For treating obesity with fecal microbiota transplants, some people's poop might be better than others'

By Asher Jones
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Certain people have gut microbes that are particularly good at establishing themselves in recipients of fecal microbiota transplants, according to a study that suggests these "super-donors" could improve the use of these transplants for treating obesity.

The gut microbiome has a hand in many diseases, including obesity, and there's evidence that transplantation of fecal microbes from healthy donors can help recipients lose weight. But the success of these treatments is likely to hinge on whether a donor's specific gut bacteria establish in the recipient. To learn more about this process, researchers, who published their findings May 13 in *Microbiome*, tracked gut bacteria in obese adolescents who received a transplantation of microbes harvested from multiple lean donors.

"We were really interested in this idea of competition between microbiomes and the idea of people being able to be a sort of super-donor: that some people have

microbiomes that are better than others at modifying a microbiome in an individual and causing clinical resolution," said Justin O'Sullivan, a co-author of the study and a professor at the Liggins Institute at the University of Auckland.

Bacteria begin to colonize the human gut at birth, and the gut microbiome is continually shaped throughout life by factors such as diet, environmental pollutants and disease. Research in rodents and humans shows that these intestine-dwelling microscopic communities affect key body processes, such as immunity and cognition.

Imbalances in gut microbiota, or dysbiosis, have been linked with illnesses such as obesity, metabolic diseases, immune disorders and inflammatory intestinal conditions. To restore the balance of gut microbes and treat these problems, many researchers are investigating the utility of transplanting microbes from the stool of healthy donors.

In some countries, fecal microbiota transplants have become the standard treatment for Clostridium difficile, a bacterium also known as C. diff, which causes severe diarrhea and inflammation. Such transplants can also successfully treat obesity in mice.

"Just by transmitting the appropriate microbiome from the donor, you can turn a fat mouse into a thin mouse, and they lose a huge amount of weight, like 20% of their body weight," said study co-author Wayne Cutfield, a professor of pediatric endocrinology at the Liggins Institute.

But the effects of such transplants on weight loss and other health outcomes are much more variable in people, according to O'Sullivan and Cutfield. One reason is that donor microbes may not always establish well in recipients' guts.

"We don't know the rules as to how microbes from one person actually engraft and change the microbiome of another," O'Sullivan told *Fastinform*. "We're trying to work those out with studies like this."

The study tracked microbes from multiple donors as part of a larger investigation into fecal microbiota transplantation for treatment of adolescent obesity, the childhood version of a complex disease that may have genetic, environmental and social causes and is linked with a host of health problems.

O'Sullivan, Cutfield and their colleagues recruited four male and four female lean donors who passed a rigorous vetting process that eliminated those with potentially transmissible conditions, such as allergies or infections. After collecting fecal samples from these healthy donors, the researchers cleaned and filtered out the bacteria and packaged them into double-walled capsules, specially designed to pass through the stomach and release their contents in the small intestine.

The team also enlisted 87 overweight New Zealand teenagers as recipients. Over the course of two days, half of the volunteers swallowed 28 capsules containing bacteria from four donors of the same sex as the recipients.

The other half gulped placebo capsules containing only saline.

To measure the composition of the recipients' microbiomes, the researchers analyzed stool samples collected prior to treatment and at six, 12 and 26 weeks after treatment. They also analyzed the donors' stool microbiomes.

"We weren't really sure what would happen in terms of whether one [donor's microbiome] would win out or they would all contribute equally. But, in fact, it's very clear that there were winners and losers," O'Sullivan said.

There was both a male and a female super-donor who contributed the lion's share of donor microbes that established in recipients' microbiomes. Some of the bacteria could still be found in the recipients' guts after six months, which marked the end of the experiment.

"Because of the way we were able to analyze the sequence data, we were actually able to see and really track individual strains from the donor, so we know it is the organism that came from the donor, the exact same clone," O'Sullivan said. "I was pretty amazed by that myself."

According to Cutfield and O'Sullivan, it's not clear what was special about the two super-donors' microbiomes, but both had high microbial and gene diversity and a high ratio of Prevotella-to-Bacteroides, a metric of bacterial composition that has been linked with diet and lifestyle.

More work is needed to figure out whether bacteria that established in recipients' guts were responsible for the health benefits observed after transplantation. The researchers previously reported no difference in weight loss between the treatment and placebo groups. However, compared with teenagers who received placebos, those who received the fecal microbiota capsules showed improvements in metabolic syndrome, a collection of conditions that includes high blood pressure, high blood glucose and abdominal body fat, a risk factor for diabetes and heart disease.

Although super-donors contributed the most bacteria to recipients' microbiomes, O'Sullivan notes that other donors also contributed.

"There are different niches, and it's about filling those niches within the microbiome, within that community. Bacteria have different jobs; they have different environments," he said. "Certain microbes from different places will fill parts of those environmental niches, and it's not exclusive just to one donor, but super-donors do dominate the change."

With a wider diversity of donor microbes, it's more likely that some will find a niche to inhabit in the donor community, meaning that multidonor fecal microbiota transplantations could do a better job at treating disease than those from a single donor can.

But the researchers hope that, down the road, donors won't be needed at all.

"It's incredibly time-consuming and expensive to screen human donors," Cutfield explained.

It's also potentially dangerous, O'Sullivan added. Feces can contain infectious material, and there have been rare cases where transplant recipients became sick or died.

If the researchers can identify specific bacteria or groups of bacteria that are most important for treating specific conditions, the microbes could simply be grown in the lab.

"Fecal microbiota transplantation, I don't think, has a long-term future as a therapeutic. I think microbial modification in the gut does. ... But there'll be ways to do it in a way that introduces new organisms, like probiotics, where we actually understand more of the rules of what's happening, and we're doing it in a targeted manner," O'Sullivan said.

But there's still much to learn about the rules that govern these bacterial communities, the researchers said.

Despite receiving bacteria from the same donors, recipients' microbiomes varied widely after transplantation, highlighting that other factors, such as diet and the recipient's biology, also affected the outcomes of transplantations in ways that are not yet fully understood.

In future work, the researchers will examine the effects of fecal microbiota transplantations in participants with

anorexia nervosa and autism, because pilot studies in animals have pointed toward potential benefits.

The study, "Strain engraftment competition and functional augmentation in a multi-donor fecal microbiota transplantation trial for obesity," published May 13 in Microbiome, was authored by Brooke C. Wilson, Thilini N. Jayasinghe, Valentina Chiavaroli, Darren M. Svirskis, Yannan Jiang and William Schierding, University of Auckland; Tommi Vatanen, University of Auckland and The Broad Institute of MIT and Harvard; Karen S.W. Leong, José G.B. Derraik, Benjamin B. Albert, Wayne S. Cutfield and Justin M. O'Sullivan, University of Auckland and A Better Start – National Science Challenge; Kathryn L. Beck and Cathryn A. Conlon, Massey University; and David J. Holland, Counties Manukau District Health Board.