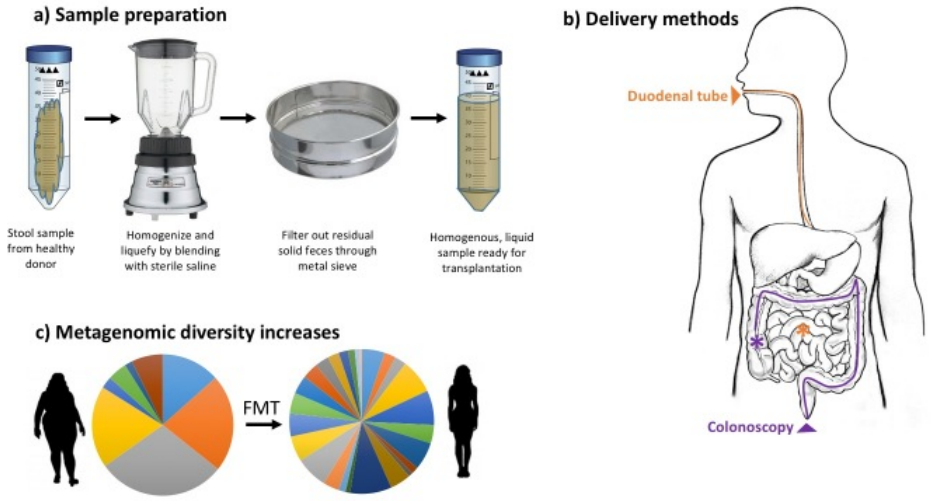

Figure 1

Fecal Microbiota Transplantation schematic. A) Donor fecal matter is blended with saline solution and pushed through a metal sieve to achieve a homogenous liquid solution. **B)** Processed fecal microbiota is either delivered via a duodenal tube or colonoscopy. **C)** Representative data showing metagenomic diversity increases following FMT from lean donor to obese recipient.

Processed fecal matter is typically delivered into the gastrointestinal tract of the patient by colonoscopy or duodenal tube/upper endoscopy (Fig 1B). While delivery route often varies from study to study, no statistically significant difference in outcome is reported between the delivery methods for the treatment of CDI [11,34]. This finding remains to be validated for the treatment of other diseases, such as IBD or obesity. Regardless, it is important to consider the potential risks associated with each potential delivery route.

The protocol for FMT is widely variable, as summarized in Table 1, and standardization of this technique should help elucidate FMT's efficacy.

Table 1

Variability in fecal microbiota transplantation methodology.

Points of variability	Potential methodology	Potential implications
Patient preparation	Type/length of antibiotic treatment, duration of colon preparation	State of patient's gut microbiome could impact susceptiblity to transplant
Donor	Patient relative, 'super donor', designer cultures?	The identification of 'super-donors' hints at the possibility of moving toward the creation of safer, more standardizable synthetic probiotic communities
Sample preparation	Aerobic vs anaerobic; fresh vs frozen vs lyophilized	A recent clincal trial reported no difference in clincal resolution between using fresh or frozen fecal sample for transplantation
Administration	Duodenal tube, colonoscopy, enema, pill	Maximizing practicality of this technique while maintaing efficacy could impacts its prescription and cost
Delivery site	Colon, small intestine	Spatial dynamics of the human microbiome remains poorly characterized, but could results in more targeted therapy

Insulin Sensitivity Transferred from Donors to Recipients

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Recent studies in animal models show a functional relationship between the gut microbiome and obesity and its associated metabolic disturbances. For example, obesity and insulin resistance in adult rats on a high-fructose diet was reversed with orally administered antibiotics or oral FMT from control rats [13]. Transplanting fecal matter from twins discordant for obesity into germ-free mice was recently examined [35]. Mice populated with the microbiome from the obese twin had increased adiposity and decreased bacterial diversity compared to mice populated with the microbiome from the lean twin. These results demonstrate the ability of the microbiome to alter the metabolic phenotype of the host.

To date there has only been one published study testing the efficacy of FMT specifically for treatment of metabolic disorders in humans. The hallmark characteristic of metabolic syndrome is insulin resistance, where cells are hypo-responsive to insulin and therefore cannot maintain glucose homeostasis. Fecal microbiota from healthy, lean donors transferred through a duodenal tube to obese individuals diagnosed with T2D affected host metabolism [12]. The study compared patients who received allogenic transplant (n = 9) (i.e. stool from a healthy donor) to autologous transplantation (n =

9) (i.e., their own stool). Although there was no reported difference in body mass index six weeks after transplantation, there was a significant increase in insulin sensitivity (as measured by the median rate of glucose disappearance) and fecal microbiota diversity, and decrease in fecal SCFA in the allogenic versus autologous group. These promising results have been widely cited and inspired multiple clinical trials (discussed below). Although FMT can induce microbiome alteration towards the donor population for up to 24 weeks post-FMT [29], further studies are need to determine whether FMT can have long-term effects on insulin sensitivity or weight.

