Can feeding the gut microbiome treat malnutrition?

Jyoti Madhusoodanan *Science Writer*

When children suffer malnutrition, their gut microbiomes suffer as well. Although malnourished children gain some weight and grow better when fed a nutrient-rich supplement, they fail to catch up to their well-fed counterparts. Their gut microbiomes also fail to recover.

This conundrum weighed on microbiologist Jeffrey Gordon, who for more than a decade has tracked how a poor diet affects children's health in Bangladesh, Malawi, and other parts of the world. So Gordon and his team at the Washington University School of Medicine in St. Louis, MO, began to gauge the precise role that the microbiome might play in the connections between diet and health.

Over time, the team started to home in on food as the link between the microbiome and human health. In April, they reported that a unique mix of foods such as peanuts, bananas, and more that supported the growth of age-appropriate microbes helped restore the health of malnourished toddlers—and was more effective at improving their health than standard supplements used to treat malnutrition (1). Their food blend worked not just by feeding the kids but by feeding their microbes too.

The team's work is helping to find "better ways to define a healthy microbiome," Gordon says, potentially using diet to help the malnourished microbiomes recover. It's not the only approach aiming to treat ailments by targeting microbiota—other studies are looking to treat diabetes and other metabolic conditions.

Causal Connection

Changes in the gut microbiome have been correlated with allergies in babies, Alzheimer's disease, cancers, and several other diseases, making our bacteria an appealing target to treat a variety of conditions. But attempts to apply these data to "fix" the microbiome have had limited success. That's in part attributable to a long struggle to define exactly what

Ensuring that malnourished children and their microbiomes recover requires more than just dietary supplements. Image credit: Shutterstock/Dana Ward.

Published December 8, 2021.

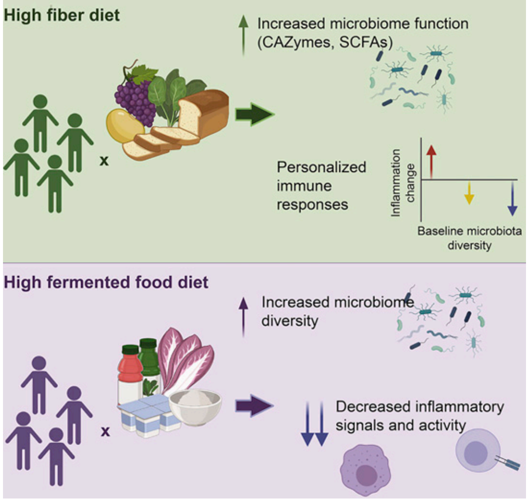
a "healthy" microbiome looks like, says Justin Sonnenburg, a microbiologist at Stanford University in Palo Alto, CA. Researchers have consistently found that individuals have a "core" microbiome, the activities of which remain consistent over long periods of time, but the composition of this core community differs based on a person's lifestyle, habits, or health.

Gut microbes associated with a Western-style diet have been linked to inflammatory disorders, diabetes, and other diseases. But the microbiomes of healthy people in developed countries are also starkly different from those of people in hunter–gatherer communities. And within an individual, diet, exercise, sleep, and many other factors can shift the proportions and activity of various species greatly from one day to the next, or even over the course of a single day. "There's just such a huge array of species," Sonnenburg says. To promote overall health, "it's not quite clear what facets of the microbiome we would be trying to maintain or change."

Discerning this answer was part of Gordon's aim. Through a series of studies, his team mapped out how the microbial community develops in a healthy child and how that process is disrupted in malnutrition.

In 2014, the researchers sampled gut bacteria from children up to age 2 with and without malnutrition and found consistent differences in the proportions and species of bacteria present (2). Microbial communities in children with malnutrition appeared more similar to those from well-fed children who were younger. Even after children in the former group were fed standard supplements, their microbiomes failed to recover from malnutrition.

The researchers transplanted microbial samples from under-nourished infants and their healthy counterparts into germ-free mice to test whether these differences could account for differences in the children's health. The mice responded much like the children:



Diet has a big impact on microbiome function, potentially pointing to ways to improve long-term health. Image credit: Reprinted from ref. 3, with permission from Elsevier.

Despite eating the same foods, those mice with underdeveloped microbiomes failed to gain weight and thrive as well as those with age-appropriate microbes. Transplanting bacteria from healthy animals into malnourished ones improved their microbiome and helped the animals thrive.

For children in resource-poor regions, though, such transplants wouldn't be a practical solution. These microbes only grow in the absence of oxygen, making them expensive to culture, store, and turn into probiotic pills, which are the most common way to deliver beneficial bacteria to the gut. "The question was, what could we do to repair the microbiota of these kids that was both culturally acceptable and scalable?" says Gordon.

Food Fix

In recent years, efforts to repair the gut microbiome have focused on two approaches: probiotic supplements that aim to deliver beneficial gut bacteria, and fecal microbial transplants (FMT), which aim to supplant a disease-linked microbiome with a "healthy" one. Neither one offers a clear path forward for treating malnutrition. Probiotic pills could prove not only expensive to manufacture and distribute on a large scale, but also less than effective. There's still scant evidence of long-term benefit from adding what are presumed to be beneficial bacteria. FMT has not been tested in the context of malnutrition and would pose cultural and logistical challenges in resource-poor regions where malnutrition is common. And the procedure has only proven effective in very limited conditions, such as gut infections caused by *Clostridium difficile*. "FMT is like restarting a computer to fix a problem," says gastroenterologist Purna Kashyap of the Mayo Clinic in Rochester, MN. "Sometimes it works and sometimes it doesn't."

