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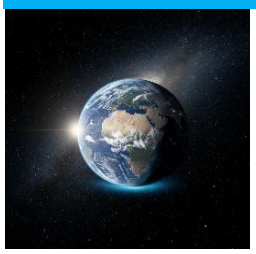

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Gut Microbiota in Type 2 Diabetes Mellitus: Mechanistic Pathways, Microbiota-Targeted Strategies, and Clinical Implications - A Narrative Review

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder increasingly associated with alterations in the composition and function of the gut microbiota. A growing body of evidence suggests that microbial metabolites, immune modulation, and intestinal barrier integrity play a key role in regulating insulin sensitivity and chronic low-grade inflammation. This narrative review synthesizes current mechanistic, clinical, and translational evidence on the gut microbiota–metabolic axis in T2DM, with particular focus on short-chain fatty acids (SCFAs), bile acid signaling, branched-chain amino acids (BCAAs), tryptophan metabolites, and novel microbiota-derived compounds. Key pathways discussed include metabolic endotoxemia, incretin regulation, immune modulation, and the influence of the microbiota on pharmacotherapy and lifestyle factors such as diet and physical activity. Clinical studies indicate that changes in the microbiota correlate with glycemic control, markers of inflammation, and disease progression, while microbiota-targeted strategies — including dietary interventions, prebiotics, probiotics, and selected antidiabetic drugs — may contribute to improved metabolic outcomes. However, heterogeneity in study design, population differences, and methodological limitations currently hinder causal interpretation. Future studies combining multiomic approaches with personalized interventions may help elucidate the therapeutic potential of microbiota modulation in T2DM. Overall, the gut microbiota appears to be a dynamic regulator of immunometabolic homeostasis and a promising target for future precision-based strategies in the management of metabolic diseases.
Keywords: gut microbiota; type 2 diabetes mellitus; dysbiosis; insulin resistance; short-chain fatty acids; metabolic endotoxemia; microbiome-targeted therapy

1. Introduction: Gut Microbiota–Metabolic Axis

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by impaired glucose homeostasis resulting from insulin resistance and pancreatic β-cell dysfunction. In recent years, increasing attention has been paid to the role of the gut microbiota as a key regulator of host metabolism and a contributing factor in the pathogenesis of metabolic diseases.[1,2] The gut–metabolic axis involves complex interactions between gut microorganisms, their metabolites, and the host's immune and endocrine systems, integrating metabolic, immunological, and neuroendocrine signaling pathways.

The human gut microbiota consists predominantly of bacteria belonging to the *Firmicutes* and *Bacteroidetes* phyla, which together constitute the majority of the microbial community, while *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* are present in smaller

proportions.[3] Under conditions of microbial homeostasis, SCFA-producing bacteria support intestinal barrier integrity, regulate energy metabolism, and maintain immunological balance.[4,5] Microbial metabolites — including SCFAs, tryptophan derivatives, BCAAs, and secondary bile acids — participate in the regulation of intestinal hormone secretion (including glucagon-like peptide-1 [GLP-1]), modulate insulin signaling, and influence immune cell function.[5–7] Concurrently, lipopolysaccharides (LPS) produced by Gram-negative bacteria can activate innate immune receptors and promote chronic low-grade inflammation, which is considered a key element in the pathophysiology of T2DM.[1,8]

A growing body of evidence suggests that alterations in gut microbiota composition are not simply a consequence of metabolic disease, but may actively contribute to its development by modulating the immunometabolic axis and disrupting intestinal barrier integrity. Integrating microbiome composition data with microbial metabolite profiling provides new insights into pathogenic mechanisms and points to potential therapeutic strategies targeting the gut microbiota.[4,9]

2. Dysbiosis Patterns Across the T2DM Spectrum

Gut microbiota dysbiosis in T2DM involves both taxonomic and functional changes that vary depending on disease stage. Numerous studies have reported increased abundance of opportunistic bacteria — including *Escherichia coli*, *Enterococcus*, *Fusobacterium*, and *Ruminococcus* — accompanied by decreased abundance of butyrate-producing taxa, which is associated with increased production of pro-inflammatory metabolites and impaired intestinal barrier integrity.[1,5,10] These findings suggest a functional shift in the microbiome rather than a complete loss of microbial diversity.

