Fecal Microbiota Transplantation to Prevent and Treat Chronic Disease: Implications for Dietetics Practice

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THE INCIDENCE OF CHRONIC DISEASE IS A GROWING public health concern because 133 million Americans live with at least one condition.[1] Chronic disease is costly to treat, altogether accounting for 75% of US health care spending and it is the country's leading cause of mortality.[1] A multitude of factors are responsible for the increasing prevalence of chronic health conditions. One such factor believed to influence the development of chronic conditions is the gut microbiome.[2] Rehabilitating the microbiome can alleviate pain associated with chronic conditions and reduce the cost of symptom management.[3]

The microbiome, gut bacterial content, is unique to each individual based on diet, presence of disease or infection, and other factors.[3] The microbiome is involved in various processes within the human body, including immunity, metabolic health, and brain function.[4,5] Although there is a general definition of a healthy gut, specifics of the actual makeup of it vary based on population, geography, lifestyle, and more.[6] For instance, athletic populations have distinct microbiota compositions, with an increased ratio of *Bacteroidetes* to *Firmicutes*, compared with inactive populations.[7] Geographical differences will certainly cause differences in microbiota composition due to availability and consumption of specific foods.[8] Further, the functional redundancy, or highly conserved gene composition or functional capacity of the microbiome across human beings is potentially considered a marker of a healthy microbiota.[9] Although microbiota diversity and richness have been shown to promote a healthy gut, the diverse bacteria do function analogously while being made up of similar genes. Determining which microbes benefit the gut is also an area of uncertainty because the potential effects of some microbes are known but the research is not exhaustive. Some bacteria known to have beneficial effects are *Bifidobacterium*, *Faecalibacterium*, and *Roseburia*, all having anti-inflammatory properties.[10] However, not all bacteria are always beneficial[11] and can become pathogenic and disease causing,[12] depending on their quantity in the gut and host lifestyle factors.[5,10] Such bacteria include *Escherichia coli* and *Salmonella typhimurium*.[13] These bacteria can produce toxins that hinder protective mechanisms the body has in place to fight pathogens.[13]

Gut dysbiosis, the alteration of the microbial community leading to negative health outcomes, can be caused by many factors, such as antibiotic use, stress, or poor diet.[5] These factors can cause excessive growth of harmful bacteria and increased susceptibility to pathogens in the gut causing dysfunction and disorder, presenting as disease or inflammation.[3,5] For example, high dietary intake of animal-based protein can cause an imbalance in the gut and lead to cardiovascular disease.[14] Although short-chain fatty acids (SCFAs) can be beneficial to the human body, such as contributing to cellular energy use or stress alleviation, SCFAs can also be another potential source of gut dysfunction and inflammation in the intestinal microbiome.[3,15] SCFAs can pass through the blood–brain barrier and cause neurological symptoms.[16] Gut bacteria have a mutually beneficial relationship in healthy people and studies in mice have shown that without the microbiome there would be abnormalities.[3]

Gut dysbiosis is not stagnant and thus has the potential to be modified. For example, as fecal microbiota transplantation (FMT) becomes more widely used, the ability of diet to modify the microbiota has also been appreciated.[17] Registered dietitians (RDs) could play an integral role by working with patients who have undergone FMT to sustain the newly colonized gut and provide education on appropriate foods for an improved outcome. RDs should be aware of FMT and be prepared to provide suitable interventions. This commentary describes the potential of FMT to be used as an alternative and prominent treatment of chronic disease linked to inflammation and reduced gut microbiome diversity. By increasing microbiota diversity and richness, FMT can be a cost-effective and long-lasting treatment that may prevent relapse of infections or disease and improve medical costs.

AN OVERVIEW OF FMT

The earliest use of FMT was in the 16th century, documented in a Chinese emergency medicine handbook.[18] FMT is the infusion of feces filtrated from a healthy donor into the intestines of a recipient to manage a disease.[19] After infusion, the "healthy" bacteria colonize the gut in dysbiosis,

promoting symbiosis and ridding the gut of dominant, harmful bacteria by outcompeting them.[20]

Current methods of FMT include fecal suspension in the form of an enema, infusion through nasoduodenal tube, infusion through the upper gastrointestinal (GI) tract using a nasogastric tube, colonoscopy, or by swallowing a capsule.[19] FMT delivery methods have been administered in various experimental settings, including hospitals or homes, but because FMT is still considered an investigational treatment for most conditions, a clinical setting is recommended.[21,22] To donate fecal matter for FMT, there is an extensive screening process regarding existing conditions, allergies, lifestyle practices, and medication use of the potential donor.[23] The stool and blood of potential donors are screened for communicable diseases.[24] More successful outcomes have been documented in donors who share similar microbiome characteristics with a recipient before infection or disorder; however, similar advantages are noted in donors who may not have similar microbial intestinal makeup but are healthy.[19]

