



THE GUT MICROBIOME: A NOVEL ENDOCRINE ORGAN IN TYPE 2 DIABETES PATHOGENESIS AND MANAGEMENT

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ABSTRACT

Type 2 diabetes (T2D) is a major global health issue, with rates still on the rise. Projections indicate that over 700 million adults could be affected by 2045. While we know traditional risk factors like genetics, obesity, and lifestyle, the human gut microbiome has become an important factor in the disease's development and a possible target for new treatment strategies. This narrative review summarizes current research on the complex relationship between the gut microbiome and T2D. It looks into the changes in microbial composition and function seen in dysbiosis and how gut microbes affect glucose balance in the body. We discuss how microbial metabolites, like short-chain fatty acids, bile acids, and branched-chain amino acids, interact with the body to influence insulin sensitivity, inflammation, and gut barrier health. The review also examines the potential of microbiome-focused interventions, such as dietary changes, prebiotics, probiotics, and fecal microbiota transplantation, as supplements to standard T2D treatments. A key focus is the effect of glucose-lowering medications, particularly metformin, on the gut microbiome, suggesting a possible two-way interaction. Despite encouraging findings, the field faces challenges like differences in study methods, the need for larger and more diverse groups, and the difficulty in turning correlational data into concrete causes and effective treatments. The review concludes that a better understanding of the gut microbiome's role in T2D could lead to personalized, microbiome-based diagnostics and treatments, thus improving diabetes management.

KEYWORDS: microbiome, T2D, microbiota transplantation, dysbiosis.

INTRODUCTION

Type 2 diabetes (T2D) is a widespread metabolic disorder marked by long-term high blood sugar. This condition results from a mix of insulin resistance and gradual failure of pancreatic β -cells.^[1] Its global

prevalence has reached epidemic levels, affecting millions of people and posing a serious threat to public health systems. Current estimates show that T2D makes up around 90% of all diabetes cases, with projections suggesting that 783 million adults could be impacted by

2045.^[2] The financial burden is just as alarming, surpassing \$825 billion each year in healthcare costs and lost productivity.^[3] Traditional treatment methods focus on lifestyle changes and medications designed to boost insulin sensitivity or increase insulin production. However, the ongoing rise in cases and the difficulty of maintaining stable blood sugar levels in many patients highlight the urgent need to better understand the disease's underlying causes and to develop new therapeutic options.

In recent years, the human gut microbiome, which consists of trillions of bacteria, viruses, fungi, and other microorganisms in the gastrointestinal tract, has been identified as a key factor in regulating metabolism and immune function.^[4] Often called a "virtual endocrine organ," the gut microbiome influences the body through a complex network of interactions involving food components, microbial by-products, and body signaling pathways.^[5] A balanced and diverse gut microbiota is crucial for metabolic stability, aiding in the digestion of complex carbohydrates, vitamin production, and maintaining gut barrier health. When this balance is disrupted, a condition known as dysbiosis occurs.^[6] Dysbiosis has been linked to many chronic diseases, including inflammatory bowel disease, obesity, and, importantly, T2D.^[7]

The idea that dysbiosis in the gut microbiome contributes to T2D development is backed by an increasing amount of evidence.^[8] Studies comparing people with T2D to healthy individuals often find changes in microbial composition, typically showing a decrease in overall diversity and shifts in specific bacterial groups.^[9] While results can differ among populations, a common finding is a changed ratio of the two dominant bacterial groups, Firmicutes and Bacteroidetes, though the specifics of these changes are debated. More consistently, there is a reduced presence of butyrate-producing bacteria, like *Faecalibacterium prausnitzii* and *Roseburia* species, which is notable because butyrate plays a key role in gut health and insulin sensitivity.^[10] Additionally, changes in how the gut microbiome functions in T2D, especially regarding the production of important metabolites, are thought to be central to how the disease develops.^[11]

