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Therapeutic Potential of Fecal Microbiota Transplant in the Treatment of Obesity

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Cover Page Footnote

Adult obesity causes & consequences | overweight & obesity | CDC. (2018). Retrieved from https://www.cdc.gov/obesity/adult/causes.html Alang, N., & Kelly, C. R. (2015). Weight gain after fecal microbiota transplantation. Open Forum Infectious Diseases, 2(1), ofv004. 10.1093/ofid/ofv004 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26034755 Allen, J. M., Mailing, L. J., Niemiro, G. M., Moore, R., Cook, M. D., White, B. A., . . . Woods, J. A. (2017). Exercise alters gut microbiota composition and function in lean and obese humans. Medicine and Science in Sports and Exercise, 10.1249/MSS.0000000000001495 Arkkila, P. Fecal Microbiota Transplant in the Treatment of Morbid Obesity. (2018) Retrieved from https://clinicaltrials.gov/ct2/show/NCT03391817 Bäckhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., . . . Gordon, J. I. (2004). The gut microbiota as an environmental factor that regulates fat storage. Proceedings of the National Academy of Sciences, 101(44), 15718-15723. de Clercq, N. C., Frissen, M. N., Groen, A. K., & Nieuwdorp, M. (2017). Gut microbiota and the gut-brain axis: New insights in the pathophysiology of metabolic syndrome. Psychosomatic Medicine, 79(8), 874-879. 10.1097/PSY.0000000000000495 Graessler, J., Qin, Y., Zhong, H., Zhang, J., Licinio, J., Wong, M. -., . . . Bornstein, S. R. (2013). Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: Correlation with inflammatory and metabolic parameters. The Pharmacogenomics Journal, 13(6), 514-522. 10.1038/tpj.2012.43 Jayasinghe, T. N., Chiavaroli, V., Holland, D. J., Cutfield, W. S., & O'Sullivan, J. M. (2016). The new era of treatment for obesity and metabolic disorders: Evidence and expectations for gut microbiome transplantation. Frontiers in Cellular and Infection Microbiology, 6, 15. 10.3389/fcimb.2016.00015 Jumpertz, R., Le, D. S., Turnbaugh, P. J., Trinidad, C., Bogardus, C., Gordon, J. I., & Krakoff, J. (2011). Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. The American Journal of Clinical Nutrition, 94(1), 58-65. doi:10.3945/ajcn.110.010132 Marotz, C. A., & Zarrinpar, A. (2016). Treating obesity and metabolic syndrome with fecal microbiota transplantation. The Yale Journal of Biology and Medicine, 89(3), 383-388. Martinez, K. B., Pierre, J. F., & Chang, E. B. (2016). The gut microbiota: The gateway to improved metabolism. Gastroenterology Clinics of North America, 45(4), 601-614. 10.1016/j.gtc.2016.07.001 Million, M., Lagier, J. -, Yahav, D., & Paul, M. (2013). Gut bacterial microbiota and obesity. Clinical Microbiology and Infection, 19(4), 305-313. 10.1111/1469-0691.12172 Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/1469-0691.12172/abstract Million, M., Maraninchi, M., Henry, M., Armougom, F., Richet, H., Carrieri, P., . . . Raoult, D. (2012). Obesity-associated gut microbiota is enriched in lactobacillus reuteri and depleted in bifidobacterium animalis and methanobrevibacter smithii. International Journal of Obesity, 36(6), 817-825. doi:10.1038/ijo.2011.153 Turnbaugh, P. J., Ley, R. E., Hamady, M., Fraser-Liggett, C. M., Knight, R., & Gordon, J. I. (2007). The human microbiome project. Nature, 449(7164), 804-810. 10.1038/nature06244 Turnbaugh, P. J., Ley, R. E., Mahowald, M. A., Magrini, V., Mardis, E. R., & Gordon, J. I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. Nature, 444(7122), 1027. 10.1038/nature05414 Retrieved from https://www.nature.com/articles/nature05414 Ursell, L. K., Haiser, H. J., Van Treuren, W., Garg, N., Reddivari, L., Vanamala, J., . . . Knight, R. (2014). The intestinal metabolome: An intersection between microbiota and host. Gastroenterology, 146(6), 1470-1476. doi:10.1053/j.gastro.2014.03.001 Valentina Tremaroli, & Fredrik Bäckhed. (2012). Functional interactions between the gut microbiota and host metabolism. Nature, 489(7415), 242-249. doi:10.1038/nature11552 Vrieze, A., Van Nood, E., Holleman, F., Salojärvi, J., Kootte, R. S., Bartelsman, Joep F W M, . . . Nieuwdorp, M. (2012).