THE SUCCESS OF FMT TO TREAT *CLOSTRIDIUM DIFFICILE* INFECTIONS

FMT has shown the most success in treating *C difficile*, a bacterium responsible for 500,000 GI-related illnesses per year in the United States.[25] In a systematic review by Quraishi and colleagues,[20] there was a 92% success rate in the treatment of *C difficile* infections with FMT. Observational studies were found to have as high as a 90% cure rate from *C difficile* infections using FMT and a randomized control trial in individuals with recurrent *C difficile* infections showed an 81% cure rate compared with a 31% cure rate in individuals treated with an antibiotic.[26,27] As such, FMT is currently only approved for *C difficile* infections as treatment in that FMT has shown the most success. Due to the remarkable results of FMT in treating *C difficile* infections, experts are investigating other ways in which FMT can be used.[24]

POTENTIAL IMPLICATIONS OF FMT ON CHRONIC DISEASE

FMT is currently being investigated for the treatment of cardiometabolic, neurological, psychiatric, neoplastic, autoimmune/inflammatory, and GI disorders.[19] This wide range of potential treatment with FMT demonstrates the importance of the microbiome and potential for a cost-effective, safe treatment for chronic disease. Although trials have begun in human beings for many chronic conditions, it is important to note as conditions are discussed in this section, that additional research is required to determine whether or not FMT should be considered and approved as a recommended intervention for these chronic diseases.

Metabolic Health

Changes in diversity of the microbiome seem to play an important role in altering metabolic functions that cause disease.[28] Certain microbes that promote dysbiosis have been identified to cause obesity in mice,[29] affecting metabolic homeostasis and causing insulin resistance. Research suggests[30] that FMT from a donor with a diverse and balanced microbiome may be able to correct for insulin resistance. Due to the nature of the microbiota's ability to alter the host's metabolic phenotypic expression, it is promising that FMT can increase insulin sensitivity in a person with type 2 diabetes.[31] Specific microbes that have shown promise to improve insulin sensitivity are *Bacillus* spp,[32] *Bifidobacterium*, and *Butyricimonas*[33] by potentially reducing adipose tissue inflammation.[34]

Cancer

Animal research has shown promising effects of FMT in treating cancer symptoms and complications such as cachexia or progression of malignancy in several types of cancers, including lung cancer, colon cancer, or leukemia.[35,36] For example, *Enterococcus hirae* and *Barnesiella intestinihominis* bacteria can inhibit the growth and progression of malignancy related to colon cancer.[35] These bacteria with potential antitumor promoting mechanisms can be introduced into the gut via FMT after a cancer diagnosis, or be transplanted into those at high-risk of developing cancer due to organ damage and inflammation as a preventive treatment.

Psychiatric Disorders

The intimate connection between the gut and brain has led to investigation of FMT as a treatment of psychiatric disorders, such as mood disorders, substance use disorder, and eating disorders.[37] Examples of potential mechanisms of the gut and brain relationship is through immune, endocrine, and neural pathways. For example, a gut in dysbiosis has increased levels of SCFAs and these specifically influence the vagus nerve.[37] Chinna and colleagues[37] proposed that psychiatric symptoms, such as compulsivity and anxiety, could be managed by transferring microbiota of individuals without psychiatric disorders to individuals with these disorders.

Neurodegenerative Diseases

Research has shown promise of FMT in treating neurodegenerative diseases such as Parkinson disease (PD). For example, evidence from animal studies suggests that components of the microbiome can either prevent or promote PD.[38] Many patients with PD experience GI symptoms before their diagnosis, indicating an important relationship between the gut and nervous system. Animal studies have demonstrated that FMT from non-PD to PD mice reduces SCFA make-up in their gut.[38] Similarly, gut microbiota from PD mice transplanted into non-PD mice can cause motor abnormalities.[21] Although these animal studies have been promising for the future of FMT, extensive research is needed to understand the mechanisms of using FMT to treat PD or other neurodegenerative diseases in human beings.

INFLUENCE OF FMT ON PUBLIC HEALTH AND DIETETICS PRACTICES

The utilization of FMT in clinical settings will have an influence in public health as the prevalence of chronic disease continues to rise. RDs have the potential to play a key role in the success of FMT. To help optimize FMT success, RDs may provide nutrition counseling services as part of health care teams.