The connections between gut dysbiosis and impaired glucose metabolism are complex. They include: 1-Impact on the immune system and low-level inflammation: Dysbiosis can weaken the intestinal barrier, increasing permeability and allowing bacterial toxins, such as lipopolysaccharide (LPS), to enter the bloodstream.^[12] This causes a prolonged inflammatory state that can lead to insulin resistance in other tissues. 2- Production of microbial by-products: Short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which result from fiber fermentation, have shown positive effects on blood sugar management by promoting the release of gut hormones, reducing inflammation, and improving insulin signaling.^[13] In contrast, other by-products, such as

branched-chain amino acids and trimethylamine N-oxide (TMAO), are linked to a higher risk of insulin resistance and T2D.^[14] 3-Interactions with blood sugar-lowering medications: Notably, the effectiveness of certain diabetes drugs, especially metformin, may be partly shaped by their effects on the gut microbiome, adding complexity to the interplay between the body, microbes, and medication.^[15]

This narrative review intends to provide an overview of the current evidence regarding the gut microbiome's role in managing T2D. It will examine the typical characteristics of gut dysbiosis in T2D, clarify possible mechanisms connecting microbial populations to blood sugar control, and critically assess the potential of microbiome-modulating treatments as new strategies for preventing and treating this challenging disease.

METHODOLOGY

This narrative review was designed to summarize and critically evaluate current studies on the gut microbiome's role in the development and treatment of type 2 diabetes (T2D). A systematic search of the literature was carried out using databases such as PubMed, Google Scholar, and Ovid MEDLINE for articles published mainly between 2010 and 2025. The search strategy included a mix of Medical Subject Headings (MeSH) terms and keywords, such as: "gut microbiome" OR "gut microbiota," AND "type 2 diabetes" OR "T2D" OR "T2DM," AND "pathogenesis" OR "dysbiosis" OR "short-chain fatty acids" OR "mechanisms," AND "management" OR "therapy" OR "probiotics" OR "prebiotics" OR "diet" OR "metformin."

The inclusion criteria covered original research studies (both observational and interventional), systematic reviews, meta-analyses, and high-quality narrative reviews published in English. Studies focused solely on type 1 diabetes, animal models without human relevance, or publications not in English were excluded. The initial search yielded many articles, which were screened by their titles and abstracts. The full texts of potentially relevant papers were retrieved for eligibility assessment.

Data extraction concentrated on key themes: (1) changes in gut microbiome composition and diversity in T2D patients compared to healthy individuals, (2) proposed pathways linking the microbiome to glucose metabolism, (3) the effects of existing T2D treatments (e.g., metformin) on the microbiome, and (4) evidence for microbiome-targeted therapy options. As this review is narrative, the synthesis of evidence is qualitative and thematic, aiming to offer a broad overview and critical insights rather than a statistical meta-analysis.

DISCUSSION

Gut Microbiome Dysbiosis in Type 2 Diabetes: Compositional and Functional Shifts

A key aspect of the relationship between the gut microbiome and type 2 diabetes (T2D) is the dysbiosis

observed in affected individuals. This dysbiosis involves noticeable changes in both the makeup and the functional potential of the gut microbial community.^[16] Many studies have shown that people with T2D tend to have lower gut microbial diversity (alpha-diversity) compared to those with normal blood sugar levels. Reduced diversity is seen as a sign of an unstable and unhealthy gut ecosystem, which is less resilient to changes and linked to various diseases.^[17]

At the phylum level, much focus has been on the ratio of Firmicutes to Bacteroidetes (F/B ratio). Early research indicated that a higher F/B ratio was typical of T2D and obesity. However, later studies have painted a more complex and inconsistent picture, with some showing an increase, others showing a decrease, or no significant change in this ratio (18). This inconsistency highlights the effects of factors like geography, diet, genetics, and research methods, suggesting that the F/B ratio alone is not a reliable marker for T2D. More consistent changes can be seen at lower taxonomic levels. For example, multi-country studies have identified specific species that are consistently increased or decreased in T2D.^[9] Species like *Clostridium citroniae*, *Clostridium bolteae*, and *Escherichia coli* are often found to be higher, while beneficial species like *Coprococcus eutactus* and *Faecalibacterium prausnitzii* are usually lower.^[19] The loss of butyrate-producing bacteria, such as those from the genera *Faecalibacterium* and *Roseburia*, is particularly noteworthy, given butyrate's crucial role in maintaining gut barrier function and reducing inflammation.^[10]