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Evaluating Fecal Microbiota Transplant as a Therapeutic Treatment of Obesity

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Abstract

Obesity is a worldwide epidemic with physical, emotional and economic strain. The associated multitude of comorbidities exacerbate the economic burden this disease has on the healthcare system, yet struggle persists in the endeavor to find successful treatment options and understand all facets of metabolism. While it is known that the human microbiome impacts disease, until recently this has not been sufficiently studied. The gut microbiome is further becoming identified as a metabolic organ having a significant impact on host metabolism. Lean individuals harbor a more diverse microbiota, extracting less energy from food sources. In contrast, an obese individuals' microbiota is less diverse, yet extracts more energy from food. The obese gut microbiome changes with weight loss and exercise, becoming more diverse. While it is not yet clear how long these changes last, at a minimum, increased intestinal microbiome diversity is associated with an increased host metabolism. Establishing the ideal gut microbiome is yet to be determined. Probiotics and prebiotics may alter this microbiome though no clear evidence exists suggesting that this alteration can diversify in a way to increase metabolism long term, yet antibiotic use can decrease diversity permanently (Ursell et al., 2014).[1] Gut modulation via fecal microbiota transplant (FMT) may become an effective therapeutic option for the treatment of obesity. Most widely known as a successful treatment for C. difficile colitis, FMT has the potential to substantially impact obesity treatment and its subsequent comorbidities.

Nature of the Problem

The World Health Organization defines obesity in adults as a body mass index (BMI) equal to or greater than 30, and overweight as a BMI equal to or greater than 25.[2] Worldwide, approximately 1.9 billion adults are overweight, with 650 million of those classified as obese. This worldwide epidemic is responsible for economic drain and is associated with several chronic disorders and comorbidities including but not limited to; all-cause death, lower quality of life, cardiovascular disease, cancer, sleep apnea, liver disease, and infertility. As per the Centers for Disease Control, the healthcare cost of obesity in 2008 was $147 billion.[3] Ideally, more effective treatment options will decrease the incidence and the cost associated with obesity. Identifying the human gut microbiota as a metabolic organ, finding optimal stool donors, and additional interventions that optimize this microbiota may greatly enhance the understanding of obesity, and its associated treatment options. Furthermore, increasing the acceptance of FMT treatment will

[1] Ursell, L. K., Haiser, H. J., Van Treuren, W., Garg, N., Reddivari, L., Vanamala, J., . . . Knight, R. (2014). The intestinal metabolome: An intersection between microbiota and host. *Gastroenterology, 146*(6), 1470-1476. doi:10.1053/j.gastro.2014.03.001

[2] WHO | obesity. Retrieved from http://www.who.int/topics/obesity/en/

[3] Adult obesity causes & consequences | overweight & obesity | CDC. (2018). Retrieved from https://www.cdc.gov/obesity/adult/causes.html

pave the way to further utilize an optimal microbiome to modify other disease processes.

The layman's view is that most lean individuals simply have a faster metabolism, this is far from the truth. Historically metabolism has been studied using the Basal Metabolic Rate (BMR) which was first defined in 1924.[4] BMR is derived from a standard calculation using height, weight, age, and gender as the sole factors affecting metabolism. This tool determines total daily energy expenditure or the number of calories burned at rest. Throughout history, various studies have looked at potential factors in addition to BMR that may affect metabolism such as genetics, race, biochemical parameters, environmental factors, health status, and diet composition.[5] Identifying the gut microbiota as a metabolic organ combines both old and new data. Scientific evidence of the human microbiome and its impact on disease has existed since the 1880s. This knowledge has only recently expanded with the National Institutes of Health Common Fund Human Microbiome Project of 2007. This project was established with the mission of generating research resources which have been the basis for several studies analyzing the human microbiota and its role in overall health and disease.[6] Manipulation of gut microbiome is a promising therapy not only for obesity, but also a plethora of other conditions including but not limited to; autoimmune disease, mood disorders, Type II Diabetes, and dermatologic conditions.

