

The Gut Microbiome in Type 2 Diabetes

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The surfaces of the human body exposed to the environment are colonized by microbes—the majority of which reside in the intestinal tract. Collectively, the microbial cells that live in and on us (bacteria, eukaryotes, viruses, fungi, and archaea) make up our *microbiota*, and their genetic material constitutes our *microbiome*. There are at least 100 times more genes in the human microbiome than in the human genome.^{1,2}

With the help of recent technologic advances in genetic sequencing, we're beginning to understand more about this vast biological habitat. We know that the microbiota plays a role in vitamin production, energy harvest and storage, and fermentation and absorption of undigested carbohydrates. It also has bidirectional influence on the central nervous system and neuropsychologic health and is involved in the maturation and development of the immune system.

A healthy biome is characterized by bacterial diversity and richness. Gut microbiota is mostly comprised of Firmicutes (64%), Bacteroidetes (23%), Proteobacteria (8%), and Actinobacteria (3%).² The distribution of these bacteria is largely determined by diet; individuals who follow a diet high in animal fat have a *Bacteroides*-dominant pattern, whereas those who follow a carbohydrate-rich diet tend toward a *Prevotella*-dominant pattern.¹⁻³

Lack of bacterial diversity and overgrowth of pathobacteria results in *dysbiosis*, an imbalance in the gut's microbial composition. Alterations in the proportions of bacteria are thought to result in metabolic disease. As such, dysbiosis is correlated with obesity and diabetes, as well as other diseases (eg, inflammatory bowel disease, multiple sclerosis, Crohn disease, and rheumatoid arthritis).¹⁻³ At this time, however, it

is unclear whether these bacterial imbalances cause or result from disease.

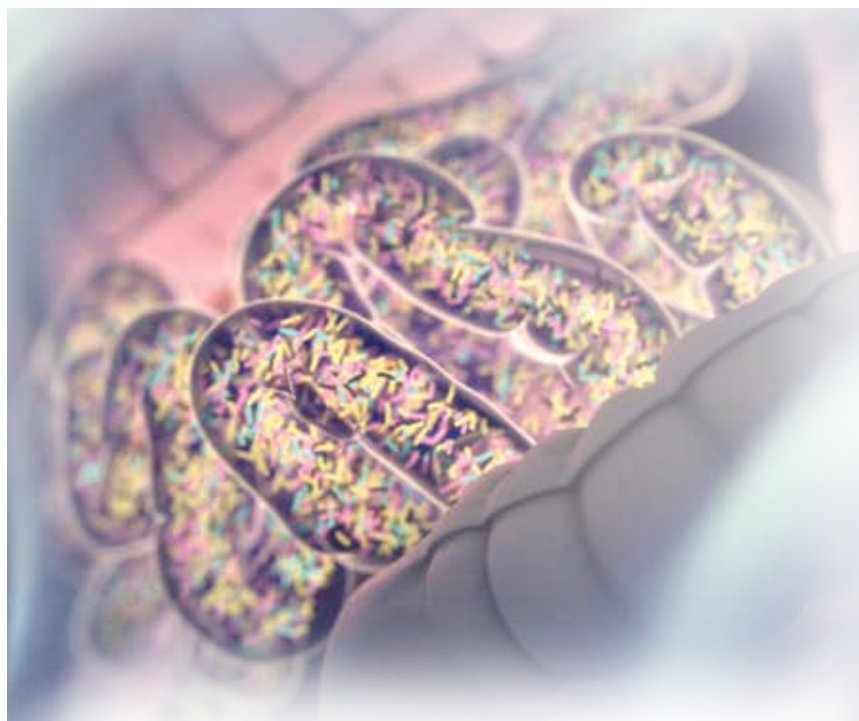
ROLE IN TYPE 2 DIABETES

The microbiome of patients with type 2 diabetes (T2DM) is characterized by reduced levels of Firmicutes and *Clostridia* and an increased ratio of Bacteroidetes:Firmicutes (this ratio correlates with plasma glucose concentration).^{4,5} Interestingly, although T2DM and obesity are closely related, available data indicate that gut microbiome changes are not always identical between these two patient populations. In some studies, the microbiome of obese individuals involves a *decreased* Bacteroidetes:Firmicutes ratio, in contrast to the increase seen with T2DM—which raises the question of whether the same or different factors cause these two entities.^{1,5-7}

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Patients with T2DM also have decreased amounts of butyrate-producing bacteria in their microbiomes. Butyrate, acetate, and propionate are short-chain fatty acids (SCFAs) fermented in the large intestine by bacteria from dietary fiber. These SCFAs play an important role in energy metabolism and are critical for modulating immune responses and tumorigenesis in the gut. Butyrate, in particular, provides energy for colonic epithelial cells. By feeding colonic cells, butyrate helps to maintain intestinal integrity and prevent translocation—a process that moves gram-negative intestinal bacteria across the lumen of the gut, causing endotoxemia. Endotoxemia triggers a low-grade inflammatory response, and low-grade inflammation is thought to underlie T2DM.^{2,5,6}

Therapeutic interventions—such as dietary modifications, prebiotics, probiotics, antibiotics, metformin, fecal transplantation, and bariatric surgery—can effectively alter the composition of gut bacteria. It has been proposed that these interventions could be harnessed to prevent and treat T2DM in the future.² So, what might these interventions have (or not have) to offer?