Beyond simply listing bacterial types, the effects of these compositional changes are crucial. Metagenomic analyses show that the gut microbiome of T2D patients is richer in pathways related to oxidative stress response, sulfate reduction, and the metabolism of simple sugars.^[11] At the same time, pathways for bacterial movement, flagellar assembly, and butyrate production are often reduced. A significant finding in a large study linked a specific strain of *Prevotella copri* to T2D. This strain has a greater ability to produce branched-chain amino acids (BCAAs), and high blood levels of BCAAs are known to increase the risk of insulin resistance and T2D. This indicates that it's not just whether a microbe is present but also what it can do functionally that impacts the host's metabolism.^[14] Additionally, viruses that infect bacteria, called bacteriophages, are emerging as potential players in these functional changes by affecting the metabolic activities of their bacterial hosts. Overall, the evidence shows that T2D is linked to a less diverse gut microbiome, a loss of key beneficial bacteria, and functions that may increase inflammation and insulin resistance.^[20]

Mechanistic Pathways Linking the Gut Microbiome to Glucose Homeostasis

The link between gut microbial dysbiosis and T2D symptoms operates through several complex pathways.

These pathways mostly involve microbial metabolites that interact with host receptors and cells, influencing metabolism and immune responses.

Short-Chain Fatty Acids (SCFAs): SCFAs, including acetate, propionate, and butyrate, are produced when bacteria ferment dietary fiber in the colon. They are among the most researched microbial metabolites concerning metabolic health. Butyrate is the main energy source for colon cells, helping maintain a strong intestinal barrier and preventing the leakage of inflammatory molecules into the bloodstream.^[13] Propionate and acetate enter the portal circulation and can affect glucose metabolism in the liver and other tissues. SCFAs also serve as signaling molecules by binding to specific G-protein-coupled receptors (GPCRs), like GPR41 and GPR43. This binding prompts the release of gut peptides such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) from intestinal L-cells. GLP-1 boosts glucose-dependent insulin release, inhibits glucagon production, and slows gastric emptying, all of which help control blood sugar levels.^[21] Thus, the known benefits of high-fiber diets are partly due to increased production of these helpful SCFAs by a healthy gut microbiome.

Bile Acid Metabolism: Gut bacteria significantly change primary bile acids made in the liver into secondary bile acids. This change is not just a side effect but a key signaling event. Secondary bile acids strongly activate the farnesoid X receptor (FXR) and the Takeda G-protein-coupled receptor 5 (TGR5). Activating TGR5 on intestinal L-cells boosts GLP-1 release, while FXR signaling in the liver can regulate glucose and fat metabolism.^[22] Dysbiosis in T2D can alter the composition of the bile acid pool, disrupting these delicate signaling pathways and contributing to metabolic issues.

Intestinal Barrier Integrity and Inflammation: A healthy gut microbiome supports the integrity of the intestinal barrier. Dysbiosis, particularly from losing SCFA-producing bacteria, can weaken this barrier, leading to what is called a "leaky gut." This allows bacterial endotoxins, like lipopolysaccharide (LPS), to enter the circulation. LPS triggers an immune response, resulting in chronic low-grade inflammation marked by pro-inflammatory cytokines such as TNF- α and IL-6.^[12] These cytokines activate pathways that disrupt insulin signaling in muscle, liver, and fat tissues, leading to insulin resistance.