Additional clinical trials are necessary to validate the effects of FMT in those with obesity or metabolic syndrome. Importantly, these studies should be randomized, include autologous controls, contain meticulous metadata and track long-term microbiome and patient outcome data. ClinicalTrials.gov lists four ongoing clinical trials testing FMT for metabolic syndrome treatment. A phase 2 clinical trial at Massachusetts General Hospital is evaluating the impact of FMT capsules on a primary outcome of body weight reduction over 18 weeks [ClinicalTrials.gov ID NCT02530385]. An Italian phase 3 clinical trial is tracking glucose homeostasis over a 6-month period following FMT in combination with diet and exercise [ClinicalTrials.gov ID NCT02050607]. Researchers from China's Nanjing Medical University are evaluating the results of a phase 3 clinical trial on a single, nasogastric-delivered FMT on T2D over a two-year period [ClinicalTrials.gov ID NCT01790711]. A Canadian double-blind pilot study is testing FMT efficacy in both metabolic syndrome and non-alcoholic fatty liver disease, which is closely associated with obesity [ClinicalTrials.gov ID NCT02496390].

The results from these clinical trials should give us a better idea of the microbiome's functional role in human metabolic disorder. Future studies must be designed to identify which bacterial populations or functional microbe-host relationships underlie this phenomenon.

Super-Donors

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The selection of a donor for FMT is not standardized, although there is general consensus for the need to do so [36]. Initially, donors were typically family members identified by the patient. However, recent studies highlight the practical advantages of using standardized volunteer donors and creating screened biobanks [31,34]. In general, donors are screened for healthy bowel movements according to the Bristol stool chart, communicable diseases, recent travel history and antibiotic history.

In subsequent publications and conferences, Vrieze et al. noted that the patients who had a more robust improvement of insulin sensitivity after FMT received transplantation from the same limited number of donors [37]. That is, a minority of donor samples elicited a robust response, whereas other samples had no effect on patients' metabolism. The success of the intervention, hence, could be attributed to "super-donors." Studies on the effects of FMT in alleviating symptoms of IBD have similarly observed that fecal samples from certain donors have a much greater therapeutic effect on multiple recipients [38]. Currently there is no way to identify super-donors until after experiments have started. More recent FMT studies try to identify super-donors earlier in order to perform more rigorous analysis of their microbiome for the identification of therapeutic microbiota, which could allow for the design of a better alternative to FMT.

There is a strong social stigma with FMT [39]. Because fecal matter is difficult to standardize, the ethical and social complications in transplanting feces, and the difficulty in monetization, alternatives to direct FMT are being actively pursued [40]. Gel capsules of fecal microbiota is a promising new technique which excludes the need for any gastrointestinal procedure [34,41] and is preferred by patients [42,43]. In fact, private companies already deliver FMT through oral capsules, mainly for the treatment of CDI. However, it is unclear whether these capsules are as effective as FMT itself.

Another potential treatment is to design and produce probiotics in a donor-independent fashion. For example, the Vrieze et al., study identified increased butyrate-producing microbes in patients with

increased insulin sensitivity following FMT [8]. If the increase of butyrate-producing bacteria is important for improvement of metabolic symptoms, then there is a possibility for more direct treatment of metabolic syndrome through pro/pre-biotics, which would be easier to control and administer.

Potential Risks

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One challenge with FMT is the difficulty in finding accurate measures of adverse reactions. Thus far, a vast majority of recipients are ill and it is difficult to differentiate between normal disease progression and the effects of FMT. Nevertheless, although hundreds of individuals have undergone FMT, few negative outcomes have been reported, even in immunocompromised patients [44]. The majority of negative symptoms reported are mild, including diarrhea or fever [45-47]. Mortality has been observed in FMT trials, however it was attributed to unrelated causes in severely ill or elderly patients. Microbiota can predispose susceptibility to atherosclerosis using causative evidence in mice and correlative evidence in humans [48]. In addition, the spread of transmissible disease, while not reported, is still a viable threat, especially to the immunocompromised (e.g. IBD patient on immunomodulatory therapy, HIV patient with CDI). These reports underscore the importance of rigorous donor screening. Finally, these risks have to be tempered with the morbidity and mortality associated with obesity and its associated metabolic diseases, which as of yet have few effective treatments.

Surprisingly, obesogenic properties of the gut microbiome can be transmitted through FMT as well. A case report documented the transmission of an obese phenotype from an overweight donor to a lean patient following FMT for CDI treatment [49]. The donor was a young, obese relative undergoing rapid weight gain at the time of donation. The recipient was an individual who had never been obese. After receiving FMT, the recipient had rapid unintentional weight gain that could not be explained by recovery from CDI alone. Interestingly, the recipient reported increased appetite. These observations remain controversial given that it is a case report. However, it is consistent with rodent studies where transfer of fecal matter from obese mice to germ-free mice transmits the metabolic phenotype [35]. Regardless, the results of this report have affected FMT protocol at many institutions that now exclude obese donors from donating.

Conclusion

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FMT remains an exciting therapy with abundant potential. Nevertheless, there has been a lack of controlled, randomized trials for metabolic disease. Initially, the FDA considered FMT an IND, making it difficult for practitioners to use until all other therapeutic options had been exhausted. However, in 2014 the FDA stated that it would exercise enforcement discretion, allowing physicians to use FMT without IND applications for the treatment of CDI. For more investigational indications of FMT, an IND application with the FDA is still required.

Given the amount of controlled clinical studies currently testing FMT for metabolic syndrome we should have a clear indication in the next few years of whether or not microbiota changes are causative or correlative in this rising epidemic, and whether altering the gut microbiome through FMT or similar procedures will provide new therapeutic options for obesity and its associated metabolic disorders.

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Abbreviations

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FMT	Fecal microbiota transplant

SCFA	short chain fatty acid
BA	bile acid
CDI	*Clostridium difficile* infection
IBD	Inflammatory bowel disease
IND	investigational new drug
T2D	type 2 diabetes

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