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MINI-REVIEW

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Treating Obesity and Metabolic Syndrome with Fecal Microbiota Transplantation

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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.

INTRODUCTION

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.

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†Abbreviations: 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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GUT MICROBIOTA AND HOST METABOLISM

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

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.

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.

INSULIN SENSITIVITY TRANSFERRED FROM DONORS TO RECIPIENTS

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

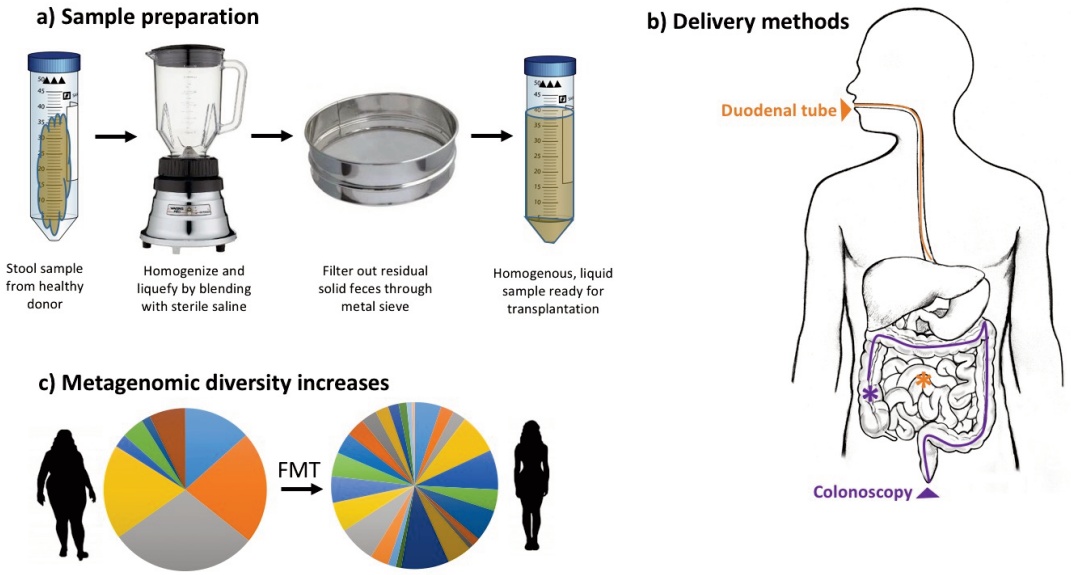

Figure 1. Fecal Microbiota Transplantation schematic. A) Donor fecal matter is blended with saline solution and pushed through a metal sieve to achieve a homogenous liquid solution. **B)** Processed fecal microbiota is either delivered via a duodenal tube or colonoscopy. **C)** Representative data showing metagenomic diversity increases following FMT from lean donor to obese recipient.

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

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

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

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/prebiotics, which would be easier to control and administer.

POTENTIAL RISKS

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 unin-

tentional 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

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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