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REVIEW ARTICLE

Gut microbiome: influence on the clinical and nutritional treatment of type 2 diabetes mellitus

Microbioma intestinal: influencia en el tratamiento clínico y nutricional de la diabetes mellitus tipo 2

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Abstract Type 2 diabetes mellitus (T2DM) is a complex metabolic disease in whose pathophysiology the gut microbiota plays a key role, influencing systemic inflammation, insulin sensitivity, and glycemic homeostasis, thus conditioning the response to clinical and dietary treatments. The objective of this study was to analyze the influence of the gut microbiota on the pharmacological and dietary treatment of T2DM based on current scientific evidence. This systematic review, conducted according to the 2020 PRISMA guidelines, analyzed 27 studies published between 2014 and 2024, identifying that gut dysbiosis, characterized by a reduction in beneficial bacteria and an increase in pro-inflammatory species, is associated with poorer metabolic control in patients with T2DM. The most effective interventions included probiotics, prebiotics, synbiotics, high-fiber diets, and drugs with microbiota-modulating effects, such as metformin and SGLT2 inhibitors. Evidence suggests that modulation of the gut microbiota represents a promising complementary therapeutic strategy; however, methodological limitations still exist, highlighting the need for more robust clinical studies to support its widespread application.

Keywords type 2 diabetes mellitus, gut microbiome, prebiotics, probiotics, emerging therapies.

Resumen La diabetes mellitus tipo 2 (DM2) es una enfermedad metabólica compleja en cuya fisiopatología interviene el microbioma intestinal, el cual influye en la inflamación sistémica, la sensibilidad a la insulina y la homeostasis glucémica, condicionando la respuesta a los tratamientos clínicos y dietarios. El objetivo fue analizar la influencia del microbioma intestinal en el tratamiento farmacológico y dietario de la DM2 a partir de la evidencia científica actual. Esta revisión sistemática, realizada bajo las directrices PRISMA 2020, analizó 27 estudios publicados entre 2014 y 2024, identificando que la disbiosis intestinal, caracterizada por la disminución de bacterias beneficiosas y el aumento de especies proinflamatorias, se asocia con un peor control metabólico en pacientes con DM2. Las intervenciones más eficaces incluyeron probióticos, prebióticos, simbióticos, dietas ricas en fibra y fármacos con efecto modulador del microbioma, como la metformina y los inhibidores de SGLT2. En conjunto, la evidencia sugiere que la modulación del microbioma intestinal constituye una estrategia terapéutica complementaria prometedora, aunque persisten limitaciones metodológicas que requieren estudios clínicos más robustos para su aplicación generalizada.

Palabras clave diabetes mellitus tipo 2, microbioma intestinal, prebióticos, probióticos, terapias emergentes.

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PUBLIS EDITORIAL

Introduction

Type 2 diabetes mellitus (T2DM) is recognized as a chronic metabolic syndrome characterized by persistent hyperglycemia, resulting from insulin resistance and insufficient insulin secretion. Its prevalence and the burden of microvascular and macrovascular complications make it one of the major public health problems worldwide (Sikalidis & Maykish, 2020). Traditionally, its management has focused on agricultural treatment, standardized dietary intervention, and the promotion of physical activity; however, recent evidence demonstrates that other biological factors, such as the composition of the gut microbiome, play a relevant role in metabolic regulation and the progression of confinement (Cunningham et al., 2021).

The gut microbiome, understood as the collection of microorganisms, genes, and metabolites that inhabit the gastrointestinal tract, has been identified as a dynamic ecosystem with essential digestive, immunological, and endocrine functions. Its alteration, associated with dysbiosis, is linked to the pathophysiology of metabolic disorders, including T2DM (Baars et al., 2024). Several studies have shown that changes in microbial diversity and composition influence systemic inflammation, insulin sensitivity, and glucose homeostasis, thus affecting both the progression of diabetes and the response to clinical and dietary interventions (Sharma et al., 2022).

Advances in technologies such as next-generation sequencing, metagenomics, and metabolomics allow for a more precise characterization of the relationship between the gut microbiota and T2DM (Fu et al., 2023). Based on these findings, we identified microorganisms associated with a favorable metabolic profile, such as Akkermansia. muciniphila and Faecalibacterium prausnitzii, as well as pro-inflammatory bacteria predominant in patients with poor glucose control (Adeshirlarijaney & Gewirtz, 2020). At the same time, we can resort to therapeutic strategies aimed at modulating the microbiome, including personalized diets enriched with fermentable fiber, prebiotics, and probiotics, to optimize fatty acid production and reduce systemic inflammation (Chiou et al., 20121; Iatcu et al., 2024).

Gallardo and García (2024) emphasized that ultra-processed foods or junk food, characterized by high energy density, low nutritional value, and broad social acceptance, negatively affect diet quality and risk perception, thereby reinforcing the need for comprehensive therapeutic approaches. Within this framework, the study of the gut microbiome emerges as a central element for understanding the interactions between diet, metabolism, and clinical response, offering new perspectives for the clinical and nutritional management of T2DM.

Although traditional dietary interventions have proven effective in glucose control and cardiovascular risk reduction, their standardized characteristics do not account for interindividual microbial heterogeneity (Sharma et al., 2022). In contrast, microbiome-based personalized diets improve therapy efficacy by tailoring the diet to the patient's microbial profile, but their clinical application is hampered by limitations related to cost, standardization, and technological availability (Qin et al., 2025; Murugesan et al., 2025). In this context, it is relevant to systematize the available scientific evidence to understand the role of the gut microbiome in T2DM and compare traditional dietary supplements with those based on microbial personalization. Therefore, the objective of this research was to analyze the influence of the gut microbiome on the pharmaceutical and dietary treatment of T2DM based on current scientific evidence.

Methodology

The systematic review follows the PRISMA 2020 guidelines, aiming to ensure transparency, reproducibility, and methodological rigor in the identification, selection, analysis, and synthesis of scientific evidence related to the influence of the gut microbiome on the clinical and nutritional management of T2DM (Page et al., 2021). The research requirement is formulated using the PICO model, defining how patients with T2DM are treated, how interventions are implemented in clinical therapies or foods aimed at modulating the gut microbiome, how probiotics, prebiotics, functional diets, or fecal microbiota transplantation are used, compared to standard treatments or placebo, and considering changes in glucose parameters, inflammation, gut microbial composition, and associated metabolic complications (Methley et al., 2014).

Inclusion criteria include original studies and systematic reviews published between 2014 and 2024, in English or Spanish, that analyze the relationship between the gut microbiome and the treatment of T2DM in humans and animal models. Opinion pieces, editorials, letters to the editor, case reports, studies focused exclusively on type 1 diabetes mellitus and other metabolic disorders, and studies published without full-text access or with insufficient information for analysis are excluded. The literature search will be conducted between April 1 and 10, 2025, using specialized databases such as PubMed, Scopus, and Web of Science. Science, Embase, and Google Scholar, using a strategy that combines MeSH terms and keywords using booleans, adapted to the specific criteria of each database and applied with filters by language, document type, and time range (2014-2024).

The study screening and selection process is managed by the Zotero bibliographic management system, where duplicate records are initially identified and removed. Subsequently, studies are selected in consecutive stages: a first review of titles and abstracts and a second evaluation of the full text of

the preselected articles, according to established criteria. A matrix is used for data extraction and analysis, which includes information on methodological characteristics, types of intervention, clinical and metabolic variables assessed, main results, and limitations. The results are presented narratively, organized according to the types of intervention and the observed metabolic and clinical effects, and are based on the PRISMA 2020 guidelines, including a flowchart of the selection process and summary tables of the analyzed evidence.

Results and discussion

Search according to the PRISMA 2020 flowchart

The search strategy was conducted in five academic databases (Figure 1). Initially, a total of 5830 records were identified, distributed as follows: 1200 in PubMed, 1050 in Scopus, 980 in Web of Science, 1100 in Embase, and 1500 in Google Scholar. After removing duplicates, 4500 unique records remained for evaluation.