Purpose of this Project Proposal

This literature review will address the role of fecal microbiota in obesity. The general view is that most lean individuals simply have a faster metabolism, this is far from the truth. Scientific evidence of the human microbiome and its impact on disease has existed since the 1880s. This knowledge has only recently expanded with the Human Microbiome Project of 2007 (HMP).[6]

Significance to the Profession

Obesity is a comorbid disease which also carries a social stigma. The media correlates beauty with low body weight. This is identified in the vast majority of advertisements evidenced by the typically thin model selling everything from tools to fashion. Television and movies follow suit. This all affects an obese individuals' self-esteem and body image. Finding additional factors that affect metabolism will provide a pathway to success for those who struggle to attain the ideal body weight. Identifying gut microbiota as a metabolic organ has the

[4] McNab, B. (1997). On the utility of uniformity in the definition of basal rate of metabolism. *Physiological Zoology, 70*(6), 718-720. doi:10.1086/515881

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potential to change the way we view and think about obesity. Diet and exercise alone are not the only factors in a successful weight loss program. Consistencies are beginning to emerge, identifying complementary tools to help those who suffer from the obesity epidemic.

Unidentified variables influencing body habitus exist, until now intestinal microbiota was one of them. Several intestinal microbiome studies are currently in progress focusing on this relatively newer thought process, however, enough information exists to enhance the understanding of the role the human microbiota has on body composition. While clinical applications and benefits are still in the early stages of research, the correlation between the lack of diverse gut microbiota and obesity may significantly impact treatment options for obesity.

Research Question

A literature review will be conducted based on the following question: Does Fecal Microbiota Transplant (FMT) have a therapeutic role in the treatment of obesity?

LITERATURE REVIEW

Therapeutic Potential

The idea of incorporating FMT as a treatment for obesity emerged in 2004 with a study that looked at gut microbiota as a factor in metabolism. Completed at the Washington University School of Medicine, this study fed stool from traditionally raised mice to germ-free mice. Results showed a 60% increase in body fat content and insulin resistance in germ-free mice, fourteen days after intestinal colonization, despite no change in caloric intake.[7]

The Human Microbiome Project (HMP) completed in 2007, identified our metabolic landscape, displaying a connection between the variable human microbiome and disease.[6] This project was an international summary reflection of multiple works, connecting medical and environmental microbiology to identify new pathways of disease intervention. This background created the opportunity to intentionally manipulate gut microbiota, subsequently optimizing an individual's host metabolism. We now know the digestive capacity of the gut microbiota influences the nutrient and caloric value of food. Turnbaugh et. al., initially identified the gut microbiome as a contributing factor in the pathophysiology of human obesity.[8] Moving on to establish that the obese microbiome has an increased capacity to harvest energy from food and that the intestinal microbiota not only differs between the lean and obese but is also transferable between human subjects.

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[7] Bäckhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., . . . Gordon, J. I. (2004). The gut microbiota as an environmental factor that regulates fat storage. *Proceedings of the National Academy of Sciences, 101*(44), 15718-15723.

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What is in the gut?

The human gut microbiota is primarily made up of bacterial organisms residing in the colon. In addition to bacteria, a smaller percentage is made up of archaea, eukaryotes, and viruses. The two major bacterial dominant phyla in the human gut include Firmicutes and Bacteroidetes, followed by Proteobacteria and Actinobacteria which altogether account for 97% of the gut microbe population.[9] A greater percent body fat correlates with a greater ratio of Firmicutes to Bacteroidetes, hence obesity is associated with changes in the amount of at least two of these major phyla.[10] Generally, Bacteriodetes are decreased and Firmicutes increased in obesity resulting in an increase Firmicutes to Bacteriodetes ratio (Table 1). Some small studies have found controversial and conflicting results regarding the optimal microbiota profile, and the different phenotypes associated with body mass index. This is most likely the result of the various less abundant species of each phylum, different methodologies, and an increase in newer data and knowledge.[11]