Gut microbiota composition is shaped by environmental factors acting from the earliest stages of life. Gestational age at birth influences microbiome development, as preterm infants exhibit reduced bacterial diversity and increased colonization by potentially pathogenic microorganisms, which may modulate the risk of metabolic disorders in later life.[11] Diet plays a central role: complex carbohydrates serve as the primary substrates for commensal bacteria, whereas Western dietary patterns — characterized by low fiber intake and high consumption of ultra-processed foods — limit substrate availability and promote dysbiosis.[11]

The human microbiome can also be categorized according to dominant enterotypes, primarily communities dominated by *Bacteroides* or *Prevotella*, which are associated with long-term dietary patterns and remain relatively stable over time. The *Bacteroides* enterotype is more commonly observed in individuals consuming diets rich in animal fats and proteins, while the *Prevotella* enterotype is associated with carbohydrate-rich diets, potentially contributing to metabolic differences between populations.[11]

At the taxonomic level, a decrease in metabolically protective bacteria is accompanied by an increase in taxa associated with inflammation and insulin resistance through LPS production.[1,12,13] Elevated blood glucose correlates with reduced microbial diversity and taxonomic changes, including increased abundance of *Granulicatella* and *Prevotella*, associated with a higher risk of T2DM development.[11] In prediabetic states, increased levels of *Escherichia*, *Shigella*, *Collinsella*, *Senegalimassilia*, and *Allisonella*, along with decreased levels of *Enterococcus*, *Intestinibacter*, and *Anaerostipes*, may reflect early functional changes preceding overt disease.[11]

Microbiome changes also depend on disease progression. In early dysglycemia, taxonomic differences are relatively minor, whereas advanced T2DM is characterized by marked

functional changes and modifications in microbial metabolite profiles.[14] Later disease stages are associated with increased abundance of taxa such as *Hungatella* and the *Clostridium innocuum* group, along with reduced levels of butyrate-producing bacteria, reflecting progressive metabolic and inflammatory disturbances.[14] Altered expression of tight junction proteins such as ZO-1 has been correlated with BMI, glycemia, and blood pressure, highlighting the link between dysbiosis and increased intestinal permeability.[11]

Metagenomic studies further highlight the functional dimension of dysbiosis, including reduced SCFA production and elevated levels of pro-inflammatory metabolites such as BCAAs and LPS.[9] Concurrent changes in microbiota composition and metabolite profiles suggest that dysbiosis may act as a contributing factor to T2DM pathogenesis rather than merely a consequence of metabolic dysfunction.[4,9]

3. Mechanistic Pathways Linking Microbiota With Insulin Resistance

3.1. Intestinal Barrier Dysfunction and Metabolic Endotoxemia

Patients with early insulin resistance have been found to have reduced diversity of butyrate-producing bacteria — including members of the *Christensenellaceae*, *Marvinbryantia*, and *Ruminococcaceae* families — which correlates with increased HOMA-IR and worsening metabolic parameters.[1,4,9] Reduced levels of *Faecalibacterium prausnitzii* and other SCFA producers are associated with impaired intestinal barrier integrity and facilitate translocation of LPS into the systemic circulation.[2,9,15] An additional regulatory element of the barrier–endotoxemia axis is intestinal alkaline phosphatase (IAP), which reduces LPS toxicity through dephosphorylation, thereby limiting metabolic endotoxemia and inhibiting systemic inflammation; in animal models, IAP reversed metabolic endotoxemia, while significantly reduced fecal IAP levels have been reported in patients with T2DM.[5]

LPS activates the TLR4 receptor, leading to activation of the NF-κB and MAPK signaling pathways and increased production of pro-inflammatory cytokines — including TNF-α, IL-1, and IL-6 — thereby promoting chronic low-grade inflammation and impairing insulin signaling through serine phosphorylation of IRS.[3,8] SCFA deficiency reduces the expression of tight junction proteins, including ZO-1, and impairs regulatory T cell activity, increasing intestinal permeability.[16,17] Experimental models have demonstrated that butyrate deficiency is associated with an approximately 50% reduction in ZO-1 expression and increased intercellular permeability, highlighting the importance of bacterial metabolites in maintaining intestinal barrier integrity.[3]