In the selection stage, the titles and abstracts of the 4500 records were examined, excluding 3200 that did not meet the theoretical criteria of interest. Subsequently, in the eligibility stage, 1300 full-text message reports were analyzed, of which 1273 were eliminated for various reasons: 392 for irrelevant study design, 312 for including populations unrelated to T2DM, 221 for gut microbiome data, and 348 for other reasons (such as insufficient methodology or irrelevant results).

Finally, 27 studies will be included in the systematic review to meet the inclusion criteria. To ensure transparency and methodological rigor in the selection of scientific evidence, this procedure adheres to the PRISMA 2020 guidelines.

Effects of the gut microbiome on the digestive, endocrine, immune, and nervous systems in relation to T2DM

Table 1 compiles 27 studies examining the connection between the gut microbiota and T2DM, including book chapters, clinical trials, experimental studies, and systematic reviews. These works address therapeutic interventions, pathophysiological mechanisms, and limitations in the research. Systematic reviews represent 65% of the studies and focus on mechanisms such as dysbiosis, inflammation, and the incidence of bacterial metabolites, as well as dietary, probiotic, and pharmaceutical therapies. Clinical trials (15%) are primarily pilot studies with small sample sizes (≤ 60 patients). As noted by Palacios et al. (2017), 10% of these studies use murine models of obesity and T2DM to evaluate interventions such as symbiotic or pharmaceutical therapies. The remaining 10% consists of book chapters with theoreti-

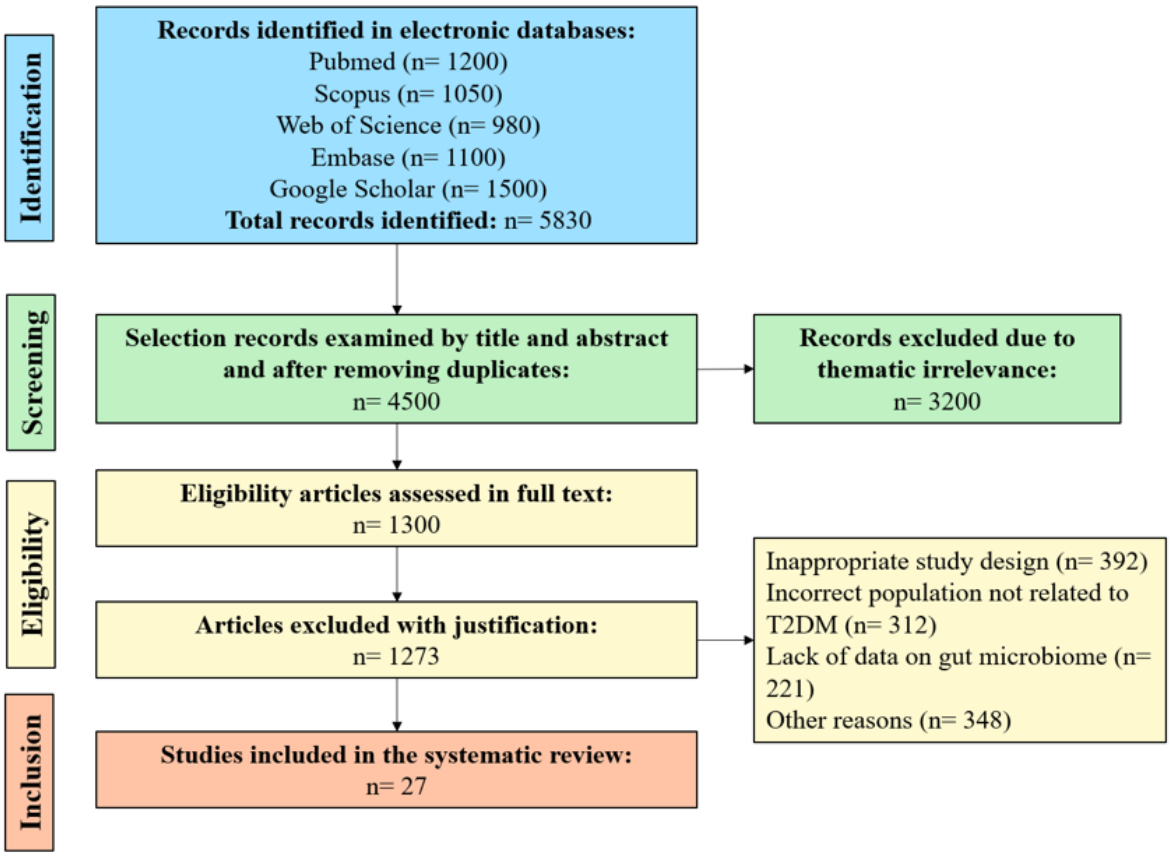

Figure 1. PRISMA flowchart to represent the item selection process.

Table 1. Synthesis of evidence from the T2DM microbiome

Reference	Type of study	Sample characteristics	Type of intervention and duration	Microbiome analysis method	Clinical and metabolic variables	Results major	Conclusions	Limitations
Dzięgielewska-Gęsiak et al. (2022)	Cohort comparative	2 T2DM groups (Met vs Met+Ins), 5-10 years of training	Pharmacological (Met against Met+Ins) / 5-10 years	New sequencing generation	Glucose, HbA1c, lipids, and kidney function	No differences in the microbiome, Met+Ins for glucose control	Insulin can delay late complications	Sample small
Stepanova (2024)	Revision	N/A	Review of SGLT2 inhibitors	N/A	Glucose, weight, blood pressure, microbiota	Possible modulating effect of SGLT2i on the microbiota	Potential use in personalized treatment	Lack of evidence clinic straight
Palacios et al. (2017)	Rehearsal clinic pilot	60 adults with recent prediabetes/ T2DM	Multispecies probiotic vs placebo / 12 weeks	Metagenomics + fecal metabolomics	Blood glucose, lipid profile, inflammation, and intestinal permeability.	Improvement of glucose and metabolic parameters with probiotics	Probiotics can prevent/control T2DM	Study pilot, monitoring short-term
Star and others (2024)	Comparative clinical trial	Prediabetics on metformin	Metformin vs Metformin + Linagliptin	16S rRNA in feces	Glucose, inflammation, metabolic markers	Metformin and linagliptin modify bacterial composition and improve their markers	Pharmaceutical intervention can modulate the gut microbiota	Design is limited by maximum size and a lack of long-term instructions.
Baars et al. (2024)	Revision	N/A	Diet and medications	Study review	Glucose, HbA1c, microbiota, SCFA, LPS	Modulation of the microbiota impacts immunity and metabolism.	Personalized treatment based on the microbiome	High heterogeneity and lack of methodological standardization
Fu et al. (2023)	Revision	N/A	Probiotics, prebiotics, pharmaceuticals	Metabolomics microbial	SCFA, LPS, TMAO, bile acids	The microbiota regulates key metabolites in T2DM	Therapeutic potential of bacterial metabolites	Important evidence in animal models
Cunningham et al. (2021)	Revision	N/A	Diet, prebiotics, synbiotics	Literature review	Glucose, insulin, and intestinal permeability	Causal relationship between dysbiosis and T2DM	Prediction and therapy of microbiota factors	Studies heterogeneous