Consultation with RDs to improve dietary intake and nutritional status could also have the potential to support long-term success of FMT.[39] Once a new microbial

community is introduced into the gut, the host must provide prebiotics,[40] which are defined as "substrates that are selectively utilized by the host microorganisms conferring a healthy benefit."[41] RDs could develop meal plans and prescribe specific medical nutrition therapies to support an FMT patient's new gut microbiota and prevent any deficiencies or potential negative outcomes. RDs are also proficient in solving nutrition challenges,[42] which may be integral for long-term FMT success. Nutrition challenges can include working with patients to integrate a meal plan contextually relevant to the patient's culture and medical history. To enhance patient success, RDs can work with patients to help them overcome personal barriers to altering their diet such as helping them to identify strategies for increasing food access.

RDs can also play a role in future diet-related research studies. For example, fiber intake has been identified as a means of managing intestinal diseases and preventing flare-ups. Clancy and colleagues[17] explored the relevance of dietary intake of fiber, according to the dietary guidelines, to patients with irritable bowel syndrome and inflammatory bowel disease (IBD) who received FMT. RDs assessed participants' food diaries and it was determined that these FMT patients had higher intake of fiber than the population average. Although studies have looked at the effects of FMT in patients with irritable bowel syndrome and IBD, few have controlled for dietary intake; and this is a niche that should be explored with controlled trials and in which RDs should be included. RDs are trained in dietary assessment and should have an integral role in research focused on the relationship between dietary intake and FMT interventions.

LIMITATIONS OF FMT

Although FMT is promising in treating chronic diseases connected to gut dysbiosis, the long-lasting effects of FMT still need to be determined due to the lack of trials that control for diet and short-term studies dominating the literature.[26] One challenge of post-FMT is providing proper nutrients to the newly established microbiome to maintain symbiosis. Healthy microbiomes contain a balance of bacteria and can only survive based on what the host, a human being in this case, consumes. In the case that there is a change in diet that does not support this balance, healthy bacteria will diminish and the microbes previously present in the dysbiotic gut will return.[26] Therefore, evidence-based nutrition therapy provided by RDs can be a tool for prolonging FMT success. Long-lasting effects of FMT have been questioned after FMT patients reported side effects, such as IBD flare-ups, although it is not clear whether they would have occurred even without the transplantation.[19] Accordingly, Wang and colleagues[43] conducted a systematic review to determine the reported mild and serious side effects following FMT. The most common side effect reported was stomach discomfort, including symptoms such as constipation, vomiting, cramping, and bloating.[43] Some serious side effects were reported in the literature, although not as frequent, and included pathogen infections. More precise measures of these adverse effects will aid in differentiating between disease- or FMT-related symptoms.[2]

Lastly, there are social and cultural stigmas associated with transplantation of fecal matter into an individual from someone else.[2] This stigma can have some influence on FMT being perceived as a valid and effective treatment. If this stigma is widely accepted, institutions may not want to invest in a treatment that no one is willing to use no matter how encouraging outcomes may be.

THE FUTURE OF FMT

Advances in sequencing technologies can be used to identify biomarkers for disease to produce more customized therapies for improved effectiveness and availability of FMT.[44] Advancements in the selection of specific species and the method of transplantation of the donor stool may improve outcomes of FMT.[44] Determining the perfect microbial composition is difficult because of several factors, including bacterial diversity, variability of microbiota make-up between individuals, function of some bacteria, and establishment of species that are still unknown in the GI tract,[39] but determining a range of "healthy" microbiota may help develop criteria for the highest standard of donor microbiota.[44] Even in the case that FMT is not used directly to treat chronic diseases, it may result in new discoveries in the pathophysiology of these diseases and potentially other discoveries in microbial remedial uses.[45]

The potential role that RDs could have in the use of FMT to treat and manage chronic conditions is promising, but several steps are required to make FMT a reliable and effective treatment option.[45] For FMT to become widely accepted as a form of treatment for gut dysbiosis disorders, more randomized controlled trials that include research on post-FMT nutrition are needed. Once dietary guidelines are established, RDs could incorporate evidence-based practices that support the provision of nutrients to maintain symbiosis. Overall, RDs have a potential role in ensuring the success of FMT to improve chronic conditions, and as a result, improving population health.[36,46,47]

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

I. Opoku-Acheampong and T. McLaud collectively decided on the significance of the topic to offer perspectives and context on through a commentary. I. Opoku-Acheampong and T.McLaud wrote the first draft of the commentary. O. Anderson provided guidance on the topic specifically on the relevance to the dietetics field, critically reviewed the text, and wrote additional text required for a commentary manuscript. All authors reviewed subsequent drafts of the manuscript.

THE ART OF DIETETICS

As the slugs waged war on their tops, these sweet nantes carrots kept doing their thing underground. Carrots for the win!.

Photo taken by Laura Holtrop, MS, RDN.

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