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We commend the authors of "Weight Gain After Fecal Microbiota Transplantation" for describing this case of obesity after a fecal microbiota transplant (FMT). Fecal microbiota transplant is a highly effective therapy for recurrent *Clostridium difficile* infection (r-CDI), and the authors discuss possible unintended consequences in a patient after successful FMT, which could be due to alteration of the gut microbiota.

Strengths of this study include (1) detailed information about the clinical course of the patient receiving FMT for r-CDI and (2) characteristics of the FMT donor, the patient's daughter. This experience led to a change in FMT donor policy at the authors' institution. The authors do not identify the mechanism for transmission of the obese phenotype, directly demonstrate a causal relationship, or study the patient's microbiome over time. They do identify several factors that may have contributed to weight gain after FMT in the patient. These include, but are not limited to, resolution of CDI, antibiotic use, treatment for *Helicobacter pylori* infection, stress related to illness, older age, and genetic factors. There is no discussion of eating patterns or changes in eating patterns in these related and presumably cohabitating individuals. These possibilities aside, there is a growing body of data exploring the relationship between host body mass index (BMI), host metabolism, and the gut microbiota. The transmission of an obese phenotype after therapeutic FMT for r-CDI has not been reported previously, to our knowledge.

There are differences in the gut microbial structure between lean and obese individuals [1]. A complex relationship exists between BMI and gut microbes, and this association cannot be reduced to a correlation between specific bacterial taxonomic groups and host BMI [2, 3]. Studies of the gut microbiome in monozygotic twins with discordant BMIs have advanced the knowledge of the gut microbe-host BMI interaction by demonstrating transmissibility and reversibility of the obese phenotype. In studies by Ridaura et al [4], germ-free mice receiving a stool lavage from an obese twin developed significantly greater adiposity than mice infused with the lean twin's microbiota, and this effect was lessened when the 2 groups were cohoused (mice are normally coprophagic). The expression of microbial genes important for detoxification and stress responses were more prominent in germ-free mice that received the obese twin microbiome compared with the lean twin flora [4]. There is also new evidence that host genetics influence the structure of the gut microbiota, and in a study of more than 400 twin pairs, specific bacterial taxa were found to be more "heritable" than others [5]. It is possible and perhaps even likely that the weight gain in the case reported was influenced not only by microbial communities transmitted during FMT, but also by genetic factors common to the FMT donor and recipient.

In controlled, randomized, and double-blinded human studies described by Vrieze et al [6], transfer of a lean microbiota to individuals with metabolic syndrome was associated with improved insulin sensitivity when compared with controls (individuals with metabolic syndrome who received an infusion of their own stool). In this study, butyrate-producing bacterial strains (known to activate intestinal gluconeogenesis) were increased in both lean stool samples and lean individual's intestinal biopsies [6]. Animal studies have shown that a relative paucity of butyrate-producing bacteria in the gut is associated with increased insulin resistance, and butyrate supplementation can reverse insulin resistance in diet-induced obesity in mice [7, 8]. A reduction in butyrate-producing bacteria can be achieved using antimicrobial agents directed at Gram-positive organisms, and by this mechanism, a loss of butyrate-producing organisms has been suggested as an explanation for the increase in BMI observed in patients treated with vancomycin for treatment of infective endocarditis [9, 10]. Bacterial products from the gut have been shown to enter the serum and affect distal organs. A recent murine study showed that manipulating gut flora in germ-free maternal mice affected the

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blood-brain barrier in their offspring, starting in utero and persisting into adulthood [11]. Another study showed that ingestion of *Lactobacillus rhammnosus* altered behavior in mice via GABA receptors in the central nervous system, a phenomenon that appeared to be mediated by the vagus nerve [12]. These studies take the concept of "you are what you eat" to breathtaking new heights and certainly should stimulate further study!