Reference	Type of study	Sample characteristics	Type of intervention and duration	Microbiome analysis method	Clinical and metabolic variables	Results major	Conclusions	Limitations
Sharma et al. (2022)	Revision	N/A	Bioactive nutritional	Studies previous	Glucose, inflammation, and insulin resistance	Bioactives restore eubiosis and improve metabolism	Use of polyphenols and prebiotics	Evidence clinic limited
Chiou et al. (2021)	Experimental in animals	We are obese because of high-fat diets	Symbiotic with Adlay + probiotics / 12 weeks	Fecal metagenomics	Glucose, insulin, lipid profile, IL-6	Increased obesity, inflammation, and microbiota	Effective symbiosis in the mouse model	Not applicable to humans
Majait et al. (2023)	Revision	N/A	Probiotics, antibiotics, fecal transplant	Study review	Acids biliary microbiota	Bile relationship Key acids in T2DM	Biliary modulation as a therapeutic strategy	High heterogeneity in studies
Iatcu and others (2024)	Revision	N/A	Prebiotics (inulin, FOS, GOS, RS)	Revision	Glucose, insulin, SCFAs	Prebiotics improve the microbial and glucose profile	Prebiotics are useful in the control of T2DM	Further evidence clinic required
Sato et al. (2017)	Revision	N/A	Diet, microbiota	Revision	SCFA, LPS, inflammation	Dysbiosis alters fatty acids, permeability, and glucose.	Normalizing the microbiota to prevent T2DM	Differences in ethnicities/ methods
Pizarro and others (2024)	Chapter book	N/A	Diet (hydrated charcoal)	Revision	Firmicutes/ Bacteroidetes, intestinal permeability	Carbohydrates, Modular composition microbial	Diet as a cornerstone in microbiota management	Lack of controlled trials
Murugesan and others (2025)	Revision	N/A	Diet, nutraceuticals, synbiotics	Revision	LPS, inflammation, glucose	The disease induces systemic inflammation and T2DM	Restoring the microbiota reduces inflammation and improves metabolism	Studies are preliminary in humans

Reference	Type of study	Sample characteristics	Type of intervention and duration	Microbiome analysis method	Clinical and metabolic variables	Results major	Conclusions	Limitations
Sharma et al. (2024)	Chapter book/ review	N/A	Symbiotics	Revision	Glucose, insulin	Synbiotics improve metabolism and bacterial profile	Alternative promising in T2DM	Clinical evidence in humans is lacking
Qin et al. (2025)	Revision	N/A	Probiotics, FMT, natural products	Revision	HbA1c, insulin, SCFAs	Probiotics and FMT modulate the microbiota and glucose parameters	Potential therapeutic therapy confirmed in preclinical models	Move on to robust clinical studies
Negm (2023)	Chapter book	N/A	Microbiota modulation	Revision	Inflammation, permeability, glucose	The microbiota influences T2DM through inflammation and endotoxemia	Microbiota as a therapeutic target	Evidence indirect
Ng et al. (2024)	Revision	N/A	Medicine traditional Porcelain	Revision	Glucose, insulin, and profile bacterial	Medicinal plants modulate the microbiota and reduce insulin resistance	Integration of traditional medicine in the management of T2DM	Studies in humans are limited
Adeshirlarijaney and Gewirtz (2020)	Revision	N/A	Diet, prebiotics, fecal transplant	Revision	Glucose, inflammation	The disease promotes T2DM during chronic inflammation	Microbial modulation is useful in prevention	Lack of consensus methodological
Sikalidis and Maykish (2020)	Revision	N/A	Diet, antibiotics	Revision	Glucose resistance has insulin	Dysbiosis alters metabolism and immunity in T2DM	Microbial modulation is key in prevention	Lack of trial clinics
Oluwaloni et al. (2023)	Revision	N/A	Drugs, diet, prebiotics	Revision	Glucose, HbA1c, microbiota	Dysbiosis associated with T2DM; improved regulatory parameters	Necessary to validate interventions dietary	Scarcity of studies longitudinal

Reference	Type of study	Sample characteristics	Type of intervention and duration	Microbiome analysis method	Clinical and metabolic variables	Results major	Conclusions	Limitations
Sivadas et al. (2025)	Revision	N/A	Probiotics, FMT	Revision	Glucose, insulin, SCFAs	Probiotherapy and fecal transplantation improved glucose control	Potential clinic important	Lack of evidence is solid
Ebrahimi et al. (2025)	Meta-analysis and multivariate analysis	946 samples (9 studies)	Without application (comparison between patients with T2DM and controls)	16S rRNA sequencing + data mining + LEfSe	N/A (focus on taxonomy)	Twenty-three genes and four cell lines were identified as microbial markers of T2DM (e.g., increased *Prevotella*, reduced *Bacteroides*).	Computational analysis allows the identification of robust microbial biomarkers in T2DM	Lack of direct clinical input, purely a bioinformatics approach
Martínez-Carrillo et al. (2024)	Observatory study	Patients with T2DM (n=40)	Comparison of carbohydrate consumption	Massive sequencing of 16S rRNA	Glucose, HbA1c, bacterial diversity	Changes in microbial diversity according to the type and amount of carbohydrates	A high-carbohydrate diet significantly affects the microbiota in T2DM	There are no details on durability or control of other variables.
Martínez-Carrillo et al. (2024)	Multicenter cohort study	8,117 metagenomes from the US, China, Europe, and Israel	Observational, cross-sectional	Metagenomic shotgun	Glucose, HbA1c, bacterial metabolism	Functional and taxonomic alterations associated with T2DM; involvement of specific species such as *Enterocloster bolteae*	Strain analysis offers potential mechanisms involved in T2DM	Completion of the interpretation for inter-cohort variability

Reference	Type of study	Sample characteristics	Type of intervention and duration	Microbiome analysis method	Clinical and metabolic variables	Results major	Conclusions	Limitations
Razavi et al. (2024)	Case-control studies	36 participants (18 with T2DM and 18 healthy controls)	There was no intervention; it was a cross-sectional observational study.	Real-time PCR (qPCR) on DNA extracted from feces	Do not analyze specific clinical/ metabolic variables	Greater abundance of *Bacteroides* and *Bacteroidetes* in T2DM; greater presence of *Firmicutes* and *Actinobacteria* in controls; no differences in other taxa	T2DM is associated with intestinal dysbiosis; the use of probiotics/ prebiotics may help control the blockage.	Small sample size; cross-sectional design; spurious clinical and metabolic data; limited microbiome analysis
Valencia-Castillo et al. (2024)	Cohort study	5 mother-infant pairs with and without GDM (Colombia)	Cross-sectional observation	16S V3–V4 Sequencing + SILVA	Intestinal microbiota and breast milk	Maternal dysbiosis associated with gestational diabetes, reduction of *Bifidobacterium* and *Sutterella*	Gestational diabetes affects the microbial composition of both the mother and the child	Small sample size, results not generalizable

cal texts lacking original data.

Among the interventions evaluated, probiotics and synbiotics (e.g., Lactobacillus, Bifidobacterium) were shown to improve glucose levels, reduce inflammation, and increase microbial diversity, according to Sharma et al. (2022) and Palacios et al. (2017). Prebiotics (inulin, FOS, GOS) increase the production of short-chain fatty acids (SCFAs), such as butyrate, and reduce LPS levels. Metformin and SGLT2 inhibitors modulate the gut microbiota (increasing Akkermansia), and metformin can induce resistance. High-fiber, low-fat diets restore the Firmicutes/Bacteroidetes balance, although fecal-oral transmission (FMT) benefits the most in preclinical models.

16S rRNA sequencing (70% of clinical studies) and metagenic/metabolomic techniques to identify bacterial species and metabolites such as SCFAs, TMAO, and LPS. Clinical variables assessed include blood glucose, HbA1c, insulin resistance, lipid profile, and inflammatory markers (IL-6, TNF-α, LPS). Regarding the gut microbiota, we analyzed the abundance of Akkermansia, Bifidobacterium, and the Firmicutes/Bacteroidetes ratio.

The results confirm that dysbiosis in T2DM is characterized by reduced microbial diversity, an increase in Firmicutes, and a decrease in Bacteroidetes (Cunningham et al., 2021). The mechanisms involved in the production of short-chain fatty acids (SCFAs), which improve insulin sensitivity, and the pro-inflammatory role of lipoproteins (LPS) are described. The most promising interventions are based on probiotics and high-fiber diets, which restore eubiosis and improve glycemic parameters. However, limitations remain, such as the small number of studies (only 20% of clinical trials include more than 100 participants), the lack of standardized methods, and the predominance of preclinical evidence (30% in animals). Furthermore, probiotic trials require short periods (≤12 weeks).

