

Update on the Gut Microbiome for the Primary Care Clinician

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KEY TAKEAWAYS

- The gut microbiome, sometimes referred to as the “organ” we do not know we have, is a dynamic ecosystem that plays an important role in human health and disease.
- Alterations in the gut microbiome (dysbiosis) are associated with wide-ranging disease states, including metabolic diseases like type 2 diabetes mellitus (T2D).
- Growing evidence suggests improved gut microbiome composition from targeted microbiome interventions leads to improvement in glycemic control in patients with T2D.

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DISCLOSURES

Dr. Miller discloses that she serves on the advisory board and speakers bureau for Abbott Diabetes, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk; on the advisory board for AstraZeneca, Merck, Plenity, and Sanofi-Aventis; and does research for Abbott Diabetes and Pendulum Therapeutics. Dr. Neumiller discloses that he

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THE GUT MICROBIOME: A DYNAMIC “MICROBIAL ORGAN”

The understanding of the role of the gut microbiome in health and disease continues to evolve rapidly.¹ Within the gut resides a complex ecosystem composed of trillions of microorganisms.² While microbiota research extends at least back to the 19th century (providing the foundation for our modern understanding of microbiology and infectious disease),³ microbiome science has advanced dramatically over the past several decades with the advent of high throughput DNA sequencing coupled with enhanced computational capabilities.⁴ It is now recognized that commensal gut bacteria provide multiple benefits to the host, including serving an important role by competing with pathogenic organisms, thus preventing colonization and associated illness.⁵ This vast gut ecosystem, primarily residing in the colon but with contributions coming from the entire alimentary canal, impacts multiple aspects of human physiology and metabolism both within the gut and systemically, leading some to refer to the gut microbiome as an underappreciated “organ.”^{2,6} The microbiome is important in immune system development, especially as it relates to the recognition of self vs non-self host cell proliferation, energy biogenesis, biosynthesis of vitamins, steroid hor-

mones, neurotransmitters, and metabolism of amino acids, dietary nutrients, bile salts, drugs, and other xenobiotics.¹ Notably, gut bacteria generate short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, through anaerobic fermentation of dietary fiber.⁷ SCFAs serve as a primary energy source for the intestinal epithelium. Butyrate is also an important signaling molecule for the immune system, as well as lipid metabolism, glucose homeostasis, and neurogenesis.^{1,8,9}

While the microbiome is clearly important in maintaining human health, numerous factors can influence the composition and function of the microbiome. Key factors include host genetics, geography, birth mode (cesarean vs vaginal delivery), nutrition during infancy (breast vs formula feeding), dietary practices, age, exercise, exposure to antibiotics, childhood immunizations, and other medications, as discussed below.¹⁰

Medication use: Medication use can have a significant impact on microbiome diversity and function. Antibiotics are well known to interfere with the balance of the gut microbiome.¹ Use of potent, broad-spectrum antibiotics reduces gut microbial diversity, including loss of important species of gut bacteria.¹¹ Disruption of the gut ecosystem increases susceptibility to colonization by pathogenic

microorganisms, with broad-spectrum antibiotic use typically preceding *Clostridioides difficile* infection and increasing the risk for colonization by other antibiotic-resistant organisms such as vancomycin-resistant *Enterococcus*.¹¹ Restoration of the gut microbiome is an important treatment strategy for recurrent *C difficile* infection, with fecal microbial transplantation from normal-weight, healthy individuals serving as an effective strategy to resolve the infection in resistant cases and/or in cases refractory to other treatment approaches.¹ Beyond the increased risk for gut colonization by pathogenic bacteria, perturbation of the gut microbiome promotes dysbiosis and risk for associated disease, as discussed in more detail later.¹¹ Other medications also impact the gut ecosystem. Multiple glucose-lowering medications, including metformin and incretin-based therapies, have been noted to influence the composition of the gut microbiome.¹² In fact, an increase in beneficial gut bacteria observed with metformin treatment has been suggested as a supporting mechanism in the treatment of type 2 diabetes mellitus (T2D).¹³

Dietary practices: Diet impacts the composition and diversity of the gut microbial community.¹⁴ The Western diet (high in protein and fat; low in fiber) is associated with reductions in key beneficial bacteria species, including SCFA producers as well as *Akkermansia muciniphila*, which is integral in maintenance of the gut mucin layer.¹⁵ SCFAs carry out important physiologic functions, and decreased SCFA production is associated with disease development.⁶ Furthermore, the composition and size of the bile acid pool are impacted by microbial metabolism of bile acids in the gut.¹⁶ Dietary impacts on microbiome composition can result in alterations in bile salt metabolism. Conversion of primary bile salts to secondary bile acids, which are integral to lipid and glucose metabolism, is facilitated by microbiota in the colon.¹⁷

Geography and environment: Interindividual differences in gut microbiome composition are highly associated with an individual's geographic location.¹⁸ Geographical differences in eating patterns also affect the gut microbiome. Environmental influences such as gardening and having pets can also contribute to the overall gut biome population.

