Nutrition Considerations for Microbiota Health in Diabetes

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Recently, it has become accepted that the tiny microbial cells harbored by the human gut play a significant role in health and in certain disease states, including obesity, diabetes, and cardiovascular disease. Although many details remain unclear, new technologies have uncovered many of the physiological benefits the human microbiota provides the host. A healthy gut microbiota plays a role in health, but imbalances can become pathological, increasing inflammation and contributing to metabolic dysfunction. Diet plays a significant role in shaping the composition and function of the microbiota. Eating patterns high in fruits, vegetables, whole grains, and legumes promote the abundance of healthier bacteria that produce short-chain fatty acids and other health-promoting metabolites. This article reviews the functions of the microbiota, how it is formed, and nutritional strategies to improve gut health.

Functions of the Microbiota

The human body harbors >100 trillion organisms; these are mostly bacteria, but also include archaea, viruses, parasites, and fungi, which together make up the microbiota (1,2). In the human body, these tiny microbial cells outnumber human cells by 10 to 1 (2–5). The microbiome, which is the collective genome of the microbiota community living in our gut, outnumbers the human genome by 100- to 200-fold (2–5).

New nonculture-dependent technologies have led to the identification of 1,000 species and >3 million microbial genes, providing evidence of the symbiotic relationship this "organ" has with the human host (1,2,4). Known functions of the microbiota include degradation of nondigestible polysaccharides, synthesis of vitamins, strengthening of the microvilli, and protection of the host from pathogens by maintaining healthy gut barrier integrity (3,5–7). The gut microbiota is instrumental in the normal development of innate and adaptive immunity (4).

Factors Shaping the Composition of the Microbiota

The composition of the human gut microbiota is highly individualized, with marked variations in the species present. The development of a healthy microbiota is highly influenced by several factors: how a baby is delivered at birth, diet and nutrition, genetics, antibiotic use, illness, and the environment (5).

Vaginally delivered babies are exposed to *Lactobacillus*, *Prevotella*, and *Sneathia* species, whereas cesarean section–delivered babies, bypassing the exposure of important foundational species present in the vaginal pathway, are dominated by bacteria present on the skin such as *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species (8). Breastfed infants have higher populations of the genus *Bifidobacterium* and healthy strains of *Ruminococcus*,

important foundational species, with lower counts of *Escherichia coli*, *Clostridium difficile*, *Bacteroides fragilis*, and *Lactobacillus* species compared to formula-fed infants (5). Galacto-oligosaccharides, known prebiotics, are a key component in breast milk that increases the proliferation of *Bifidobacterium adolescentis* and *Bifidobacterium catenulatum* (9).

Bacterial communities become more complex as solid food is introduced in young children and are as complex by the age of 2 or 3 years as they are in adults. The adult microbiota is relatively stable but can be temporarily altered by changes in diet, disease, and environment. As other organ systems age, so too does the microbiota, becoming more susceptible to dysbiosis (alteration or imbalance of the microbiota) in elderly people (5). Age-related changes may be related to dietary changes related to the loss of sensation to taste and smell, tooth loss, and chewing difficulties (10).

Antibiotics are thought to have made permanent changes in the human microbiome, reducing microbial diversity and healthy strains and thus decreasing resistance to pathogens associated with disease (2). Exposure to antibiotics during the first postnatal months has been associated with a higher BMI later in life (11). Similarly, long-term use of antibiotics is associated with weight gain in adults (12).

Some researchers have cautioned that unintentional exposure to antibiotics may have contributed to the rise in obesity. In the United States, >70% of antibiotics are used in livestock, primarily to produce quicker weight gain with less feed (13). About 75% of the antibiotics given to feedlot animals are excreted in manure, contaminating surface water and groundwater and making their way into the food supply (13).

Dysbiosis, Obesity, and Diabetes

Some studies indicate that obese individuals have a higher propor-

tion of the phyla Firmicutes and Actinobacteria and a reduced abundance of Bacteroidetes than their lean counterparts (2). Low gene count, also reported in obese individuals, is associated with weight gain, insulin resistance, dyslipidemia, inflammation, and fatty liver (4,14). A reduction in the abundance of the genus *Prevotella* and a higher count of *Staphylococcus aureus* has been reported in obese woman (5). *S. aureus* has been reported to trigger inflammation related to obesity in children (5).