Advances in the analysis of the gut microbiome and its implication in T2DM

Emerging technologies have revolutionized the study of the gut microbiome in T2DM, incorporating next-generation sequencing (NGS), metagenomics, metabolomics, and multi-omics pathways. These tools allow for the characterization of taxonomic composition, the identification of functional signatures, and the correlation of microbial profiles with glucose control and therapies employed (Dzięgielewska-Gęsiak et al., 2022; Valencia-Castillo et al., 2025). As a result, metabolism has been shown to be key for bacterial metabolites, such as medium-chain fatty acids (SCFAs), lipopolysaccharides, and trimester N-oxidase, including inflammation, insulin resistance, and intestinal barrier dysfunction (Fu et al., 2023). The integration of metagenic, transcriptomic, and metabolomic data has broadened our understanding of the immune mechanisms involved in T2DM and has provided insights for their application in personalized medicine (Baars et al., 2024). However, despite the predominance of in silico infusions, anaerobic culture of specific bacteria remains essential to validate microbial functions and study their direct impact on metabolism and systemic inflammation (Pizarro et al., 2024).

Regarding microbial composition, evidence indicates that patients with T2DM exhibit a significant decrease in glucose-producing bacteria, such as Roseburia and Faecalibacterium, which are associated with impaired carbohydrate metabolism and increased insulin resistance (Iatcu et al., 2024). Simultaneously, we have reported an increase in pro-inflammatory bacteria, such as Ruminococcus and Prevotella, along with a reduction in Akkermansia, contributing to the microbial imbalance and inflammatory state characteristic of the disease (Oluwaloni et al., 2023). Some studies suggest that these changes may constitute microbiota biomarkers of poor glycemic control, and they observe specific profiles associated with metabolic dysfunction in patients with T2DM (Baars et al., 2024).

Microbiome-based clinical interventions show very promising results. The use of prebiotics, probiotics, and synbiotics promotes the proliferation of beneficial short-chain fatty acid (SCFA)-producing bacteria, improves insulin sensitivity, and reduces intestinal inflammation (Iatcu et al., 2024). Fecal microbiota transplantation (FMT) is emerging as an innovative strategy to restore microbial balance, with preliminary results suggesting improvements in glucose metabolism, inflammation, and lipid profile in experimental models of T2DM, although its clinical application requires further evidence (Singh & Bhadauriya, 2025). Similarly, personalized nutrition based on the gut microbial profile is presented as an attractive alternative to optimize glucose control and reduce the risk of glucose entrapment progression, although controlled clinical trials are needed to confirm its efficacy (Meloncelli et al., 2023).

Microbial metabolites are fundamental to glucose homeostasis. Short-chain fatty acids (SCFAs), especially butyrate, propionate, and acetate, influence insulin sensitivity, intestinal barrier integrity, and the regulation of energy metabolism by modulating inflammation, the secretion of intestinal hormones such as GLP-1 and PYY, and fatty acid oxidation (Cunningham et al., 2021; Chiou et al., 2021; Sharma et al., 2022; Fu et al., 2023; Baars et al., 2024). Thus, triplet-derived metabolites and bile acids modified by the microbiota influence pancreatic β-cell function, immune regulation, and hepatic gluconeogenesis through the activation of receptors such as AhR, FXR, and TGR5 (Majait et al., 2023; Baars et al., 2024; Qin et al., 2025; Murugesan et al., 2025). Eviden-

ce suggests that modulating these metabolites through dietary, probiotic, and pharmacological interventions, such as metformin use, represents a promising therapeutic approach, reinforcing the relevance of the gut-microbiota-metabolism pathway in the development of innovative and personalized strategies for the comprehensive management of T2DM (Adeshirlarijaney & Gewirtz, 2020; Szymczak-Pajor et al., 2025).

Mechanisms of influence of the intestinal microbiome on T2DM

Intestinal dysbiosis is recognized as a central component in the pathology of T2DM, characterized by a reduction in microbial diversity, the predominance of pro-inflammatory bacteria, and a reduction in beneficial species that produce short-chain fatty acids (SCFAs), such as Faecalibacterium. prausnitzii and Roseburia spp. (Iatcu et al., 2024; Szymczak-Pajor et al., 2025). This microbial imbalance promotes a pro-inflammatory intestinal infection that compromises the integrity of the epithelial barrier and facilitates the translocation of bacterial endotoxins, particularly lipopolysaccharides (LPS), affecting the systemic circulation. Activation of Toll-like receptors, primarily TLR4, triggers a low-grade inflammatory response mediated by pro-inflammatory molecules such as TNF-α, IL-6, and IL-1β, directly contributing to reduced insulin resistance and the progression of T2DM (Sato et al., 2017; Adeshirlarijaney & Gewirtz, 2020). Furthermore, other metabolites derived from dysbiosis, including some secondary bile acids and protein fermentation products, modulate inflammation and metabolism in glucose control, solidifying dysbiosis-inflammation as a relevant therapeutic target (Sharma et al., 2022; Baars et al., 2024).

Microbial metabolites, especially short-chain fatty acids (SCFAs) derived from the fermentation of non-digestible dietary fiber, are key to metabolic regulation and glucose homeostasis. Acetate, propionate, and butyrate exert beneficial effects on insulin sensitivity, intestinal barrier function, and resistance to inflammation (Iatcu et al., 2024; Ng et al., 2024). However, they are produced by bacteria such as Faecalibacterium. prausnitzii and Roseburia Scleroderma spp., constitute an essential energy source for colonocytes and promote the expression of intercellular junction proteins, reduce endotoxin translocation, and decrease metabolic inflammation (Sato et al., 2017; Szymczak-Pajor et al., 2025). Therefore, propionate and acetate activate G protein-coupled receptors (GPR41 and GPR43), which modulate the secretion of incretin hormones such as GLP-1 and PYY, promoting post-prandial glucose control and appetite regulation (Baars et al., 2024). Additionally, SCFAs have epigenetic effects through the inhibition of histone deacetylases, regulated genes involved in inflammation and energy metabolism (Sharma et al., 2022). In patients with T2DM, the increased production of these metabolites is associated with metabolic dysfunction and microbial imbalance (Oluwaloni et al., 2023), which negates their relevance as therapeutic drugs (Qin et al., 2025).

Bile acid metabolism represents another key mechanism through which the gut microbiota influences metabolic homeostasis in T2DM. Primary bile acids, synthesized in the liver, are transformed into secondary bile acids by intestinal bacterial enzymes, which modify their profile and their ability to activate metabolic receptors such as FXR and TGR5 (Negm, 2023; Baars et al., 2024). Activation of these receptors regulates essential processes such as hepatic gluconeogenesis, lipid metabolism, insulin sensitivity, and GLP-1 secretion (Zhang, Zhang et al., 2024). In patients with T2DM, alterations in the gut microbiota are associated with unfavorable bile acid profiles, resulting in insulin resistance and lipidemia. However, interventions that modulate the microbiome, such as prebiotics and probiotics, have the capacity to restore beneficial bile acid profiles and improve glucose parameters (Ng et al. 2024; Qin et al., 2025). Together, we consolidate the microbiota-bile acid-metabolic receptor relationship as a fundamental component in the pathology and therapeutic approach to T2DM (Negm, 2023).

Clinical treatment of T2DM based on modulation of the gut microbiome

Figure 2 summarizes the role of the gut microbiome in the pathology of T2DM and the proposed intervention strategies. Under conditions of intestinal dysbiosis, an increase in lipopolysaccharides (LPS) and a reduction in short-chain fatty acids (SCFAs) are observed, which contribute to the stability of a state of systemic inflammation and the loss of insulin resistance (Fu et al., 2023; Baars et al., 2024). This phenomenon has been documented in both T2DM and gestational diabetes (GDM), including the reduction of propionate and, among other things, the activation of inflammatory cells and the polarization of macrophages caused by pro-inflammatory M1 cells (Baars et al., 2024).