Physical activity: Exercise not only improves body composition, but also contributes to gut microbial diversity.⁸ Notably, elite athletes appear to have greater microbiome diversity, including enriched bacterial species, including *A muciniphila*, adept at producing SCFAs.⁸ The maintenance of appropriate SCFA production has been hypothesized as 1 mechanism by which physical activity promotes health and enhancement of gut barrier integrity.¹⁹

Birth mode and nutrition during infancy: The developing infant microbiome is highly influenced by the mother's microbiome.²⁰ Mode of delivery at birth is an important variable, with infants born by cesarean delivery having low bacterial diversity compared with vaginally delivered infants.²¹ In addition to mode of delivery, formula feeding (vs breastfeeding) has an important impact on the composition and diversity of the microbiota of infants.²² While current evidence demonstrates differences in the development of the gut microbiome between breast- and formula-fed infants, additional research is needed to better understand the long-term impact of these differences.

Host genetics: While environmental influences have a large impact on microbiome composition, host genetics also play a role. Twin studies have demonstrated that microbiomes of monozygotic siblings have greater similarity compared with those of dizygotic siblings.²³

Age: As discussed previously, multiple factors can impact the developing gut ecosystem during childhood, and microbiome composition remains dynamic until the age of 3 to 4 years, when it becomes fully mature.²⁴ Microbiome diversity is decreased in the elderly and may contribute to important physiologic, neurologic, and immunologic changes observed in older adults.¹

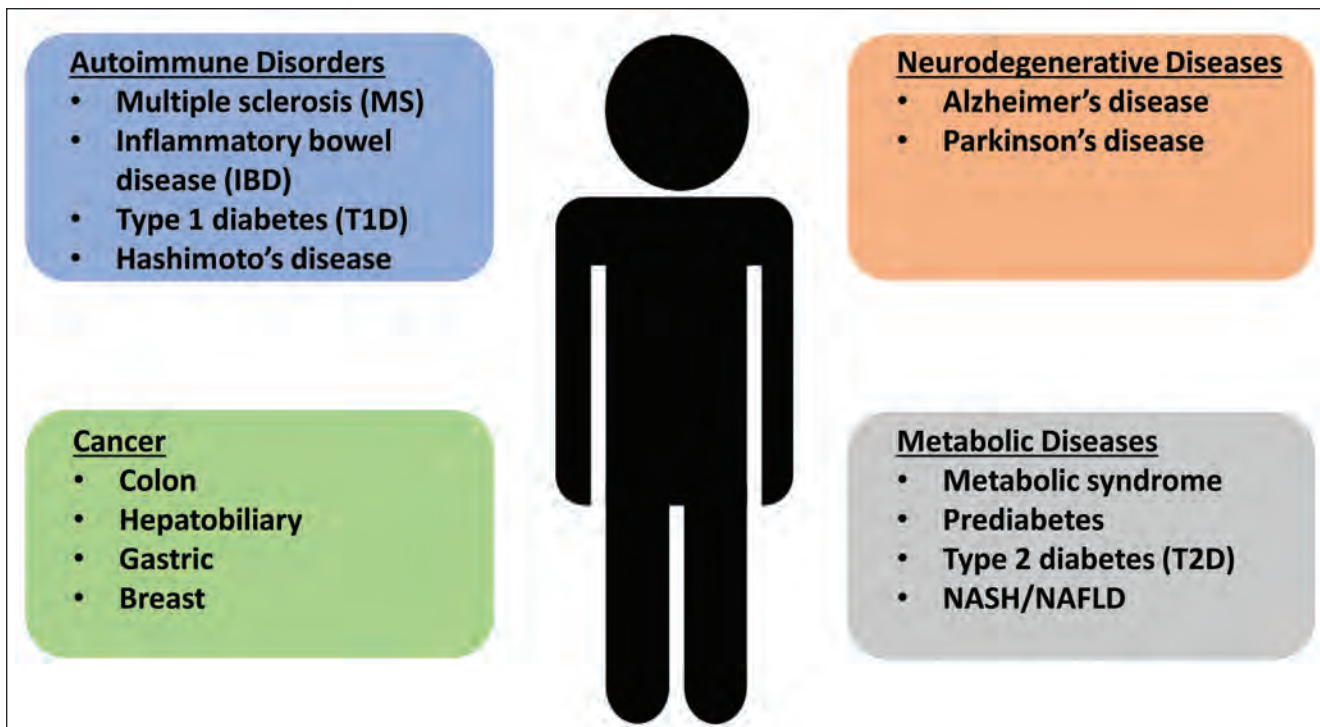
Stress and anxiety: The microbiome-gut-brain relationship is emerging as an important connection. Lower microbiome diversity has been associated with increased stress and anxiety levels, with consumption of foods containing naturally occurring probiotics or prebiotics associated with lower stress and anxiety levels in 1 study.²⁵