Dysbiosis related to type 2 diabetes has produced similar findings, with reductions in *Bifidobacterium* and *Faecalibacterium prausnitzii*, two bacteria known to have anti-inflammatory effects (6). Bacterial genes associated with oxidative stress are more abundant in type 2 diabetes, whereas butyrate-producing bacteria and those associated with vitamin synthesis are diminished (4). *Akkermansia muciniphila* abundance is inversely associated with obesity and diabetes and is known to control fat storage, adipose tissue inflammation, and glucose metabolism (4). Interestingly, metformin and prebiotics have been reported to increase the abundance of *A. muciniphila* (4).

It is not entirely understood how dysbiosis causes metabolic dysfunction. It is hypothesized that alterations in the microbiota interfere with intestinal permeability, allowing lipopolysaccharide (LPS), a component of gram-negative bacteria cell walls, to enter the host and thus contributing to inflammation and subsequent insulin resistance and type 2 diabetes (2,3,5,6). A high fat intake has been associated with elevated LPS and inflammation in humans (3,6). Weight gain can also initiate an inflammatory response, causing an increase in pro-inflammatory factors in the adipose tissue and also affecting metabolism in the liver and muscle tissues (3,5). It has also been proposed that the microbiota controls fatty acid metabolism, which has not been confirmed in humans

(2). Incretin hormones that regulate appetite and insulin sensitivity tend to be lower in people with type 2 diabetes and may be controlled by metabolites produced by the microbiota (2,3,5).

Nutrition and the Microbiota

Modulation of host microbiota with diet, prebiotics, or probiotics may offer potential therapies for improvements in body weight and glycemic control for the prevention and treatment of type 2 diabetes.

Eating Patterns and Food Groups

Dietary habits play a significant role in shaping the microbiota, providing substrates that determine the assortment of metabolites produced. Many researchers have suggested that a Western eating pattern may have altered the genetic composition and metabolic activity of the human microbiome, significantly contributing to modern diseases (15). Eating patterns higher in whole grains, fruits, vegetables, and legumes have been found to induce a more diverse microbial population, increasing the abundance of protective species while reducing the abundance of pathobionts and the production of inflammatory factors (16). High-fat, animal-based diets are associated with a low gene count and a higher abundance of bile-tolerant bacteria because fat causes more bile acids to be secreted (15).

Microbial metabolism of fat and protein in the colon can result in the formation of toxic metabolites such as ammonia, phenolic and indole compounds, amines, and sulfides (9,17). Carnitine and choline found in red meat and eggs are metabolized by gut microbes to produce trimethylamine, which is absorbed and further metabolized in the liver to trimethylamine-N-oxide (TMAO), a metabolite linked to the formation of atherosclerotic lesions (16). A recent study found that TMAO production after an L-carnitine challenge was dependent on microbiota

composition. Comparing participants following a vegan, vegetarian, or omnivore dietary pattern, both vegan and vegetarians had significantly lower plasma TMAO levels compared to omnivores (16).

Significant differences in terms of microbial composition and health have been demonstrated between plant-based or agrarian eating patterns and Western eating patterns. De Filippo et al. (18) compared the fecal microbiota of 14 young children (ages 1–6 years) living in rural Africa and consuming a high-fiber, low-fat diet to that of 15 children of matched age from Europe and consuming a Western eating pattern. The African children's diet was high in cereals (millet and sorghum), legumes (mostly black-eyed peas), and vegetables. They consumed little meat other than occasional chicken or termites during the rainy season. In contrast, the European children's diet was higher in animal protein, sugar, starch, and fat and had almost half the amount of dietary fiber found in the African children's diet. The African children's microbiota was significantly higher in Bacteroidetes and lower in Firmicutes compared to the European children. A higher ratio of Firmicutes to Bacteroidetes is associated with obesity and diabetes. The African children also had an abundance of the genera *Prevotella* and *Xylanibacter*, both having significant anti-inflammatory effects, which were completely lacking in the European children. The European children's microbiota had an abundance of the genus Bacteroides, consistent with a high-fat, high-meat diet. The African children's microbiome was more genetically diverse and contained a lower prevalence of the pathobiont *Enterobacteriaceae* and a higher amount of short-chain fatty acid (SCFA) production compared to the European children.