A high-fat diet may further exacerbate metabolic endotoxemia by reducing tight junction protein expression and prolonging the postprandial period, thereby increasing LPS translocation. Conversely, probiotic bacteria such as *Lactobacillus rhamnosus* GG have been shown to protect the epithelial monolayer from tight junction disruption.[18] Gut microbiota dysbiosis also promotes increased production of pro-inflammatory metabolites — including LPS and BCAAs — thereby intensifying metabolic endotoxemia and insulin resistance.[5,6]

3.2. Short-Chain Fatty Acids and Energy Metabolism

Short-chain fatty acids — butyrate, propionate, and acetate — are produced through microbial fermentation of dietary fiber and represent a key component regulating glucose metabolism.[3,6,19–21] Butyrate stimulates enteroendocrine cells to secrete GLP-1 and peptide YY (PYY), increasing insulin secretion and limiting glucose release into the bloodstream.[6,19] It also supports intestinal barrier integrity by upregulating tight junction protein expression.[1,15] Propionate similarly promotes GLP-1 and PYY secretion and regulates hepatic

glucose production; its supplementation has been associated with reduced food intake and preserved insulin sensitivity.[3,6,19]

In T2DM, a decrease in SCFA-producing bacteria — including *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Eubacterium rectale* — has been observed alongside an increase in opportunistic taxa such as *Escherichia–Shigella* and *Enterococcus*, which is associated with decreased SCFA production and increased inflammatory activity.[1,3,5] SCFAs mediate their effects through FFAR2 (GPR43) and FFAR3 (GPR41) receptors expressed in adipocytes, immune cells, and intestinal enteroendocrine cells, contributing to the regulation of lipid and glucose metabolism.[6,15,22,23] Butyrate may also inhibit histone deacetylase expression by activating FFAR2, exerting anti-inflammatory effects and supporting immunometabolic balance.[24]

3.3. Immune Modulation

T lymphocytes are key mediators of the immune response and differentiate into Th1, Th2, Th17, and Treg subsets. Th1 and Th17 cells perform pro-inflammatory functions, while Treg cells exhibit immunosuppressive activity that limits chronic inflammation.[6] Microbial metabolites — including SCFAs, secondary bile acids, and tryptophan catabolites — regulate Treg differentiation and the Th17/Treg balance. SCFAs promote Treg differentiation by inhibiting HDAC activity and increasing histone acetylation at the *Foxp3* locus, as well as by activating GPR41 and GPR109a receptors, leading to increased IL-22 secretion.[6] Simultaneously, SCFAs inhibit T-bet and RORγt expression, limiting Th1 and Th17 proliferation and reducing IL-17 levels.[6] SCFAs also modulate B cell function by increasing acetyl-CoA availability and activating mitochondrial metabolism, thereby enhancing plasma cell differentiation and IgA production at the intestinal barrier.[6]

Tryptophan metabolites — including indole and its derivatives — regulate B cell immune functions through aryl hydrocarbon receptor (AhR) signaling and inhibition of EBF1 and PAX5 expression.[5] Under dysbiosis conditions, SCFA deficiency reduces Treg activity and increases intestinal permeability, facilitating LPS translocation and TLR4 activation, which promotes chronic low-grade inflammation and disrupts insulin signaling pathways.[5,6,16]

3.4. Bile Acids and FXR/TGR5 Signaling

The gut microbiota regulates bile acid metabolism through bacterial enzymes such as bile salt hydrolases, converting primary bile acids into secondary metabolites that influence host metabolism.[6,20,24] Bile acids function as signaling molecules interacting with farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5), participating in the regulation of glucose and lipid metabolism.[24] Secondary bile acids activate the BA–FXR–SHP, BA–TGR5–GLP-1, and BA–FXR–FGF15/19 pathways, thereby influencing energy homeostasis and incretin secretion.[24] FXR activation induces SHP and FGF19 synthesis and inhibits CYP7A1 expression in the liver, regulating bile acid synthesis and lipid metabolism.[20,24]