ANTIBIOTICS

Antibiotics are useful for eradicating pathogenic bacteria, but they can also destroy beneficial intestinal commensals in the process. Therefore, concern about the widespread use of antibiotics in humans and livestock has increased. Subtherapeutic use of antibiotics, which has been common in farm animals throughout the past 50 years to increase growth and food production, has been shown to affect metabolic pathways—particularly with respect to SCFAs—in mouse studies.⁶

Recent data on humans have linked antibiotic treatment in early infancy to long-term effects on microbial diversity and childhood overweight. Similarly, long-term use of IV vancomycin in adults has been linked to an increased obesity risk. But it's not just long-term exposure that poses a threat; even short courses of oral antibiotics

can have profound and irreversible effects on intestinal microbial diversity and composition. For example, short-term use of oral vancomycin was found to impair peripheral insulin sensitivity in males with metabolic syndrome associated with altered gut microbiota, while amoxicillin did not.⁶

PREBIOTICS AND PROBIOTICS

Prebiotics are indigestible carbohydrates that improve host health by stimulating the growth and activity of colonic bacteria. Most prebiotics are oligosaccharides, which can travel through the upper GI system undigested. When they reach the colon, they are fermented to produce SCFAs that stimulate the growth of microbes that reside there. Prebiotics come from a wide variety of food sources, including asparagus, barley, garlic, onions, and wheat bran.^{2,3} Pickled and fermented foods (eg, kimchi, sauerkraut, yogurt, miso) are good sources of both prebiotics and probiotics.²

Bifidobacteria and *Lactobacilli* are the most commonly used strains in foods and supplements containing probiotics. These live microorganisms bring about specific changes in the composition and activity of gut microbiota: they secrete antimicrobial substances, compete with pathogenic bacteria, strengthen the intestinal barrier, and modulate the immune system.^{2,3,6} Research on human and animal models suggests that administering probiotics may help manage diabetes.²

DIETARY MODULATION

Dietary changes have been shown to modify the bacterial metabolic activity of the human gut. In one study, obese adults with T2DM were placed on either a fat- or carbohydrate-restricted diet, and it was found that their levels of Bacteroidetes increased and Firmicutes decreased.⁷

In another study, patients with T2DM adhered to one of two calorie-controlled diets: a high-fiber macrobiotic diet or a Mediterranean-style (control) diet. The macrobiotic diet was high in complex carbohydrates, legumes, fermented products, sea salt, and green tea and was free of animal protein,



fat, and added sugar. Both diets were effective at improving dysbiosis—ecosystem diversity increased, and health-promoting SCFA producers were replenished. However, the macrobiotic diet was more effective than the control diet at reducing fasting and postprandial glucose, A1C, serum cholesterol, insulin resistance, BMI, and waist and hip circumferences; and only the macrobiotic diet counteracted the inflammation-producing bacterial groups.⁸

METFORMIN

Metformin has therapeutic effects on microbial composition and SCFA synthesis. In a microbiome comparison study, patients with T2DM treated with metformin had more butyrate-producing bacteria than their untreated counterparts. The trend toward increased *Lactobacillus* seen in the context of T2DM was reduced or reversed by metformin treatment. Researchers were able to tell which patients were (and were not) treated based on their gut microbiome taxonomic signature.⁹

FECAL MICROBIOTA TRANSPLANT

Fecal microbiota transplant, also known as *stool transplant* or *bacteriotherapy*, is the process of transferring fecal bacteria from a healthy individual into a recipient. It is used in the treatment of recurrent *Clostridium difficile* colitis to replenish beneficial bacteria in the digestive tract following use of wide-spectrum antibiotics. In a double-blind randomized controlled trial, insulin-resistant men received either autologous (reinfusion of one's collected feces) or allogenic (feces from a lean donor) infusions. Allogenic transplantation resulted in significantly increased intestinal microbial diversity and increased levels of butyrate-producing species, accompanied by significantly improved peripheral muscle sensitivity to insulin.^{1,6}

BARIATRIC SURGERY

Bariatric surgery, specifically Roux-en-Y gastric bypass (RYGBP), is a powerful tool used to treat obesity. In six patients (five of whom had diabetes) treated with RYGBP,

dramatic changes to the gut microbiota were seen at three months following surgery. BMI was reduced by 15% to 32%, C-reactive protein decreased in five of six patients, and T2DM was alleviated in all. Postoperatively, there was a striking shift towards higher amounts of Proteobacteria and lower relative amounts of Firmicutes and *Bacteroides* in the gut phyla. Postoperative increases in certain bacteria were more profound than the amount in lean controls, suggesting these changes are related to alterations in the gut, not lower body weight.^{4,6}

CONCLUSION

We are just beginning to understand the microbiome and its relationship to health and disease. For patients with T2DM, a variety of interventions may be used to return the gut microbiota to health. Dietary interventions, prebiotics and probiotics, fecal microbial transplant, and bariatric surgery can influence gut microbial composition, with the goal of preventing and/or treating disease. In the future, gut microbial signatures may serve as early diagnostic markers. **CR**

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