Branched-Chain Amino Acids (BCAAs): As mentioned, certain gut bacteria contribute to BCAA production. Higher levels of BCAAs in the blood are closely linked to insulin resistance. It is thought that BCAAs produced by microbes add to this pool. Dysbiosis, characterized by too many BCAA-producing bacteria, may directly contribute to the metabolic issues associated with T2D. These interconnected

mechanisms—SCFA signaling, bile acid adjustment, barrier protection, and BCAA production—show how the gut microbiome regulates host glucose control.^[14]

The Impact of Glucose-Lowering Drugs on the Gut Microbiome

The relationship between managing T2D and the gut microbiome works in both directions. A strong example of this is how commonly prescribed glucose-lowering drugs significantly affect the gut microbiota's makeup and function. Understanding this drug-microbiome relationship is crucial for grasping how these medications work and for tailoring treatment.

Metformin: Metformin, the primary treatment for T2D, serves as a clear example. While its main action has been linked to reducing glucose production in the liver, a significant part of its effect is now understood to occur through the gut microbiome.^[15] Studies have shown that taking metformin alters the gut microbial community, increasing beneficial SCFA-producing bacteria such as *Akkermansia muciniphila* and various species of *Bifidobacterium* and *Lactobacillus*. *A. muciniphila* is especially interesting due to its link to better metabolic health, strengthened gut barrier function, and lower inflammation.^[23] Research suggests that metformin boosts the growth of these bacteria, leading to more SCFA production. The SCFAs, particularly butyrate, can improve gut health and reduce overall inflammation. Furthermore, SCFAs can promote GLP-1 release, which aids in metformin's ability to lower blood sugar. This means that metformin's effectiveness may partly rely on the presence of certain bacterial species in a person's gut, possibly explaining why responses to the drug vary among patients.^[24]

Other Medications: The effects also extend beyond metformin. Acarbose, an alpha-glucosidase inhibitor that slows carbohydrate absorption in the small intestine, creates a strong prebiotic effect by increasing undigested carbohydrates reaching the distal gut. This leads to a notable shift in microbial communities, favoring bacteria that can ferment these complex carbohydrates, such as *Lactobacillus* species. Newer drug classes like GLP-1 receptor agonists may also indirectly influence the microbiome by affecting gut movement and nutrient absorption.^[25] Understanding that diabetes medications can reshape the gut microbiome opens up new research possibilities, such as predicting drug responses based on initial microbiota or combining medications with specific probiotics to improve their effectiveness and lessen side effects.

Microbiome-Targeted Interventions for T2D Management

Understanding the gut microbiome's role in type 2 diabetes (T2D) has led to interest in developing ways to change the microbial community to enhance blood sugar control. These strategies include dietary changes and more direct microbial interventions.

Dietary Interventions: Diet is the most powerful and natural way to shape the gut microbiome. High-fiber diets, Mediterranean diets, and other plant-based eating patterns are linked to a more diverse and favorable microbial profile. Increasing fermentable fiber intake directly supports the growth of bacteria that produce short-chain fatty acids (SCFAs), leading to the positive effects described earlier.^[13] In contrast, Western diets that are high in saturated fats and refined sugars encourage an imbalance that leads to inflammation and poor glucose tolerance. Personalized nutrition advice based on a person's microbiome is a new frontier in tailored nutrition for T2D management.

Prebiotics and Probiotics: Prebiotics are non-digestible food components that selectively promote the growth of good bacteria. Probiotics are live microbes that can provide health benefits when taken in adequate amounts. Research using specific probiotic strains, especially from the *Lactobacillus* and *Bifidobacterium* groups, has shown modest but promising effects on improving blood sugar levels.^[26] Synbiotics, which combine prebiotics and probiotics, are meant to work together to support the survival and growth of helpful microbes.

Fecal Microbiota Transplantation (FMT): FMT includes transferring fecal material from a healthy donor to a recipient to help restore a healthy microbial community. Though mainly used to treat recurrent *Clostridioides difficile* infections, it is being studied for its potential use in metabolic diseases. Small studies suggest that FMT from healthy donors can temporarily enhance insulin sensitivity in people with metabolic syndrome.^[27] However, issues like long-term effectiveness, safety, standardization, and donor screening must be resolved before FMT can be considered a viable treatment for T2D.