Secondary bile acids also activate the TGR5 receptor, increasing GLP-1 secretion, improving insulin sensitivity, and affecting energy expenditure in the liver, skeletal muscle, and brown adipose tissue.[8,15,24] Microbial modifications of bile acids can simultaneously inhibit intestinal FXR and activate TGR5, thereby modulating glucose and lipid metabolism.[24]

3.5. Branched-Chain Amino Acids

Branched-chain amino acids (BCAAs) — leucine, isoleucine, and valine — are metabolites associated with metabolic disturbances observed in T2DM. Elevated BCAA levels are linked

to obesity and insulin resistance and may correlate with the risk of T2DM development.[1,3,13] BCAAs can be synthesized by gut bacteria, and their increased availability may reflect functional alterations of the microbiota associated with metabolic dysregulation.[3,23]

Mechanistically, elevated BCAA levels may activate the mTOR–p70 S6 kinase (p70S6K) pathway, promoting impaired phosphorylation of insulin receptor substrate-1 (IRS-1) and weakening insulin signaling, which leads to reduced glucose transport and insulin resistance.[3,18,23] Disruption of the PI3K–Akt axis may ensue, and these effects can be exacerbated under high-fat diet conditions, highlighting the link between BCAAs, dietary patterns, and metabolic phenotype.[13] Increased BCAA availability may also enhance hepatic gluconeogenesis and reduce peripheral glucose uptake, directly worsening glycemic control.[1,13] Elevated BCAA levels frequently coexist with broader alterations in metabolite profiles and gut microbiota composition, suggesting their involvement in metabolic regulation and disease progression.[13]

3.6. Tryptophan Metabolism and AhR Signaling

Tryptophan metabolites are an important component of the microbiota–immune system–metabolism axis and can modulate insulin resistance by activating AhR and regulating the inflammatory response. Products of bacterial tryptophan metabolism — such as indole and its derivatives — affect intestinal barrier function and immune signaling, integrating metabolic and inflammatory processes.[1] Under dysbiosis conditions, an imbalance of tryptophan metabolites may contribute to increased oxidative stress and chronic low-grade inflammation.[24] The gut microbiota converts dietary components into metabolites that regulate host gene expression and immune system maturation, highlighting the importance of the tryptophan–AhR axis as a mechanism linking dysbiosis to T2DM progression.[6]

The metabolism of aromatic amino acids (AAAs) — including tyrosine, phenylalanine, and tryptophan — also undergoes significant changes in T2DM and may influence insulin resistance. The gut microbiota, including *Bacteroides*, *Clostridium*, *Bifidobacterium*, and *Lactobacillus acidophilus*, participates in the conversion of tryptophan to indole and its derivatives via tryptophanase (TnaA) and AAA aminotransferase-dependent pathways.[18] For example, *Lactobacillus* spp. convert tryptophan to indolealdehyde and indoleacetic acid, while *Ruminococcus gnavus* metabolizes it to tryptamine, and *Clostridium sporogenes* generates aromatic propionate derivatives such as indolepropionate.[18] These metabolites may strengthen the intestinal barrier by increasing epithelial gene expression, stimulate GLP-1 secretion, and modulate serotonergic signaling affecting gastrointestinal motility and appetite regulation.[18]

In cohort studies, higher circulating levels of tryptophan and kynurenine pathway metabolites were correlated with an increased risk of T2DM, while indolepropionate showed an inverse relationship, suggesting a potential protective role.[18] The tryptophan–kynurenine pathway remains closely linked to the gut microbiota, which — by regulating IDO-1 enzyme activity — affects tryptophan availability and the balance of immunomodulatory metabolites. Introduction of specific probiotics can restore the kynurenine/tryptophan ratio, highlighting the importance of the microbiota as a regulator of the tryptophan axis in T2DM.[18]

3.7. Microbiota–Incretin Axis Beyond SCFA

Beyond classical SCFA-mediated regulation of GLP-1 secretion, the gut microbiota modulates the incretin axis through complex metabolic interactions involving secondary bile acids, bacterial metabolites, and gut hormone signaling. Intestinal bacteria convert primary bile acids

into secondary metabolites that interact with FXR and TGR5 receptors, modulating glucose homeostasis, lipid metabolism, and incretin secretion.[3,5,13,20] Activation of TGR5 in enteroendocrine cells increases GLP-1 secretion, promoting improved insulin sensitivity and glycemic control, while FXR signaling affects FGF19 expression and inhibits hepatic gluconeogenesis.[3,5,6]