While current evidence is preliminary, multiple factors including genetic, environmental, diet, exercise, and psychological stress impact the incidence of obesity. Jayasinghe, et. al. (2016) identifies the connection between obesity and metabolic disorders in relation to the potential of FMT as a treatment for obesity. Gut microbiota impacts host metabolism by promoting uptake of monosaccharides, storage of triglycerides, digestion of dietary fiber, and the synthesis of hormonal precursors.[12]

Short chain fatty acids are microbial metabolites responsible for several physiologic effects. Complex carbohydrates are metabolized by intestinal microbiota to oligosaccharides and monosaccharides, then fermented to short-chain fatty acids (SCFA) such as butyrate, propionate, and acetate.[13] Once

[9] Ursell, L. K., Haiser, H. J., Van Treuren, W., Garg, N., Reddivari, L., Vanamala, J., . . . Knight, R. (2014). The intestinal metabolome: An intersection between microbiota and host. *Gastroenterology, 146*(6), 1470-1476. doi:10.1053/j.gastro.2014.03.001

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[11] Million, M., Maraninchi, M., Henry, M., Armougom, F., Richet, H., Carrieri, P., . . . Raoult, D. (2012). Obesity-associated gut microbiota is enriched in lactobacillus reuteri and depleted in bifidobacterium animalis and methanobrevibacter smithii. *International Journal of Obesity, 36*(6), 817-825. doi:10.1038/ijo.2011.153

[12] Jayasinghe, T. N., Chiavaroli, V., Holland, D. J., Cutfield, W. S., & O'Sullivan, J. M. (2016). The new era of treatment for obesity and metabolic disorders: Evidence and expectations for gut microbiome transplantation. *Frontiers in Cellular and Infection Microbiology, 6*, 15. 10.3389/fcimb.2016.00015

[13] Valentina Tremaroli, & Fredrik Bäckhed. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature, 489*(7415), 242-249. doi:10.1038/nature11552

absorbed in the colon propionate and acetate act as substrates in the liver and peripheral organs for gluconeogenesis and lipogenesis. SCFA reduce intestinal permeability and regulate processes within the gastrointestinal tract such as water absorption and electrolytes. The types and amount of SCFAs produced are determined by how much carbohydrate is consumed and the composition of the gut microbiota. A higher number of SCFA is associated with obesity due to the increased dietary energy harvest, which translates to more calories absorbed from the diet compared to those with a lower amount of SCFA.

Table 1

Generalization of Lean and Obese Intestinal Microbiome

	Obese	Lean
Microbial Diversity	↓	↑
Firmicutes	↑	↓
Bacteriodetes	↓	↑
Proteobacteria	↑↓	↑↓
Actinobacteria	equivocal or ↑	equivocal or ↓
Firmicutes/Bacteriodetes ratio	↑	↓

Note. Conflicting data exist regarding the optimal microbiota for weight loss. Possible explanations include; (a) Firmicutes are more effective as an energy source than Bacteroidetes resulting in an increase calorie absorption, (b) association between the relative proportion of gut anaerobic and blood glucose levels, (c) abundance of various species within each phylum, (d) different methodologies, (e) participants dietary habits in specific geographic. [9, , 12, 13, 16]

Two important points to recognize are, (a) obesity is associated with microbial dysbiosis, characterized by a decreased microbial gut diversity, and lack of bacterial richness and, (b) lean individuals have a more diverse gut microbiome and more optimal metabolic homeostasis.[14]

Jumpertz, R., Le, D. S., Turnbaugh, P. J., Trinidad, C., Bogardus, C., Gordon, J. I., & Krakoff, J. (2011). Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *The American Journal of Clinical Nutrition, 94*(1), 58-65. doi:10.3945/ajcn.110.010132

[14] Martinez, K. B., Pierre, J. F., & Chang, E. B. (2016). The gut microbiota: The gateway to improved metabolism. *Gastroenterology Clinics of North America, 45*(4), 601-614. 10.1016/j.gtc.2016.07.001