Emerging Approaches: Other new strategies include using defined groups of bacteria (next-generation probiotics), such as *Akkermansia muciniphila*, which is currently being tested in clinical trials.^[28] Phage therapy, which uses viruses to target harmful bacteria, represents a very precise but still experimental method.^[20]

Challenges and Inconsistencies in Gut Microbiome Research for T2D

Despite the exciting progress, gut microbiome research in T2D faces many challenges that must be recognized. A major issue is the significant variation in methods and results across studies, making it hard to draw clear conclusions. A recent analysis of 16S rRNA sequencing studies showed considerable differences in findings, with high variability and no consistent differences in bacterial diversity or specific types between T2D and control groups across different studies. This variation comes from differences in DNA extraction methods, sequencing regions, bioinformatics processes, and statistical analyses.^[29]

In addition, most evidence so far is correlative rather than causal. While some studies suggest links between certain bacteria and T2D subtypes, proving causation in humans is difficult.^[30] The vast diversity of the human population in genetics, diet, ethnicity, and geography adds complexity, as a microbial pattern seen in one group may not apply to another. Lastly, there's the challenge of moving from identifying links to creating safe, effective, and lasting microbiome-based treatments. Many probiotic interventions have shown only modest benefits, and the long-term stability of changes from treatments like FMT is uncertain.^[19] Tackling these challenges requires larger, more prolonged studies that combine genomic, metabolomic, and clinical data from varied groups to move from general patterns to tailored treatment approaches.

Future Recommendations

Based on the current evidence, several key directions are vital for advancing gut microbiome research in T2D. First, there is a strong need for large-scale, long-term, and multi-ethnic studies. These should follow individuals from a pre-diabetic stage to the development of T2D to determine whether changes in microbes cause the disease or are a result of it, and to find predictive microbial markers.^[19] Second, research should go beyond simple taxonomic relationships towards a better functional understanding. Combining multiple omics approaches—metagenomics, metatranscriptomics, metabolomics, and proteomics—will help clarify how gut microbes and their byproducts affect host biology. Third, the interaction between the microbiome and medications deserves more attention.^[11] Understanding how a person's microbiome influences the metabolism and effectiveness of blood sugar-lowering drugs could lead to personalized treatment plans.^[24] Fourth, well-designed, randomized clinical trials with standardized methods are essential to confirm the effectiveness of microbiome-targeted treatments like next-generation probiotics, synbiotics, and FMT. These trials should clearly define goals, including blood sugar control, insulin sensitivity, and inflammation markers.^[28] Finally, exploring how the microbiome influences metabolic health from early life is a promising area. Research suggests that microbial exposure in infancy can impact long-term diabetes risk, pointing to opportunities for early preventative strategies.^[31]

CONCLUSION

The gut microbiome is a key factor in the complex mechanisms behind type 2 diabetes. Evidence shows that T2D is linked to gut dysbiosis characterized by lower microbial diversity, fewer beneficial SCFA-producing bacteria, and an increase in microbes that may drive inflammation and insulin resistance. The ways in which these relationships function are complex and involve microbial byproducts that affect hormone secretion, immune response, gut barrier health, and insulin signaling. The interaction between the microbiome and glucose-lowering drugs, especially metformin,

introduces a new aspect of drug action and emphasizes the need to consider the microbiome in treatment strategies. While promising methods to modify the microbiome are being studied, the field must address issues related to consistency, proving causation, and translating findings into effective clinical treatments. A deeper understanding of the gut microbiome's role, supported by new technologies and strong study designs, holds great potential for transforming T2D management through personalized, microbiome-based strategies for prevention, diagnosis, and treatment.

Ethical statement

- 1) This material is the authors' own original work, which has not been previously published elsewhere.
- 2) The paper is not currently being considered for publication elsewhere.

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