Difficulties with modifying the microbiome arise, in part, because an established gut community is simultaneously in constant flux—changing with food, sleep, or jet lag—and resistant to long-term change. "If you change diet, you see this very short-term perturbation where the community changes in response to the chemicals in food," Sonnenburg says. "But over time, it will rebound back to something similar to its starting state."

That starting state likely reflects an individual's core microbiome. But Sonnenburg and others have begun to find hints of how to use microbiome-directed foods to drive long-term changes in both the gut community and human health. He and his colleagues tested two dietary changes thought to benefit gut bacteria: plant-based diets high in fiber, and diets high in fermented foods such as kombucha and kefir (3). The researchers monitored changes in the participants' microbiomes as well as their health after several weeks of the diets.

Those who consumed high-fiber plant-based meals rich in fruits, vegetables, and legumes showed an increase in certain carbohydrate-digesting enzymes produced by gut microbes but no changes in the proportion of different species. Fermented foods, however, were "kind of the food equivalent of probiotics," Sonnenburg says. Those who ate more of these foods showed an increase in their gut microbial diversity and a decrease in inflammatory immune markers, perhaps because these foods are rich in so-called "prebiotic" chemicals that feed beneficial gut bacteria (see ref. 4). Still, neither group showed long-term effects on weight loss, fatigue, stress, or other general markers of well-being.

To understand those links, epidemiologist Tim Spector and nutrition researcher Sarah Berry, both at King's College in London, UK, and their team, homed in on a long-overlooked aspect of human metabolism: our response to meals. Most research on glucose or fat metabolism has focused on the levels of these chemicals after a long period of not eating. Typically, doctors will request a fasting blood test to gauge a person's metabolic health. But most people eat two or three meals a day interspersed with snacks—and every bite contributes to short, sharp rises in circulating sugars and fats. "If we were to map blood levels of these metabolites into a typical eating pattern, you actually see that we spend most of our time not fasting," Berry says. The long-term effects of diets, certain foods, or nutrients arise because of their short-term impacts on circulating metabolites, according to Berry.

The researchers also found that people's genetics showed only a weak correlation to their metabolic responses to food; rather, the microbiome composition was much more strongly associated with how certain metabolites changed after meals. In follow-up studies, the team identified specific groups of microbes associated with metabolic responses to different foods. Then the team developed a machine-learning model to predict how a person might respond to food, based on several factors including their microbiomes (5). Nearly 1,100 study participants had their microbial composition, blood glucose levels, and lipid levels assessed after eating a specific set of foods (6). They then received a set of personalized diet recommendations aimed at health outcomes such as weight loss or improving blood sugar levels in participants with diabetes.

The researchers are still studying whether the recommended dietary changes alter gut microbes as well. But the data so far suggest that "different foods promote a change in the microbiome composition," Berry says. "The more data that emerge, the more we'll start to see this symbiotic relationship: It's not enough to just consume beneficial bacteria, but we also need to ensure we're giving them the appropriate food."

Cooking up Cures

Gordon and his team wanted to find the appropriate foods for children with severe malnutrition. They designed dietary supplements using different proportions of bananas, peanuts, chickpeas, and other common foods that in laboratory tests in mice appeared to support a "healthy" microbiome. In mice carrying microbiomes of malnourished children, one specific cocktail helped transform these microbiomes to resemble those found in healthy children. When the researchers fed malnourished toddlers in Dhaka this particular supplement twice a day for three months, their health improved: The children gained height and weight in patterns similar to healthy peers—an effect not seen with the standard treatments used for malnutrition. Blood tests also showed that, compared with current remedies, children who received the microbiome-targeting supplement had higher levels of circulating proteins linked to bone growth and brain development (1). "It's a nutrient substrate that benefits both the microbes and the host," Gordon says. "We have to think of their development together."

In future studies, the group plans to test how long the benefits last and the mechanisms linking host and bacterial metabolism. They emphasize that the work does not try to define a single "normal" microbiome. Instead, their goal is to identify a community that most benefits a person's health in the context of their individual circumstances.

The results could also help parents seeking ways to optimize children's nutrition as they shift from infant diets of milk or formula to solid foods. "If we're able to connect the dots between food and the development of microbiota that drive human growth, we could have a microbiome-informed sequence of foods [to improve children's health]," Gordon says.

Their approach could also extend to other disorders where the microbiome has been implicated, he and others on the team add. "What we're trying to emphasize with our studies is that we have to change the way we think about food in many ways," says Robert Chen, Gordon's doctoral student at Washington University who co-authored the new study. The supplement, Chen adds, is a food designed with a specific purpose and specific targets. "And in that way," he says, "it is more like a bridge between food and medicine."

1 R. Y. Chen *et al.*, A microbiota-directed food intervention for undernourished children. *N. Engl. J. Med.* **384**, 1517–1528 (2021).
2 S. Subramanian *et al.*, Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature* **510**, 417–421 (2014).
3 H. C. Wastyk *et al.*, Gut-microbiota-targeted diets modulate human immune status. *Cell* **184**, 4137–4153.e14 (2021).
4 A. Katsnelson, Core Concept: Prebiotics gain prominence but remain poorly defined. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 14168–14169 (2016).
5 S. E. Berry *et al.*, Human postprandial responses to food and potential for precision nutrition. *Nat. Med.* **26**, 964–973 (2020).
6 F. Asnicar *et al.*, Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat. Med.* **27**, 321–332 (2021).