As therapeutic strategies, we propose interventions aimed at modulating the gut microbiota: the use of probiotics increases microbial diversity and promotes immune regulation, stimulating the proliferation of beneficial bacteria and the production of SCFAs (Sharma et al., 2024). Therefore, high-fiber diets stimulate bacterial fermentation and increase bacterial concentrations of SCFAs, a short-chain fatty acid with recognized anti-inflammatory and insulin-sensitizing properties (Iatcu et al., 2024). Similarly, some antidiabetic medications, such as metformin and SGLT2 inhibitors, alter the composition of the gut microbiome and the number of SCFA-producing bacteria. Depending on the patient's initial microbial profile and clinical context, these changes can have different metabolic effects (Dzięgielewska-Gęsiak et

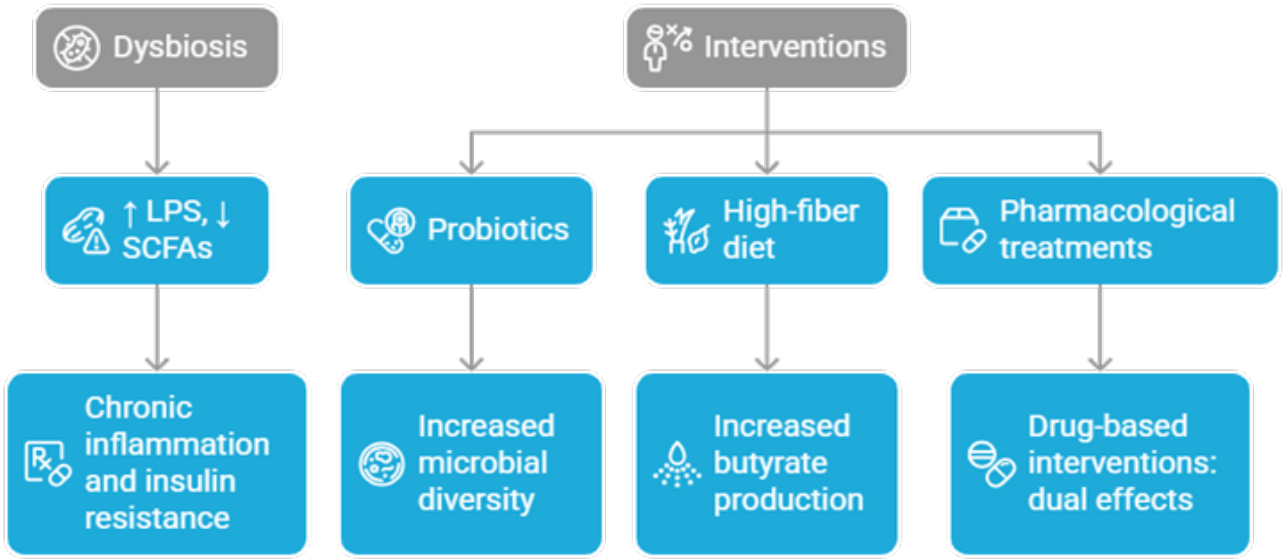

Figure 2. Relationship between the gut microbiome, dysbiosis, and interventions in T2DM.

al., 2022; Stepanova, 2024).

Personalized treatments based on individual microbial profiles, longitudinal studies to evaluate the effects of long-term interventions, and the need for robust clinical trials to validate dosage and, specifically, address the main shortcomings found are all crucial. While promising treatments exist and the gut microbiota plays an important role in T2DM, their immediate clinical application is limited by the mechanisms suggested by the gut microbiota that affect brain and metabolic function, as shown in Figure 3. This figure also illustrates how the various components of the microbiota can affect metabolism and the central nervous system. The mechanisms described are based on studies suggesting different ways in which the gut microbiota interacts with the brain and metabolic system, which may have important implications for brain and metabolic health.

The mechanisms proposed by the gut microbiota for modulating brain and metabolic function involve several key processes that connect gut health with neurological and metabolic well-being. One of the best-known mechanisms is the gut-brain axis, which refers to the restructuring of the gut microbiota to enhance metabolites related to cognitive function. It is suggested that a balanced microbiota promotes the production of beneficial metabolites that have a positive impact on cognition; therefore, maintaining a healthy microbial balance is recommended to optimize brain function (Davari et al., 2013; Pang et al., 2020; Du et al., 2024; Song et al., 2024).

Another important mechanism is inflammation and immunity, which involves reducing pro-inflammatory factors and maintaining the integrity of the blood-brain barrier (BBB). A healthy gut microbiota can help reduce systemic inflammation and protect the BBB, preventing neurological disorders such as Alzheimer's and Parkinson's. Improved immunity and BBB protection are essential for brain health (Lee et al., 2023; Li et al., 2024; Meroni et al., 2025; Bi et al., 2025).

Reducing oxidative stress is another key mechanism, as the gut microbiota influences the increase of antioxidant factors and the reduction of oxidative stress. Preventing cell damage and promoting overall brain health is vital, since oxidative esters are a major cause of various neurodegenerative diseases (Davari et al., 2013; Pang et al., 2020; Lee et al., 2023).

Furthermore, the metabolic regulation of the gut microbiota is essential for controlling glucose homeostasis and improving lipid metabolism, which contributes to the prevention of metabolic disorders such as T2DM. Maintaining a microbiota that promotes efficient metabolism is fundamental for controlling body weight and preventing metabolic changes (Qu et al., 2024; Li et al., 2024).

Neurotransmitter modulation is another interesting mechanism, as the gut microbiota has a direct impact on the levels of serotonin, dopamine, and GABA-key neurotransmitters related to the regulation of an animal's state, response, and cognitive function. This mechanism suggests that the gut microbiota could be used as a therapeutic approach for disorders associated with dysregulated neurotransmitters, such as depression and anxiety (Song et al., 2024).

In short, synaptic plasticity and neurogenesis describe how the microbiota enhances synaptic transmission and stimulates the expression of brain-derived neurotrophic factor (BDNF), which is essential for brain plasticity and neurogenesis. These processes are fundamental for learning, memory, and neuronal regeneration, which explains the importance of the microbiota for maintaining brain health (Pang et