DYSBIOSIS IS ASSOCIATED WITH MULTIPLE DISEASE STATES

Rapid development of analytical techniques to quantify gut bacteria and analyze their genes and metabolic products has expanded our understanding of the relationships between the microbiome and disease.¹ Alterations in gut microbiome composition (dysbiosis) is associated with risk for a variety of diseases (**FIGURE 1**).^{1,4,10,20,26} While dysbiosis is associated with multiple diseases, additional work is necessary to determine whether dysbiotic ecosystems are a consequence or cause of disease.¹ Nonetheless, there is great interest in leveraging the microbiome to help guide the diagnosis, prognosis, and treatment of associated diseases.¹⁰

T2D, OBESITY, AND THE GUT MICROBIOME

Gut microbiome composition is predictive of incident T2D,²⁷ and obesity is associated with diminished diversity and richness of the gut microbiome, which can be reversed through dietary intervention.²⁸ Discordant twin studies

FIGURE 1. **Dysbiosis is associated with multiple chronic disease states**^{1,4,10,20,27}

Abbreviations: NASH/NAFLD, non-alcoholic steatohepatitis/non-alcoholic fatty liver disease.

showing that fecal transplants modulate metabolism in mice provide additional direct evidence that dysbiosis contributes to the pathophysiology of obesity and metabolic disorders.²⁹ A study with human subjects showed that a transfer of intestinal microbiota increased insulin sensitivity in subjects with metabolic syndrome.³⁰ **FIGURE 2** provides a summary and discussion of key alterations in gut microbiota observed in people with obesity and T2D,^{3,10} including the observation that T2D patients have less SCFA-producing gut bacteria.⁶ Further contributing to gut dysbiosis is an inadequate population of *A muciniphila*.³¹ By maintaining the gut barrier, *A muciniphila* helps prevent systemic inflammation that can contribute to the development of insulin resistance, other metabolic abnormalities (eg, non-alcoholic steatohepatitis/nonalcoholic fatty liver disease, atherosclerosis), and cancers.^{1,6,32} As previously discussed, SCFAs are important in glucose metabolism and are theorized to affect glucose metabolism through multiple mechanisms, including stimulation of glucagon-like peptide 1 (GLP-1) release (**FIGURE 3**).²⁴

LEVERAGING THE GUT MICROBIOME TO TREAT T2D: OPPORTUNITIES AND CHALLENGES

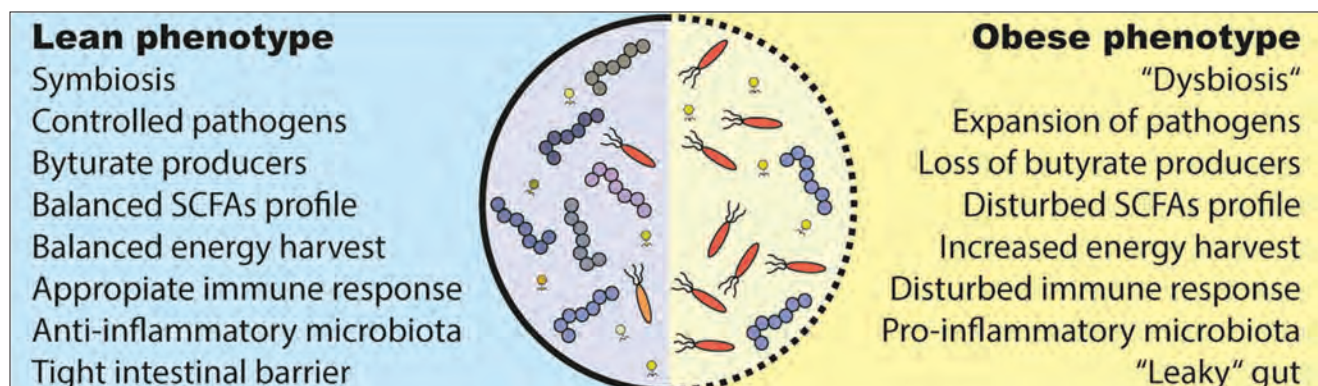
For the reasons detailed previously, there is great interest