This mechanism complements the classical action of SCFAs — which increase GLP-1 and PYY secretion via FFAR2 and FFAR3 receptors — integrating gut–pancreatic signaling with energy metabolism regulation.[1,25] SCFA production by gut bacteria enhances intestinal barrier function and reduces low-grade inflammation, which indirectly stabilizes the incretin response and promotes glucose homeostasis.[1] Simultaneously, the microbiota acts as an endocrine organ, producing metabolites capable of interacting with distant tissues — including the liver, adipose tissue, and immune system — indicating multidirectional regulation of the gut–metabolism axis.[1,6]

Under dysbiosis conditions, bile acid metabolism disorders and reduced SCFA production lead to weakened incretin signaling and impaired glycemic control. These changes may exacerbate insulin resistance by limiting GLP-1 secretion and modulating the gut–liver axis, underscoring the importance of the microbiota as an endocrine regulator in T2DM pathogenesis.[1,6,24]

3.8. Drug–Microbiota Interactions in T2DM

Pharmacotherapy of T2DM can modulate gut microbiota composition and function, with some of the metabolic effects of antidiabetic drugs attributable to their impact on the gut environment and the profile of bacterial metabolites. Metformin exerts multidirectional effects on the microbiota, leading to taxonomic and functional changes that promote improved glycemic control. Studies have shown that metformin therapy may increase the abundance of SCFA-producing bacteria and modulate intestinal carbohydrate metabolism, affecting the gut–metabolism axis and incretin secretion regulation.[3,26] Metformin also affects bile acid metabolism and the intestinal environment, which may lead to changes in hormonal signaling and improved insulin sensitivity.[3,27]

Additionally, metformin has been observed to promote the growth of bacteria such as *Akkermansia muciniphila* and other taxa associated with intestinal barrier integrity, helping to reduce LPS translocation and chronic low-grade inflammation.[18,22,28] These mechanisms indicate that the action of metformin is not limited to its effect on hepatic glucose production, but also includes modulation of the intestinal environment and the profile of bacterial metabolites participating in metabolic homeostasis regulation.[3]

Alpha-glucosidase inhibitors — including acarbose — affect the gut microbiota by delaying carbohydrate breakdown in the small intestine, increasing the availability of undigested substrates for bacterial fermentation in the large intestine. This results in increased SCFA production and changes in microbiota composition, which may support glycemic regulation and modulate the incretin response.[3,8] This mechanism is also associated with a reduction in postprandial glucose spikes and an indirect effect on host metabolism through bacterial fermentation products.[3,8]

In general, antidiabetic drugs can act both directly — by regulating host metabolism — and indirectly — by reorganizing the gut microbiota and altering the profile of bacterial metabolites. Drug–microbiota interactions include the regulation of SCFA production, bile acid metabolism, and the incretin axis, indicating that the intestinal environment is an important component of the therapeutic response in T2DM.[3,26,27]

3.9. Other Microbial Metabolites of Cardiometabolic Relevance (ImP and TMAO)

In addition to classic microbial metabolites such as SCFAs, secondary bile acids, and BCAAs, other molecules of cardiometabolic significance are attracting increasing research attention. Imidazole propionate (ImP), a bacterial histidine metabolite, has been linked to reduced gut microbiota diversity and unfavorable dietary patterns, suggesting its role as a marker of functional dysbiosis and a potential mediator of insulin resistance development.[8,13,19]

Trimethylamine-N-oxide (TMAO) is produced through bacterial metabolism of choline and carnitine to trimethylamine (TMA) and its subsequent hepatic oxidation by the enzyme FMO3. Increased FMO3 activity may reflect hepatic insulin resistance, linking microbiota metabolites to host metabolic regulation.[6,12,24,25] Elevated TMAO concentrations have been associated with an increased risk of cardiovascular and renal complications and metabolic disorders, highlighting the importance of the gut–liver axis in T2DM pathogenesis.[6,12,24,25,29]