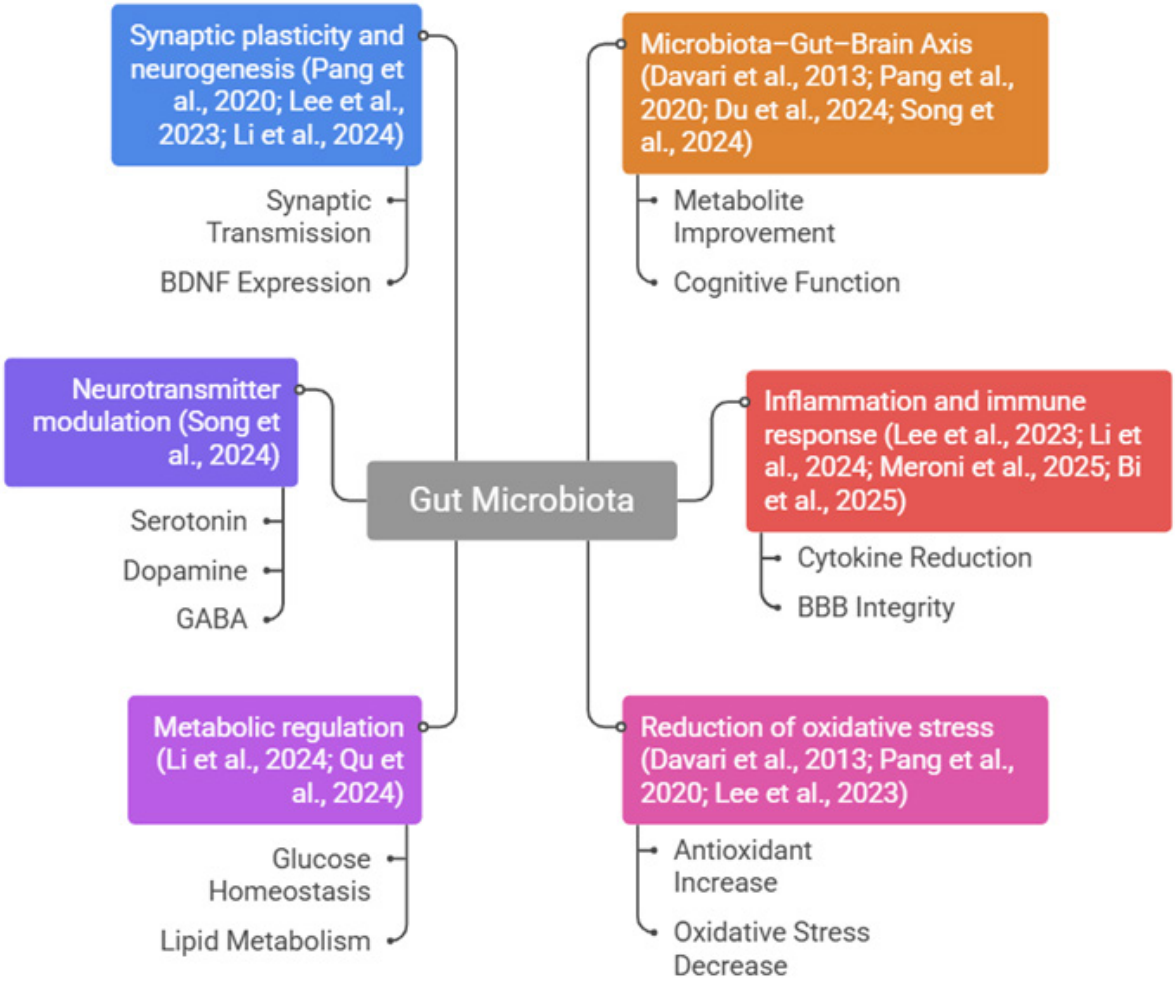

Figure 3. Mechanisms underlying the gut microbiota in the modulation of brain and metabolic function.

al., 2020; Lee et al., 2023; Li et al., 2024).

These mechanisms reflect the growing interest in the connection between the gut microbiota and various brain and metabolic functions. The influence of the microbiota on brain and metabolic function offers new perspectives for the treatment of neurodegenerative diseases, metabolic disorders, and problems related to emotional and cognitive balance. Therefore, manipulating the gut microbiota may be a promising therapeutic strategy for improving brain and metabolic health.

Figure 4 summarizes the main therapeutic applications of modular gut microbiota in patients with T2DM, presenting representative examples and their metabolic and microbiological effects. Interventions include probiotics and synbiotics, such as *Lactobacillus* and *Bifidobacterium*, which improve glucose levels, reduce inflammation, and increase microbial diversity (Palacios et al., 2017; Sharma et al., 2022).

Pharmacological interventions

The pharmacological treatment of T2DM has evolved with a comprehensive approach to glucose control, which is not limited solely to improving metabolic disorders, reducing cardiovascular disease, and modulating underlying pathophysiological mechanisms, such as chronic inflammation and gut dysbiosis. In this context, recent evidence suggests that some antidiabetic drugs have effective modulatory effects on the gut microbiota, which may contribute significantly to their metabolic and extraglycemic benefits (Negm, 2023; Baars et al., 2024; Qin et al., 2025).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, are becoming established as an effective therapeutic class for T2DM due to their hypoglycemic action, as well as their demonstrated cardiovascular and renal effects (Zhang et al., 2024). Recent studies indicate that these drugs can induce favorable changes in the composition and function of the gut microbiota, likely as a consequence of modifications to energy metabolism and substrate availability in the intestinal lumen. Several changes include an increase in short-chain fatty acid (SCFA)-producing bacteria and a reduction in pro-inflammatory microorganisms, which can be explained, at least in

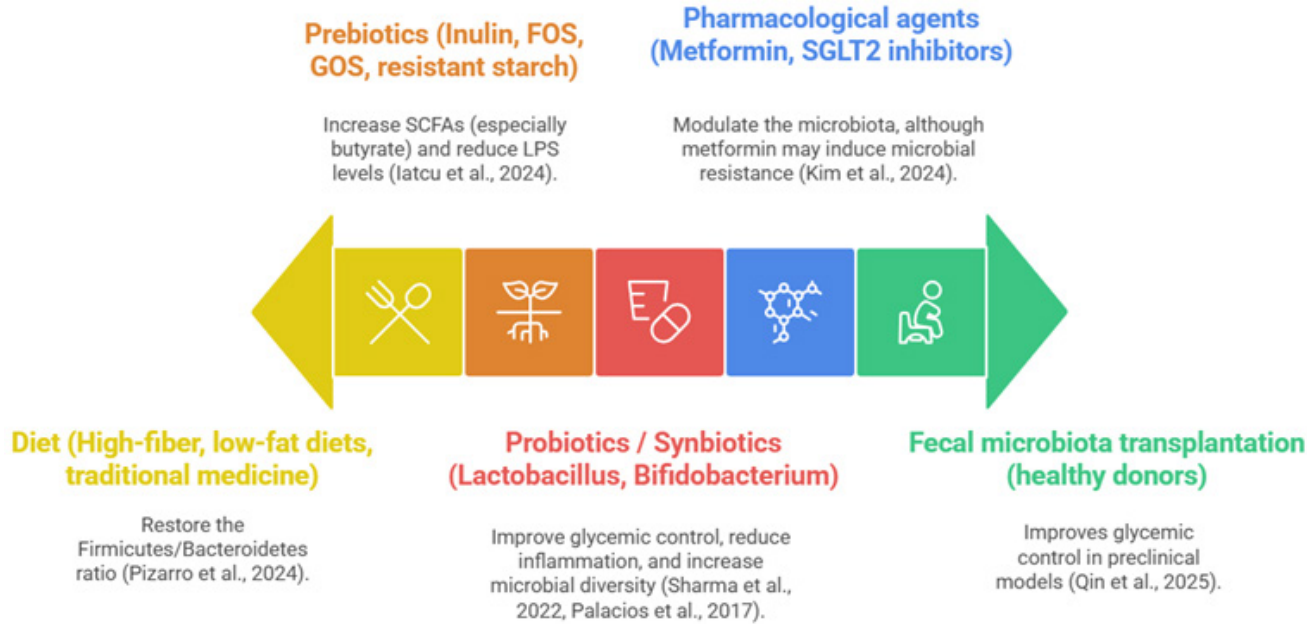

Figure 4. Therapeutic strategies modulating the intestinal microbiome in T2DM and their reported effects.

part, by the effects of weight loss, increased insulin sensitivity, and reduced systemic inflammation (Ng et al., 2024; Qin et al., 2025). Although the precise mechanisms require further elucidation, the interaction between iSGLT2 and microbiome position is a class of pharmaceutical as a therapeutic strategy with relevant metabolic and systemic effects (Zhang, Zhang et al., 2024).

Metformin, a first-line drug in the treatment of T2DM, primarily inhibits hepatic gluconeogenesis and improves peripheral glucose uptake; however, it has been recognized that part of its clinical efficacy is due to its impact on the gut microbiota (Adeshirlarijaney & Gewirtz, 2020; Szymczak-Pajor et al., 2025). Evidence shows that metformin increases the abundance of beneficial bacteria, such as A*kkermansia. Muciniphila, Butyrivibrio,* and *Bifidobacterium* species are associated with increased insulin sensitivity and reduced inflammation, as well as increased short-chain fatty acid (SCFA) production (Sikalidis & Maykish, 2020; Mohamed, 2024; Kim et al., 2024; Szymczak-Pajor et al., 2025). These microbiome-dependent effects contribute to glucose control and the modulation of metabolic and immunological processes involved in T2DM (Zhang et al., 2025). However, the magnitude of these modifications depends in part on the therapeutic context, although combination therapy with insulin does not replicate the microbial changes (Tang et al., 2024; Szymczak-Pajor et al., 2025). Taken together, the recognition of the role of the microbiome in the action of metformin presents new opportunities to optimize its clinical effect through dietary strategies or targeted symbiosis (Zhang et al., 2025; Chen et al., 2025).