in leveraging the gut microbiome to improve health and/or treat disease. Many are seeking targeted microbiome approaches with clinically validated strains that produce the key signaling molecules. Specifically, people with T2D have multiple deficiencies that can be potentially ameliorated through improved microbiome function, including 1) deficient butyrate (SCFA) production; 2) reduced production of secondary bile acids; and 3) thinning of the mucin layer and loosening of tight junctions in the epithelial layer of the gut.¹⁸ Of particular note, the genus *Akkermansia* is known to play an important role in maintaining mucin layer integrity and reducing inflammation, with significantly lower levels of gut *A muciniphila* noted in T2D.¹⁸

EVIDENCE SUPPORTING PROBIOTIC USE IN T2D

Evidence supporting probiotic use to improve glycemic control in T2D continues to expand.¹⁷ A recently published, multicenter, double-blind, placebo-controlled, randomized trial reported by Perraudeau et al enrolled 78 participants with T2D managed with diet and exercise alone, or in combination with metformin and/or a sulfonylurea.¹³ The clinical trial was designed to test the hypothesis that oral supplementation with a probiotic formulation would improve metabolic health, including improvements in mea-

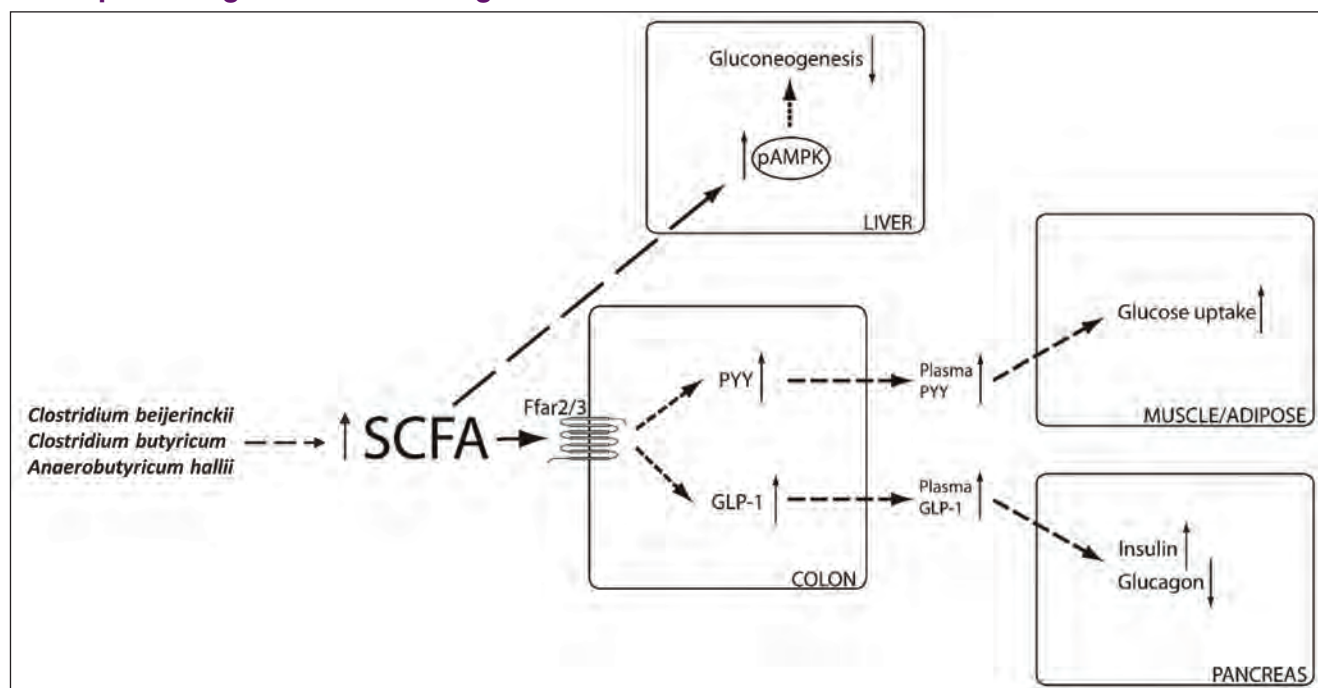
FIGURE 2. Alterations in the gut microbiota of people with obesity and diabetes