These metabolites fit into the broader concept of the microbiota–metabolism axis, in which bacterial metabolites — such as ImP, indole, and TMAO — can modulate inflammatory pathways, intestinal barrier function, and glycemic regulation, indicating their potential role as biomarkers of disease progression and targets for future therapeutic interventions.[6,12,13,24,25]

3.10. Exercise-Induced Microbiota Remodeling and Insulin Sensitivity

Physical activity represents an important factor modulating gut microbiota and host metabolism. Regular exercise increases microbial diversity and promotes the growth of butyrate-producing bacteria — such as *Faecalibacterium prausnitzii* and *Roseburia* — which is associated with reinforcement of the intestinal barrier and reduction of inflammatory markers.[25,30] Increased SCFA production may improve insulin sensitivity through regulation of lipid and glucose metabolism and by limiting LPS translocation.[6,25] Physically active individuals have also demonstrated higher abundance of *Lactobacillus* and *Bifidobacterium*, suggesting a role of lifestyle factors in shaping the microbiota–metabolism axis.[25,30]

Physical exercise may also reduce circulating levels of LPS and zonulin, thereby decreasing metabolic endotoxemia and intestinal permeability, which contributes to improved insulin signaling.[25,30] Moderate- and high-intensity aerobic training is associated with reduced gut dysbiosis and metabolic changes that may persist for several dozen hours after activity cessation, including improved glycemic control and insulin action.[25] Alterations in the *Firmicutes*/*Bacteroidetes* ratio, increased abundance of *Akkermansia*, and reduced *Proteobacteria* have also been observed, correlating with an anti-inflammatory profile and stabilization of the intestinal barrier.[25,30]

Mechanistically, physical activity enhances SCFA production and increases the expression of tight junction proteins such as ZO-1, strengthening intestinal epithelial integrity and limiting the translocation of inflammatory mediators.[25,30] Concurrently, the expansion of fiber-fermenting bacteria leads to increased production of anti-inflammatory metabolites, supporting immune regulation and improving carbohydrate metabolism in patients with T2DM.[6,25,30]

4. Clinical Evidence Linking Gut Microbiota With T2DM Outcomes

A growing number of clinical studies indicate that changes in gut microbiota composition and function correlate with metabolic parameters in patients with T2DM, including HbA1c levels, insulin resistance, and body weight. Cohort analyses have shown that reduced numbers of butyrate-producing bacteria and increased presence of pro-inflammatory taxa are associated with impaired glycemic control and low-grade inflammation.[1,5,6,18,31] Correlations between the

microbiota profile and metabolic markers such as HOMA-IR and BMI have also been observed, suggesting that microbiological changes may reflect the severity of metabolic disease.[1,6,31]

Clinical studies also confirm that modulation of the incretin axis and bile acid metabolism may be associated with changes in the gut microbiota. Real-world analyses of incretin therapies have demonstrated improved glycemic control, weight loss, and modifications in the gut environment, indicating a possible contribution of the microbiota to the therapeutic response.[1,3] These data support earlier mechanistic observations suggesting that gut bacteria may influence GLP-1 secretion and energy homeostasis regulation through bacterial metabolites and hormonal signaling.[14,19]

Interventional studies have further shown that antidiabetic pharmacotherapy can lead to taxonomic and functional changes in the gut microbiota that correlate with improved metabolic parameters, including reduced postprandial glycemia and decreased inflammation.[3,24,26] These observations suggest that some of the clinical effects of antidiabetic drugs may be mediated by reorganization of the intestinal environment and changes in the profile of bacterial metabolites.[3]

Despite the growing body of clinical data, it should be emphasized that many observations are correlational in nature, and causal relationships between microbiota composition and the course of T2DM remain the subject of ongoing research. Differences in metagenomic analysis methodologies, the impact of concomitant therapies, and population diversity make unambiguous interpretation difficult; nevertheless, the available clinical evidence points to the important role of the microbiota–metabolism axis as a potential therapeutic target in T2DM.[4,14]