Multiple factors contribute to the composition of the gut microbiome, dysbiosis and fecal microbiota diversity. These variables result in a lack of consistency in an obese individuals' microbiota composition complicating the causality between gut microbiota and energy homeostasis. "Exercise Alters Gut Microbiota Composition and Function in Lean and Obese Humans" (2017) established a relationship between exercise and changes in the gut microbiota. This small study of 32 lean and obese individuals showed a more diverse gut microbiota with regular exercise, which was sustained only if exercise continued.[15] A study by Graessler et. al. evaluated post-bariatric surgery patients to find an increased microbial diversity during weight loss, which was not sustained in those gaining weight 2 years post-procedure.[16] "Gut Microbiota and the Gut-Brain Axis: New Insights in the Pathophysiology of Metabolic Syndrome" (2017) introduced the role of the gut-brain axis and microbial diversity in metabolism.[17] De Clercq et. al., highlighted the link between host metabolism and behavior via bidirectional signaling between the gastrointestinal tract and the brain. Proceeding to further identify SCFAs effect on energy homeostasis through the regulation of gastrointestinal (GI) hormones such as cholecystokinin, glucagon-like peptide 1, peptide tyrosine-tyrosine, and leptin. Preclinical studies show that modifying rodents' microbiota through FMT results in alterations of these GI hormones, which affect not only metabolism but also behavior. Whether these findings translate to human metabolism is unclear. Therefore, the ideal microbiome may have the potential to command the gut-brain axis and positively influence the pathophysiology of metabolic disease.

FMT Therapy in Obesity

Given gut dysbiosis has been implicated in obesity, and FMT improves gut flora, further research is warranted to clarify this connection and treatment potential. FMT is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient directly altering the recipients gut microbiome to achieve optimal health. After identifying a donor, the procedure is performed via enema, encapsulation, colonoscopy, or nasogastric tube.

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[15] Allen, J. M., Mailing, L. J., Niemiro, G. M., Moore, R., Cook, M. D., White, B. A., . . . Woods, J. A. (2017). Exercise alters gut microbiota composition and function in lean and obese humans. *Medicine and Science in Sports and Exercise,* 10.1249/MSS.0000000000001495

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[17] de Clercq, N. C., Frissen, M. N., Groen, A. K., & Nieuwdorp, M. (2017). Gut microbiota and the gut-brain axis: New insights in the pathophysiology of metabolic syndrome. *Psychosomatic Medicine, 79*(8), 874-879. 10.1097/PSY.0000000000000495

A case report was published in 2015 identifying a disproportionate weight gain after FMT.[18] A 32-year-old female with recurrent C. difficile infection underwent FMT from an obese donor. This patient experienced a rapid weight gain of greater than 30 pounds despite a supervised high protein liquid diet and exercise program. The Yale Journal of Biology and Medicine published "Treating Obesity and Metabolic Syndrome with Fecal Microbiota Transplantation," this manuscript supports the exciting potential of FMT as a treatment for metabolic syndrome, citing the lack of randomized controlled trials (RCT) that currently exist, supporting the need and usefulness of further investigation into this topic.[19] This study as of the date of its publication, referenced the only relevant RCT, "Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome."[20] A randomized double-blind controlled trial, using gut microbiota transfer via gastroduodenal tube from a lean donor, vs the subjects own gut microbial infusion, showed a statistically significant improvement in peripheral insulin sensitivity 6 weeks post-treatment.

As of this writing, an RCT began January 19, 2018, at Helsinki University Hospital in Finland, "Fecal Microbiota Transplant in the Treatment of Morbid Obesity," scheduled for completion May 2020. Participants criteria include; age range 18 to 65, BMI $\geq$ 40 or BMI $\geq$35, with at least two obesity-related co-morbidities, and consent to gastroscopy administered FMT with either lean donor stool or placebo. The placebo stool is defined as the participants own feces.[21] No preliminary information is currently available.

Summary

Gut modulation via FMT has the potential to substantially impact obesity treatment and its subsequent comorbidities, becoming an effective therapeutic treatment option. A critical need remains to better understand specific gut microbiota compositions that may be used in the treatment of obesity. Showing the success of this treatment modality will increase obesity treatment options and decrease the incidence of costly bariatric surgery along with its associated risks of long and short-term complications. Potentially decreasing the incidence of obesity not only brings economic benefit resulting in less health care dollars spent, but

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also meets the needs of obese patients, leading to fewer comorbidities. Advanced optimal mapping of the human microbiome is essential to develop targeted interventions for obesity and metabolic syndrome. In addition, identifying diseases other than colitis amenable to FMT facilitates options to study and identify further conditions that may benefit from this treatment.

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