Under healthy conditions, the gut microbiota live in symbiosis and provide the host with several beneficial functions. For example, gut microbiota produce SCFAs that are used as an energy source and facilitate multiple important metabolic processes in the host. The gut microbiota observed in individuals with obesity and other metabolic diseases is often described as "dysbiotic," meaning that there is an expansion of normally underrepresented bacteria and diminished microbial diversity. A disturbed intestinal immune response and a Western diet are discussed as causes. Further, a Western diet induces a "leakiness" of the gut, which allows bacteria to cross the intestinal barrier and induce a pro-inflammatory response in the host. Finally, people with obesity show an increased energy harvest by the gut microbiota and a different SCFA profile when compared with lean individuals.

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FIGURE 3. Schematic overview of the proposed mechanisms by which targeted SCFA-producing microbes affect glucose metabolism



In the colon, SCFAs can increase PYY and GLP-1 expression. PYY has been shown to increase glucose uptake in muscle and adipose tissue, whereas GLP-1 increases insulin and decreases glucagon production in the pancreas. In addition, SCFAs have been shown to decrease hepatic gluconeogenesis.

Abbreviations: pAMPK, phosphorylated AMP-activated protein kinase; PYY, peptide YY.

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TABLE. Leveraging the gut microbiome through use of probiotics to treat T2D

<p>Opportunities</p> <ul style="list-style-type: none"> • Improvement of key derangements associated with dysbiosis <ul style="list-style-type: none"> ○ Increased butyrate production ○ Increased production of secondary bile acids ○ Thickening of mucin layer and tightening of junctions in the epithelial lining of the gut <p>Challenges</p> <ul style="list-style-type: none"> • Validation of safety for human consumption • Manufacturing challenges <ul style="list-style-type: none"> ○ Cultivation of anaerobic bacteria of interest ○ Production without exposure to animal products ○ Capacity for large-scale production

tures of glycemia. The proprietary probiotic formulation was designed to increase butyrate (eg, SCFA) production through inclusion of the butyrate-producing strains *Clostridium beijerinckii*, *C butyricum*, *Bifidobacterium infantis*, and *Anaerobutyricum hallii*, in addition to promoting health of the colonic mucin layer through supplementation with *A muciniphila*.¹³ All bacterial strains included within the study formulations were commensal organisms grown under controlled conditions (consistent with Good Manufacturing Practices) and in the absence of animal-derived products to ensure safe human use.¹³ Further, the product was formulated with food-grade ingredients and qualified as generally recognized as safe. Participants were randomized to twice-daily administration of the probiotic formulation or placebo for a duration of 12 weeks.

Use of the probiotic formulation was associated with a reduction in both the glucose total area under the curve (AUC) (-36.1 mg/dL/180 min; $P = .05$) and the incremental glucose AUC during a standardized meal tolerance test (-28.6 mg/dL/180 min; $P = .0066$), representing a significant improvement in postprandial glucose control. A trend toward an improvement in glycated hemoglobin (A1c) was also noted with the probiotic when compared with placebo (-0.6%; $P = .054$).¹³ Fecal analysis revealed an increase in stool butyrate with treatment, and plasma metabolomic analysis demonstrated increases in plasma butyrate and ursodeoxycholic acid (a secondary bile acid).¹³ Overall, findings from this trial provide additional evidence supporting the safety and glycemic efficacy of the studied probiotic formulation in patients with T2D.

Leveraging the gut microbiome through the use of innovative probiotics with the potential to restore these deficits presents both opportunities to improve health and challenges related to production and manufacturing of probiotic formulations for human use (TABLE). Notably,

probiotic preparations capable of delivering these benefits to patients are composed almost exclusively of anaerobic bacteria species that must be cultivated in the absence of oxygen, which presents manufacturing challenges.

SUMMARY

The gut microbiome clearly plays an important role in human health and disease, with dysbiosis associated with multiple disease states. A particularly strong association exists between dysbiosis and metabolic disorders, including T2D. An expanding literature base supports the use of evidence-based, disease-relevant probiotics, such as that studied by Perraudeau et al,¹³ to improve gut microbiome composition and glycemic control in patients with T2D. Future trials including larger populations with longer-term follow-up will further explore the role of specific probiotics in the treatment of T2D and other diseases associated with dysbiosis. Given the importance of probiotic bacterial composition on outcomes, healthcare providers may wish to consider recommending products with evidence of benefit. ●

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