An analysis of 153 subjects, self-declared as vegan, vegetarian, or omnivore and all following a Mediterranean diet revealed marked variations in the microbial content and metabolites produced from each eating pattern (17). The vegan group scored highest in the adherence to the Mediterranean diet, evaluated by the Healthy Food Diversity (HFD) score, indicating a higher intake of fruits, legumes, and vegetables. Higher HFD scores were associated with beneficial microbial profiles, with a greater abundance of *Rosburia*, *Lachnospira*, and *Prevotella* and a significantly higher production of SCFAs. There are significantly higher levels of *L-Ruminococcus*, a genus assigned to the *Lachnospiraceae* family, as well as higher levels of urinary TMAO in the group consuming the most protein-rich animal foods and dietary fat.

The two studies discussed above provide evidence that long-term adherence to a high-fiber, plant-based eating pattern can provide benefits to the composition of the microbiota.

A small intervention study using a strict vegetarian diet (72% carbohydrate, 16% protein, and 12% fat) for 1 month with six subjects with diabetes or hypertension demonstrated both clinical and microbial improvements (19). There were significant reductions in body weight, triglycerides, LDL cholesterol, and A1C and improvements in fasting and postprandial glucose levels. The composition and metabolites produced by the microbiota were also altered. The strict vegetarian diet resulted in a decrease in the ratio of the phyla Firmicutes to Bacteroidetes, a reduction in pathobionts, and specifically *Enterobacteriaceae*, a known pro-inflammatory species. Increases in commensal bacteria *Bacteroides fragilis*, *Prevotella*, *Lachnospiraceae* (protects against *C. difficile*), and *Ruminococcaceae* were noted, as well as reductions in inflammatory markers.

A longer-term intervention improved insulin sensitivity for 20 obese men with known coronary heart disease randomly assigned to either a Mediterranean diet or a low-fat, high-complex carbohydrate (LFHC) diet for 1 year. There was a reported increase in the abundance of *Roseburia* genus and *F. prausnitzii* for the Mediterranean diet and LFHC diet, respectively. The authors concluded that both eating patterns, which focus on an increase in fruits and vegetables, produced improvements in the microbiota, potentially reducing the risk of type 2 diabetes (20).

Epidemiological studies consistently demonstrate that dietary fiber, particularly whole-grain fiber, intake is inversely associated with type 2 diabetes and cardiovascular disease and has a beneficial impact on body weight and longevity (21–23). In a prospective, observational study, a high intake of cereal fiber was associated with a 33% lower risk of diabetes compared to a low intake. The authors proposed that whole grains may offer protection by increasing SCFA production and, in turn, their effect on increasing hepatic insulin sensitivity (22). A recent meta-analysis provided a quantitative estimation that consuming three servings of whole-grain foods per day would offer a 20% relative reduction in risk of type 2 diabetes compared to consuming a half serving (23). Other nutrients that contribute to health and are present in whole grains include minerals, vitamins, phytochemicals, phenolic compounds, lignans, and phytic acid (23). Human studies have demonstrated significant increases in the abundance of *Bifidobacterium* species and *Lactobacillus*/*Enterococcus* in participants consuming whole-grain wheat cereal (24). Other studies produced similar improvements with whole-grain barley flakes and whole-grain brown rice flakes (24).

Other foods and beverages that have improved the microbiota in human studies include red berries (specifically blueberries) that are high in anthocyanins, almonds and pistachios, apples and bananas, and red wine (24). There has been negligible research on vegetables and legumes in

TABLE 1. Criteria for Prebiotic Classification (26)

For a food or substrate to be considered a prebiotic, it must be able to:

1. Resist digestion in the small intestine
2. Be fermented by the microbiota in the large intestine
3. Stimulate the growth and metabolic activity of beneficial species to improve the health and well-being of the host

TABLE 2. Dietary Sources of Prebiotics and Their Documented Health Outcomes

Dietary Sources of Prebiotics (25,26)

Prebiotics are found in:

- Breast milk
- Leeks
- Asparagus
- Chicory
- Jerusalem artichokes
- Garlic
- Onions
- Whole-grain wheat
- Oats
- Soybeans
- Bananas

Evidence-Based Health Outcomes from Prebiotic Intake (25,30)

Prebiotic intake:

- Increases the abundance of beneficial microorganisms
- Suppresses the proliferation of pathogenic microorganisms
- Provides treatment for diarrhea
- Helps with inflammatory bowel disease
- Prevents colon cancer
- Improves the absorption of minerals, including calcium, magnesium, zinc, and possibly iron, thus improving bone mineral density (via enhancement of SCFA production)
- Reduces cardiovascular disease risk
- Promotes satiety and helps with weight loss
- Lowers colonic pH

terms of modulating the microbiota (24).