New therapeutic inserts

The recognition of the gut microbiota as a central modulator in the pathology of T2DM has driven the development of innovative therapeutic strategies that integrate the interaction between the human body, diet, pharmaceutical therapy, and the microbial ecosystem. In this regard, various interventions targeting microbiome modulation, such as the use of prebiotics, drugs with microbiome-dependent effects, specific dietary patterns, and fecal microbiota transfer, have the greatest potential to optimize glucose control and reduce variability in therapeutic response (Sharma et al., 2022; Iatcu et al., 2024; Pizarro et al., 2024; Qin et al., 2025). In particular, prebiotics such as inulin, FOS, and GOS promote the production of medium-chain fatty acids (SCFAs) and reduce metabolic endotoxemia, while drugs such as metformin and SGLT2 inhibitors promote the growth of beneficial bacteria such as *Akkermansia*, with possible contextual effects on microbial resistance (Kim et al., 2024).

In this context, personalized medicine emerges as a promising approach for managing T2DM, proposing the adaptation of dietary, pharmacological, and behavioral interventions according to each patient's clinical, genetic, and microbiological characteristics. Analysis of the gut microbiome using the following techniques allows for the identification of bacterial profiles associated with insulin resistance, poor glucose control, and an increased risk of metabolic complications (Baars et al., 2024; Zhang, Zhang et al., 2024). This information facilitates the identification of patient subgroups that could benefit from targeted interventions, such as microbiota modulators or pharmacological adjustments, highlighting the high abundance of *Akkermansia muciniphila* could predict greater resistance to metformin (Kim et al., 2024; Szymczak-Pajor et al., 2025). Its practical application represents

a path towards more precise and effective therapies (Qin et al., 2025).

Furthermore, the understanding of the gut-brain axis has amplified the therapeutic influence of microbiome modulation in T2DM, particularly in relation to the cognitive decline associated with confinement. T2DM is caused by neurocognitive and neuropsychiatric alterations, while systemic inflammation and oxidative stress are not relevant (Sikalidis & Maykish, 2020; Negm, 2023). In this context, probiotics, especially those containing *Lactobacillus* and *Bifidobacterium*, are the most capable of modulating neurotransmitter production, reducing neuroinflammation, and improving intestinal barrier integrity. Preclinical studies and preliminary clinical trials suggest benefits for memory, cognitive function, and inflammatory markers, but more extensive research is needed to confirm these findings (Sharma et al., 2022; Baars et al., 2024; Mohamed, 2024; Qin et al., 2025).

On the other hand, diabetic retinopathy, one of the most common and serious microvascular complications of T2DM, has also led to alterations in the gut microbiota. Dysbiosis can contribute to systemic inflammation, oxidation, and vascular dysfunction through the production of pro-inflammatory metabolites, such as lipopolysaccharides, which are activated when associated with retinal damage (Sato et al., 2017; Adeshirlarijaney & Gewirtz, 2020; Zhang et al., 2025). Conversely, beneficial SCFA-producing bacteria, such as *Bifidobacterium* and *Lactobacillu*s, may have protective effects by reducing inflammation and improving intestinal barrier function (Szymczak-Pajor et al., 2025).

Modulating the gut microbiota is a cross-cutting therapeutic challenge in T2DM, with implications not only for metabolism but also for cognitive and microvascular health. Approaches such as the use of prebiotics, probiotics, high-fiber and polyphenol-rich diets, and fecal microbiota transfer show promise as complementary therapies to conventional treatments (Kim et al., 2024; Iatcu et al., 2024; Qin et al., 2025; Pizarro et al., 2024). However, the consolidation of these interventions in clinical practice requires longitudinal studies and robust clinical trials to establish their effectiveness, safety, and applicability within a personalized medical model aimed at reducing complications and improving the quality of life of patients with T2DM.

Dietary recommendations based on gut microbiome balance for the comprehensive treatment of T2DM

Among the 27 studies compiled (Table 1), the dietary strategies from the clinical studies of Palacios et al. (2017) and the systematic reviews of Baars et al. (2024) and Fu et al. (2023) were selected. These studies show that high-fiber diets and the inclusion of multispecies probiotics improve metabolic parameters such as fasting glucose, systemic inflammation, and microbial diversity.

A key aspect is the analytical method used. Most studies employ 16S rRNA sequencing and metabolomics tools to identify bacterial species and metabolites such as short-chain fatty acids (SCFAs), since their production is favored by the consumption of fermentable fibers. These techniques allow for the precise correlation of dietary changes with microbiome composition and clinical indicators of T2DM.

In terms of results, it was observed that functional diets based on prebiotic fibers (inulin, FOS, GOS) increased the abundance of beneficial bacteria such as *Akkermansia* and *Bifidobacterium*, while reducing lipopolysaccharides (LPS), improving glucose homeostasis and reducing inflammation.

Dietary supplements for the management of T2DM have evolved from generalized strategies based on personalized models that consider the composition of the gut microbiome. Figure 5 summarizes the main differences between these paradigms.

Dietary interventions based on gut microbiome modulation offer therapeutic potential for the comprehensive management of T2DM according to the patient's microbial profile, improving insulin sensitivity and glucose control, and reducing mild systemic inflammation. However, the predominance of pilot studies or small studies necessitates caution in extrapolating results, hence the need for well-designed, longer-term clinical trials.

Dietary interventions

Dietary interventions aimed at modulating the gut microbiota are becoming established as a relevant complementary strategy for addressing T2DM, positively influencing glucose homeostasis, insulin sensitivity, and the mild chronic inflammation characteristic of this condition. Available evidence indicates that manipulating microbial composition and function through prebiotics, probiotics, symbiosis, and high-fiber diets allows for the creation of a more favorable intestinal environment, with a direct impact on the metabolic and immunological processes involved in T2DM (Iatcu et al., 2024; Qin et al., 2025).

Prebiotics, composed primarily of non-digestible soluble fibers such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), selectively stimulate the growth of beneficial bacteria that produce medium-chain fatty acids (SCFAs), promoting intestinal barrier integrity and modulating the immune response (Iatcu et al., 2024; Sharma et al., 2024). Clinical studies have shown that insulin and FOS supplementation improves glucose tolerance, reduces insulin resistance and inflammatory markers, and is associated with an increase in genes such as *Bifidobacterium* and *Faecalibacterium prausnitzi*i (Sivadas et al., 2025; Szymczak-Pajor et al., 2025). In a complementary way, probiotics, particularly those of *Lactobacillus, Bifidobacterium,* and

Bacillus, have more effective effects on fasting glucose, insulin sensitivity, and the reduction of pro-inflammatory cytokines, in addition to modulating the release of incretins such as GLP-1, contributing to postprandial glycemic control (Negm, 2023; Ng et al., 2024; Qin et al., 2025).

The use of synbiotics, which combine prebiotics and probiotics, is emerging as a dietary strategy with synergistic effects on modulating the gut microbiome. In experimental models of T2DM, these interventions have demonstrated improvements in insulin sensitivity, reduced blood glucose levels, and reduced systemic inflammation, associated with an increase in short-chain fatty acid (SCFA)-producing bacteria and a reduction in metabolic endotoxemia (Sivadas et al., 2025; Szymczak-Pajor et al., 2025). As a result, we observed positive modulation of incretin hormones such as GLP-1 and improvements in lipid profile and visceral adiposity, positioning them as a promising alternative therapeutic complement, though more robust clinical trials in humans are not required (Sharma et al., 2024; Baars et al., 2024; Qin et al., 2025).