5. Microbiota-Targeted Strategies: Diet, Prebiotics, Probiotics, and Nutritional Interventions

Dietary interventions are among the most important factors modulating gut microbiota composition and function in T2DM, affecting both the taxonomic profile of bacteria and the production of metabolites regulating metabolic homeostasis. A high-fat diet promotes dysbiosis by increasing the number of pro-inflammatory taxa and reducing butyrate-producing bacteria such as *Ruminococcus* and *Bifidobacterium*, which correlates with the severity of insulin resistance and inflammation.[12,18,20] In contrast, a high-fiber diet increases the abundance of carbohydrate-fermenting bacteria — including *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* — leading to increased SCFA production and improved glycemic control.[3,12,20,29] SCFAs act through FFAR2 and FFAR3 receptors, activate AMPK-related metabolic pathways, and enhance GLP-1 secretion, integrating gut–metabolic signaling.[1,19] Clinical studies indicate that increased fiber intake may lower HbA1c and improve metabolic parameters, which is associated with increased butyrate production and improved intestinal barrier integrity.[26,29]

Bioactive plant polysaccharides that modulate the gut microbiota are also attracting growing interest. Polygonati rhizoma polysaccharide (PRP) has been shown to increase the number of SCFA-producing bacteria and enhance their synthesis, which translates into strengthened intestinal barrier integrity and regulated inflammatory response.[17] SCFAs act as signaling molecules that supply energy to enterocytes, regulate their differentiation, and stabilize the structure of the intestinal epithelium. In experimental models, PRP inhibited activation of the NF-κB pathway, reducing intestinal mucosal inflammation and improving lipid metabolism, indicating the potential importance of targeted dietary interventions in modulating the microbiota–metabolism axis.[17]

Plant-based and Mediterranean diets have a particularly beneficial effect on the gut microbiota, increasing its diversity and reducing inflammatory markers and oxidative stress.[19,29] The consumption of fermented products — such as yogurt, kefir, and kimchi — promotes microbiome stabilization and improves lipid and glycemic profiles.[3,19] Dietary interventions can also modulate bile acid metabolism: oligofructose supplementation increases the production of SCFAs and secondary bile acids, while whole grains promote the growth of *Bifidobacterium* and *Akkermansia*, which is associated with improved insulin sensitivity.[6,20]

Prebiotics — such as inulin, fructooligosaccharides, and galactooligosaccharides — selectively stimulate the growth of metabolically beneficial bacteria and increase SCFA production, strengthening intestinal barrier integrity and reducing metabolic endotoxemia.[6] Their use is associated with increased abundance of *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, improved glucose tolerance, and a reduction in inflammatory markers.[1,3,5,25] Mechanistically, prebiotics modulate the immune response by increasing levels of anti-inflammatory cytokines and intestinal immunoglobulins while reducing pro-inflammatory mediators.[6,20,22]

Probiotics exert multidirectional metabolic effects, including improved insulin sensitivity, reduced HOMA-IR, and lower fasting blood glucose levels.[3,6,12,15,20,32] The most commonly studied strains belong to the genera *Lactobacillus* and *Bifidobacterium*, and meta-analyses indicate significant reductions in HbA1c following their supplementation.[4] Mechanisms of action include increased abundance of SCFA-producing bacteria, reduced colonization by opportunistic bacteria, and modulation of bile acid metabolism.[28,31,32] Of particular note is *Lactiplantibacillus plantarum*, supplementation of which was associated with improved intestinal barrier integrity, reduced inflammation, and improved metabolic parameters.[15] In clinical trials, 12 weeks of supplementation with selected strains led to reductions in HbA1c and improvements in metabolic markers in individuals with glycemic disorders.[15]

Synbiotic strategies and dietary interventions aimed at increasing SCFA production may further enhance metabolic effects through the synergistic interaction of nutrients and the gut microbiota.[19] Preliminary studies on fecal microbiota transplantation (FMT) suggest improved insulin sensitivity and increased abundance of bacteria such as *Akkermansia muciniphila* and *Roseburia*; however, the lack of standardized protocols and limited long-term data currently hinder routine use of this method.[1,19] The variability of therapeutic response indicates that the effectiveness of microbiota-targeted strategies depends on individual microbial profiles, dietary patterns, and disease stage, highlighting the need for personalized interventions in the treatment of T2DM.[8,19,29]