Prebiotics

A prebiotic is defined as "a selectively fermented ingredient that allows specific changes, both in composition and/or activity, in the gut microbiota that confers health benefits upon host well-being and health" (3,9,25). Table 1 provides the criteria used to classify prebiotics. Prebiotics are car-bohydrate compounds, mostly oligo-saccharides, that resist digestion in the small intestine and are fermented in the colon, producing SCFAs and the growth of beneficial bacteria, specifically *Bifidobacterium*, *Lactobacillus* (25), *F. prausnitzii*, *A. muciniphila* (14), and *Rominoccoccus bromii* (9).

Humans have been consuming prebiotics since prehistoric times. In fact, archaeological evidence of well-preserved coprolites has demonstrated that a typical adult male hunter-gatherer consumed 135 g inulin per day (25). The primary forms of dietary prebiotics include resistant starch, nonstarch polysaccharides, and nondigestible oligosaccharides (9,25,26). Fermentation of 100 g prebiotic can produce 20 g beneficial bacteria (25). Table 2 lists dietary source of prebiotics and their documented health outcomes.

Prebiotics improve satiety, decrease food intake, and are associated with reduced postprandial glucose levels (6,14). The mechanisms are not entirely understood, but these effects may be due to the production of SCFAs, which are ligands for G-protein–coupled receptors present on L-cells promoting the secretion of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) (3,6). Studies have demonstrated that prebiotic supplementation of 5–20 g prebiotic per day has produced changes in microbiota composition, increasing GLP-1 and PYY levels, reducing ghrelin, resulting in reduced hunger and energy intake and reduced postprandial glucose levels (3,12,27,28). Prebiotic supplementation with an inulin/oligofructose mix in obese women led to an increase in *Bifidobacterium* and *F. prausnitzii*, two bacteria reported to be reduced in type 2 diabetes (29). There was a marked reduction in serum LPS levels, reducing metabolic endotoxemia. SCFAs provide a direct energy source for colonocytes, resulting in increased thickness of the intestinal wall and reducing the risk of bacterial translocation (30). Other nutritional benefits of plant fermentation include the release of phytochemicals with anti-inflammatory and antioxidant properties and an enhanced bioavailability and uptake of minerals, including calcium, magnesium, zinc, and possibly iron (9,25,31). SCFA production reduces colonic pH, reducing the growth of pathogenic bacteria and their toxic metabolites (25). Table 3 lists the beneficial effects of SCFAs.

TABLE 3. SCFAs (4,30)

SCFAs include butyrate, acetate, and propionate. They are produced by fermentable prebiotics and other soluble dietary fiber and provide the host with many health benefits. SCFAs:

- Serve as a main fuel source for colonocytes, which strengthen the epithelium, potentially decreasing the translocation of antigens and LPS, and reduce endotoxemia and insulin resistance (butyrate)

- Reduce colonic pH, which inhibits the growth of pathogenic bacteria (butyrate)

- Enhance mineral absorption

- Stimulate the release of PYY and GLP-1, which decreases appetite and improves insulin sensitivity (propionate, acetate, and butyrate)

- Are metabolized in the liver and may play a role in reducing serum cholesterol levels (propionate)

- May enhance fatty acid oxidation and thermogenesis (butyrate)

- May activate intestinal gluconeogenesis, contributing to weight loss and glucose control (butyrate, propionate)

TABLE 4. Criteria for Probiotic Classification (32)

For a probiotic to be effective, it must:

1. Resist gastric, bile, and pancreatic digestion
2. Adhere to the mucosal and epithelial surfaces
3. Once colonized, remain metabolically active
4. Provide the host with protection from pathogens by secreting antimicrobial substances or preventing their adhesion and colonization
5. Demonstrate bile salt hydrolase activity

Probiotics

Probiotics are "live microorganisms [that], when administered in adequate amount, provide a health benefit on the host" (25,32). Popular probiotic strains belong to the genera *Bifidobacterium* and *Lactobacillus* and include yeasts such as *Saccharomyces boulardii* (7). Fermentation of foods has been used for centuries to increase the shelf life and enhance the nutrition quality and flavor of foods (32).