Therefore, a high-fiber diet is a key nutritional intervention in the management of T2DM, as it has the capacity to increase microbial diversity and promote the predominance of beneficial species through the colonic fermentation of soluble and insoluble fibers (Oluwaloni et al., 2023; Sharma et al., 2024; Ng et al., 2024). The resulting short-chain fatty acid (SCFA) production contributes to improved insulin sensitivity, stimulates incretin secretion, strengthens the intestinal barrier, and reduces systemic inflammation (Iatcu et al., 2024; Szymczak-Pajor et al., 2025). This dietary pattern modulates bile acid metabolism and the signaling of receptors such as FXR and TGR5, favorably impacting glucose and lipid metabolism (Baars et al., 2024). Evidence shows the incorporation of fiber-rich diets as a cornerstone of comprehensive

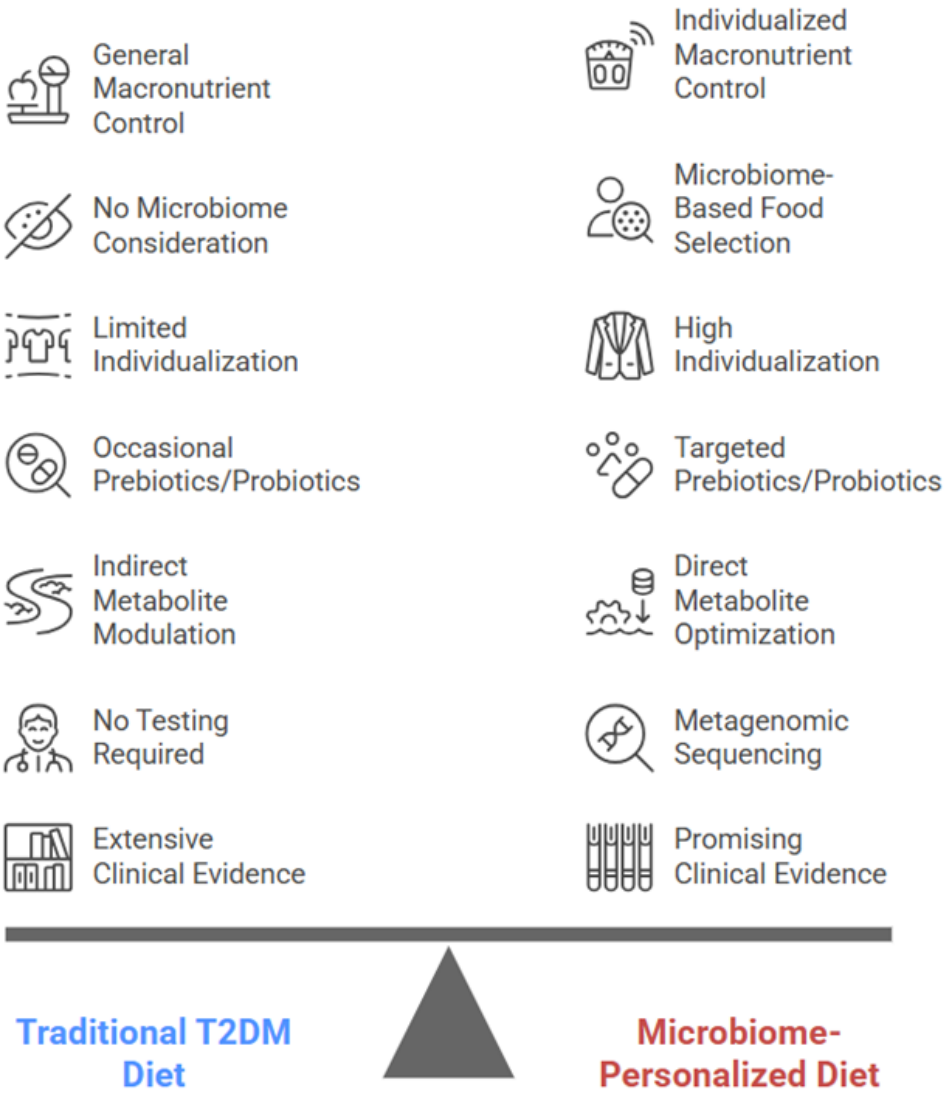

Figure 5. Comparison between traditional diet and microbiome-based personalized diet in T2DM.

therapeutic support for T2DM, due to their effectiveness in modulating the gut microbiome and improving the metabolic profile (Zhang, Zhang et al., 2024).

Comparison between traditional and microbiome-based personalized diets in patients with T2DM

The dietary management T2DM has historically focused on glucose control and the prevention of micro- and macrovascular complications. Traditionally, this approach is based on macronutrient control, calorie reduction, and weight management, prioritizing foods with a low glycemic index, unsaturated fats, and high dietary fiber intake (Pizarro et al., 2024; Baars et al., 2024). While this has proven clinically effective in improving glycemic, lipid, and anthropometric profiles, its application is only standardized and does not consider individual differences in the composition and function of the gut microbiome, which is now recognized as a relevant factor in the pathophysiology of T2DM (Ng et al., 2024; Szymczak-Pajor et al., 2025).

In response to these limitations, a personalized gut microbiome-based diet plan has emerged, suggesting that the diet be tailored to each patient's specific microbial profile. This model helps restore gut homeostasis, reduce dysbiosis, and enhance the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), through the strategic use of prebiotics, probiotics, synbiotics, and the targeted selection of fermentable foods (Sharma et al., 2022; Iatcu et al., 2024). Unlike the traditional model, this approach relies on advanced tools such as next-generation sequencing and metabolism, allowing for greater precision in the design of individualized nutritional interventions (Baars et al., 2024; Qin et al., 2025).

A comparison of the two sources shows that, while macronutrient control is common to other models, the fundamental difference lies in the degree of individualization and the explicit consideration of the gut microbiome. Personalized diets adjust nutritional ratios based on individual glucose levels, which are influenced by the microbiota, and prioritize foods that promote beneficial bacteria, such as *Bifidobacterium* or *Akkermansia muciniphil*a, associated with improvements in metabolic health and reduced inflammation (Sharma et al., 2022; Iatcu et al., 2024; Ng et al., 2024; Szymczak-Pajor et al., 2025). For example, these strategies can directly control the production of bacterial metabolites, increase SCFAs, and reduce pro-inflammatory compounds such as lipopolysaccharide (LPS) (Adeshirlarijaney & Gewirtz, 2020; Zhang et al., 2025).

However, we weigh the promising results in glucose control, insulin sensitivity, and the reduction of inflammatory markers (Kim et al., 2024; Zhang et al., 2025), as well as the challenges of clinically implementing personalized diets for major diseases, including high cost, comprehensive diagnostic testing, and limited standardization and evidence of longitudinal robustness (Zhang et al., 2024; Qin et al., 2025). In this context, some traditional diets continue to be based on extensive scientific evidence, and microbiome-based personalized diets are emerging as a strategy with high therapeutic potential. Their consolidation will depend on the development of clinical studies that support their efficacy, applicability, and cost-effectiveness in the comprehensive treatment of T2DM (Sharma et al., 2022; Qin et al., 2025).

Conclusions

Modulating the gut microbiome is emerging as a highly promising therapeutic strategy for optimizing the clinical and nutritional management of T2DM. The evidence analyzed confirmed that the gut microbiota plays a central role in regulating energy metabolism, insulin sensitivity, and systemic inflammatory processes, positioning it as a strategic target for both the prevention and treatment of this disease. In this context, interventions based on probiotics, prebiotics, synbiotics, and drugs with microbiome-dependent mechanisms have remarkable potential to improve glucose homeostasis, reduce chronic low-grade inflammation, and lower the risk of metabolic and cardiovascular complications. This is achieved through modulation of the composition and function of the gut ecosystem, strengthening the intestinal barrier, and activating key physiological genes for the gut-pancreas and gut-brain. However, the clinical translation of these findings does not present significant challenges, but it is subject to the need for controlled, longitudinal, and standardized clinical studies that integrate metagenetic analysis with individualized clinical profiles. Moving towards a personalized medicine approach is fundamental for designing microbiome-based interventions tailored to each patient's genetic, dietary, lifestyle, and microbiological characteristics, thus enabling the development of more effective, safe, and sustainable complementary therapies for the overall management of T2DM.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Statement on the use of AI

The authors acknowledge the use of generative AI and AI-assisted technologies to improve the readability and clarity of the article.

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