The published case report raises many questions about the selection of FMT donors. Guidelines are in evolution, but already there are consensus criteria for clinical testing [13]. In our healthy donor program [14], we use the expanded criteria proposed by Hamilton et al [15] that include normal BMI, testing of inflammatory markers, lipids, blood counts, electrolytes, and liver and renal function. As noted in the case report, patients may prefer family or other known contacts as stool donors rather than "professional donors." Patients may be more accepting of FMT from a psychological standpoint if allowed some discretion in selecting a donor. Although this sentiment is understandable, it is neither logical nor supported by data. The blood banking literature has consistently demonstrated that directed donations have a higher incidence of viral infections than donations from healthy volunteer donors [16], and as a result, directed donations are prohibited at many hospitals. Many patients with r-CDI are elderly, and their similarly elderly and often unwell family members are not ideal donors. In our program, we have only very rarely encountered adult patients unwilling to accept healthy donor stool, once the benefits of using this donation are explained. Some are reassured when it is noted that donors must meet standards that exceed those set for blood donors. Fecal microbiota transplant is not uniformly available, and insurance coverage for the procedure is a challenge for both practitioners and patients, despite its documented efficacy. There are numerous "do it yourself" FMT guides on the internet. It is also worth noting that today's exceptionally healthy 25-year-old volunteer donor could develop major health problems in a decade. For all of these reasons, study of the long-term outcomes of FMT, including careful analysis of donor characteristics, is important, particularly if FMT is performed in children.

An understanding of the relationship between the gut microbiota and other organ systems has the potential to transform our understanding of human health, and FMT is under investigation for the treatment of functional bowel disorders, autoimmune diseases, metabolic syndrome, and is under consideration for treatment studies in mood disorders and autism. More importantly, FMT has not been studied in large-scale controlled trials, and we have much to learn about the effects of this treatment beyond the intended restoration of a diverse microbiota, which is presumably an important mechanism for its high efficacy in the treatment r-CDI.

However, the efficacy of FMT as treatment for r-CDI is not the only reason for the rapid growth of and popular interest in FMT. Other reasons include the accessibility of the "biological material", widespread interest in complementary and natural remedies, the potential for self-administration, and, yes, the snicker factor. We hope this report will inspire further study of the mechanisms of metabolic effects of FMT, especially the clinical outcomes for recipients of nonideal donor stool. Careful study of FMT will advance knowledge about safe manipulation of the gut microbiota. Ultimately, of course, it is hoped that FMT studies will lead to identification of defined mixtures of beneficial bacteria that can be cultured, manufactured, and administered to improve human health.

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References

1. Ley RE, Turnbaugh PJ, Klein S, et al. Microbial ecology: human gut microbes associated with obesity. Nature **2006**; 444:1022–3.
2. Walters WA, Xu Z, Knight R. Meta-analyses of human gut microbes associated with obesity and IBD. FEBS Lett **2014**; 588:4223–33.
3. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature **2009**; 457:480–4.
4. Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science **2013**; 341:1241214.
5. Goodrich JK, Waters JL, Poole AC, et al. Human genetics shape the gut microbiome. Cell **2014**; 159:789–99.
6. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology **2012**; 143:913–916.e7.
7. Donohoe DR, Garge N, Zhang X, et al. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab **2011**; 13:517–26.
8. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes **2007**; 56:1761–72.
9. Thuny F, Richet H, Casalta JP, et al. Vancomycin treatment of infective endocarditis is linked with recently acquired obesity. PloS One **2010**; 5:e9074.
10. Khan MT, Nieuwdorp M, Backhed F. Microbial modulation of insulin sensitivity. Cell Metab **2014**; 20:753–60.
11. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med **2014**; 6:263ra158.
12. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A **2011**; 108:16050–55.
13. Bakken JS, Borody T, Brandt LJ, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol **2011**; 9:1044–9.
14. Youngster I, Russell GH, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. JAMA **2014**; 312:1772–8.
15. Hamilton MJ, Weingarden AR, Sadowsky MJ, et al. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. Am J Gastroenterol **2012**; 107:761–7.
16. Dorsey KA, Moritz ED, Steele WR, et al. A comparison of human immunodeficiency virus, hepatitis c virus, hepatitis b virus, and human T-lymphotropic virus marker rates for directed versus volunteer blood donations to the American Red Cross during 2005 to 2010. Transfusion **2013**; 53:1250–6.