6. Limitations and Future Directions

Despite a growing number of studies pointing to the important role of gut microbiota in T2DM pathogenesis, current scientific evidence remains burdened by numerous methodological limitations. One of the main challenges is the high heterogeneity of studies, including differences in research designs, population characteristics, methods of microbiome analysis, and dietary and therapeutic interventions used.[4,10,14,33] Many available analyses are based on cross-sectional studies, which make it difficult to determine causal relationships between dysbiosis and the development of insulin resistance. Furthermore, gut microbiota composition is strongly modulated by environmental factors — such as diet, lifestyle, medication use, and geographical origin — which limits the generalizability of results.[33]

Another limitation is the lack of standardization in microbiome analysis methods, including differences in 16S rRNA sequencing, shotgun metagenomics, and the interpretation of functional data. Studies often focus on taxonomic changes, whereas clinical significance may primarily result from differences in the profile of bacterial metabolites such as SCFAs, secondary bile acids, or tryptophan metabolites.[4,14] Moreover, many probiotic and dietary interventions are based on short-term observations, making it difficult to assess the durability of metabolic effects and long-term safety.[19]

High individual variability of the gut microbiota also remains a significant challenge. The response to probiotics, prebiotics, or dietary interventions may be strongly dependent on the patient's baseline microbiological profile, suggesting the need for a personalized approach rather than universal treatment regimens.[4,15] Many studies also point to the difficulty of distinguishing the influence of the microbiota from the effects of pharmacotherapy, especially in the context of drugs such as metformin, which can themselves significantly modulate the intestinal environment.[2,18]

Future research directions focus on the integration of multiomic data — including metagenomics, metabolomics, and proteomics — which may enable more accurate determination of the functional role of the microbiota in glucose metabolism regulation.[23] The use of machine learning models and systems biology approaches may help identify microbial biomarkers predictive of T2DM development and treatment response.[25] Increasing importance is also being attached to longitudinal studies that will allow assessment of dynamic changes in the microbiota over time and their relationship to disease progression.[2,4]

In the future, the development of microbiota-targeted therapeutic strategies may include personalized dietary interventions, the design of next-generation probiotics, and the precise modulation of bile acid metabolism and the incretin axis.[23] However, large, well-designed randomized clinical trials are needed to determine optimal treatment regimens and confirm the clinical significance of microbiota modulation in the treatment of T2DM.[2,4]

7. Conclusions

The gut microbiota plays an important role in the pathogenesis of type 2 diabetes mellitus through its multidirectional effects on host metabolism, immune response regulation, and intestinal barrier integrity. Intestinal dysbiosis is associated with reduced SCFA production, increased metabolic endotoxemia, and disturbances in the incretin axis and bile acid metabolism, which promote the development of insulin resistance and chronic low-grade inflammation.[1,3,4,6] The integration of microbial and metabolic signals highlights the importance of the gut–metabolism axis as a key element in the regulation of glucose homeostasis.

Available data indicate that interventions targeting the microbiota — including a high-fiber diet, prebiotics, probiotics, and lifestyle modifications — may exert a beneficial effect on metabolic parameters and the inflammatory profile in patients with T2DM. Antidiabetic pharmacotherapy, including metformin and α-glucosidase inhibitors, additionally affects the gut microbiota, suggesting that some therapeutic effects may result from modulation of the gut environment.[3,8,15,26] Despite promising results, the effectiveness of these strategies remains variable, underscoring the importance of individual differences in microbiota composition and the need for personalized therapy.

Current research limitations — including methodological heterogeneity, lack of standardization in microbiome analyses, and insufficient long-term clinical studies — make it difficult to clearly

define the causal role of the microbiota in T2DM.[2,4] Future research should focus on multiomic approaches, the identification of microbial biomarkers, and the evaluation of personalized dietary interventions and microbiota-targeted therapies in large randomized clinical trials.[10,22,23] Understanding the complex interactions between the microbiota, bacterial metabolites, and the immunometabolic system may ultimately enable the development of more precise therapeutic strategies for the treatment of type 2 diabetes mellitus.

Disclosure

Conceptualization	K. Szewczyk
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In preparing this work, the authors used ChatGPT (GPT-4o, OpenAI, accessed March 2025) for the purpose of language editing and grammar correction only. After using this tool, the authors reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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