Although the research has not been consistent, some probiotics studies involving healthy volunteers have shown reductions in body fat and improvements in insulin sensitivity. There have been fewer well-controlled trials involving individuals with diabetes (14). A review that included six clinical studies on individuals with diabetes found a reduction in inflammatory responses and oxidative stress, improved insulin sensitivity, and reduced fasting glucose with various probiotic dosages (33). However, further investigations are warranted to determine whether probiotics could be used for the prevention and treatment of diabetes.

Specific strains and dosage recommendations (or serving sizes of fermented foods) for diabetes have not yet been determined and therefore are not recommended for clinical practice. Interestingly, probiotics account for the largest share of the rapidly expanding functional food market (32). Table 4 and Table 5 list the criteria for probiotic classification and dietary sources of probiotics, respectively.

Nutrition Recommendations and Applications to Medical Nutrition Therapy

Whether alterations in gut microbial composition as a response to dietary change offer potential for the treatment of diabetes or diabetes risk reduction has not yet been determined.

Human studies have demonstrated that a healthy microbiota profile is associated with diets high in fruits, vegetables, legumes, and whole grains and is accompanied by favorable health outcomes such as healthy body weight, reduced inflammatory markers, and lower insulin resistance. Dietary interventional trials have provided encouraging results. Further studies are needed to determine whether these changes are sustainable and provide long-term protection from metabolic dysfunction. Prebiotic food sources not only enhance the growth of beneficial bacteria, but also provide substrates for the production of biologically active metabolites. However, there is evidence that not all individuals respond in the same manner, further highlighting the complex nature of the microbiota and its coexistence with the human host (34).

Most Americans consume only 15 g fiber per day. Increasing intake to at least 25–38 g per day, including at least 5–20 g prebiotic sources, may enhance the production of SCFAs, improve gut barrier function, reduce body weight, and improve glycemic control (25). A gradual increase in fiber intake should be recommended to avoid undesirable gastrointestinal symptoms. It has been estimated that increasing fiber intake by just 14 g per day is associated with a 10% decrease in energy intake (25). In addition to weight control and reduced insulin resistance, fermentation of dietary fiber and the resulting production of SCFAs may play a role in improving fatty acid metabolism and reducing inflammatory responses (35). Diets high in plant-based food sources also increase microbial gene diversity, which has been seen in populations where diabetes and other metabolic diseases are scarce (17). Reducing dietary fat and animal protein may provide further benefits by reducing the abundance of bile-tolerant bacteria and the deleterious metabolites produced in the large intestine.

TABLE 5. Sources of Probiotics and Reported Strains (36)

	Reported Strains
Plant-Based Probiotics	
Sauerkraut (fermented cabbage)	Lb. plantarum
	Lb. brevis
	P. acidilactici
	P. cerevisiae
	Leuc. mesenteroides
Kimchi (Korean spicy cabbage)	Lb. plantarum
	Leuc. mesenteroides
	L. brevis
Tempeh (a fermented soybean product), soy sauce, miso	Lb. plantarum
	Lb. brevis
	L. acidophilus
Water kefir	Lb. casei
	Lb. hilgardii
	Lb. hordei
	Lb. nagelii
	Leuc. citreum
	Leuc. mesenteroides
	Ac. fabarum
	Ac. orientalis
	Yeasts:
	Hanseniaosporavalbyensis
	Lachancea fermentati
	Saccharomyces cerevisiae
	Zygotorulaspora florentina
Dairy-Based Probiotics	
Yogurt	Lb. bulgaricus
	Lb. acidophilus
	S. thermophilus
	Bifidobacterium spp.
Kefir	Lb. kefir
	Lb. kefiranofaciens
	Lb. brevis

Note: strains may vary depending on processing technique. Reprinted from Ref. 34 with permission from the Academy of Nutrition and Dietetic Diabetes Care and Education Dietetic Practice Group. Ac., Acetobacter; L., Lactococcus; Lb., Lactobacillus; Leuc., Leuconostoc; P., Pediococcus; S., Streptococcus.

At present, there are no specific recommendations for probiotic use in clinical practice for diabetes. Over-the-counter products, although generally recognized as safe, may be expensive and are not regulated, so they may or may not contain the optimal strains for improving diabetes outcomes. Adding fermented foods to the diet is harmless and could potentially provide benefit to gut health. Further investigations are needed to provide more specific and individualized nutrition recommendations for modulating the microbiota to prevent diabetes or improve diabetes outcomes.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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