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Role of Gut Microbiota in Type 2 Diabetes Mellitus

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Summary

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by persistent hyperglycaemia and insulin resistance. Its global prevalence has risen to epidemic levels, affecting approximately 463 million adults in 2019. Conventional treatment strategies, including lifestyle modifications, oral antidiabetic medications, and insulin therapy, often come with side effects and may not always ensure adequate glycaemic control. Recent studies have increasingly focused on the gut microbiota as a critical factor in the pathogenesis, management of T2DM. Dysbiosis has been linked to various metabolic disorders, including insulin resistance, obesity, and T2DM. Key mechanisms through which gut microbiota influence metabolic health include alterations in microbial diversity, disruption of gut barrier integrity, oxidative stress and modulation of immune responses. These changes foster a pro-inflammatory state, leading to systemic inflammation, further exacerbating insulin resistance. Specific bacterial taxa, such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, have emerged as potential markers for T2DM, reflecting the interplay between microbiota and metabolic function. Therapeutic strategies aimed at restoring gut microbiota balance, including the use of probiotics, prebiotics, and faecal microbiota transplantation (FMT), show promising results in enhancing glycaemic control and improving insulin sensitivity. Additionally, dietary interventions that promote beneficial microbial growth are gaining attention as effective measures for prevention and management of T2DM. This

review explores the relationship between gut microbiota and T2DM, highlighting the underlying mechanisms of microbial influence on metabolic dysregulation in T2DM. It discusses the potential for gut microbiota composition to serve as a biomarker for early detection and targeted interventions in T2DM. More research is needed to elucidate the relationships between specific microbial taxa and T2DM, ultimately advancing our understanding and management of T2DM.

Keywords: T2DM, gut microbiota, glycaemic control, dysbiosis

Introduction

Type 2 diabetes mellitus (T2DM) is characterised by poor insulin secretion from pancreatic beta cells and reduced insulin sensitivity of adipose tissue, liver, and muscle, resulting in hyperglycaemia, and leads to acute and chronic complications associated with T2DM (Galicía-García *et al.*, 2024). The gut microbiota, a complex community of microorganisms residing in the gastrointestinal tract, plays a significant role in the pathogenesis, management, and potential treatment of Type 2 Diabetes Mellitus (T2DM). Recent studies indicate that gut microbiota, a complex array of microorganisms essential for metabolic processes and immune responses, significantly impacts metabolic health. An imbalance in the composition of gut microbiota, known as dysbiosis, has been associated with conditions such as insulin resistance, obesity, and diabetes mellitus (Shakya *et al.*, 2025). The human gut microbiota helps to modulate metabolism,

digestion, maintenance of intestinal barrier function, and immune modulation. Its alteration appears to be related to the development of T2DM and cardiometabolic disorders associated with overweight and obesity (Galicia-Garcia *et al.*, 2024). The gut microbiota affects glucose metabolism through various mechanisms, including the production of short-chain fatty acids, regulation of gut permeability, and interactions with the immune system, highlighting a reciprocal relationship between microbial health and metabolic function (Shakya *et al.*, 2025).

Gut microbiome dysbiosis plays an important role in the development of insulin resistance in type 2 diabetes through various mechanisms such as intestinal barrier dysbiosis, metabolic endotoxemia, Inflammation etc. Among these various mechanisms, intestinal barrier dysfunction is the most important. These dysfunction leads to a rise in intestinal permeability and translocation of bacterial components such as lipopolysaccharides (LPS) into the bloodstream. Thereby triggering mild inflammation and insulin resistance (Sharma & Tripathi, 2019). Diabetes prevalence, diabetes-related death, and diabetes-related health expenditure are increasing worldwide, with significant social, economic, and health-system impacts. Therefore, further research is needed to identify and implement new evidence-based advancements for T2DM management (Paquette *et al.*, 2023). This review explores the intricate relationship between gut microbiota and T2DM, highlighting its implications for diagnosis, therapy, and prevention.

Gut Microbiota and the Pathogenesis of T2DM

Gut microbiota dysbiosis is a central player in the pathogenesis of T2DM, influencing metabolic homeostasis, immune responses, and systemic inflammation. Key mechanisms include altered microbial diversity, disrupted intestinal barrier function, and microbiota-derived metabolite imbalances.

T2DM patients exhibit reduced gut microbial diversity and shifts in bacterial composition, including increased facultative anaerobes (*Escherichia-Shigella*, *Prevotella_9*) and

decreased beneficial taxa (*Akkermansia muciniphila*, *Faecalibacterium prausnitzii*). Western diets, antibiotics, and industrialization exacerbated these changes. Specific taxa like *Acidaminococcales* and *Bacteroides plebeius* are proposed biomarkers for T2DM (Zhou *et al.*, 2022; Chimplee, and Chotinuntakul, 2022; Baars *et al.*, 2024).

Dysbiosis damages tight junctions (e.g., reduced zonula occludens-1 expression), increasing intestinal permeability, resulting in intestinal barrier disruption. This allows bacterial products like lipopolysaccharides (LPS) to enter systemic circulation, triggering metabolic endotoxemia and chronic inflammation (Ye *et al.*, 2022; Zhou *et al.*, 2022). LPS activates Toll-like receptor 4 (TLR4), promoting pro-inflammatory cytokines (TNF- α , IL-6) that drive insulin resistance (IR) and β -cell dysfunction (Zhou *et al.*, 2022; Młynarska *et al.*, 2024).

Dysbiosis results in metabolite Imbalances, where reduced SCFAs like butyrate and acetate impair gut barrier integrity and glucose regulation, while low SCFA levels correlate with insulin resistance (Ye *et al.*, 2022; Młynarska *et al.*, 2024). TMAO promotes vascular inflammation and is linked to diabetic nephropathy (DN) (Zhou *et al.*, 2022). Harmful metabolites like branched-chain amino acids (BCAAs) and phenol derivatives exacerbate IR and inflammation (Ye *et al.*, 2022; Młynarska *et al.*, 2024).

Dysbiosis leads to decreased anti-inflammatory immune cells, such as intestinal Th17 cells and IgA⁺ cells, compromises mucosal immunity, and heightens systemic inflammation (Zhou *et al.*, 2022). Additionally, lipopolysaccharides (LPS) and extracellular vesicles originating from the gut stimulate hepatic macrophages (CR1g⁺), thereby exacerbating liver inflammation and insulin resistance (IR). The Clinical implications mostly in DN, *Haemophilus*, and *Lachnospiraceae_UCG-004* abundances correlate with disease progression, while phenyl sulfate induces podocyte damage (Zhou *et al.*, 2022). Furthermore, metabolites derived from gut microbiota, such as trimethylamine N-oxide (TMAO) and LPS, are linked to cardiovascular complications.

Gut Microbiome Dysbiosis and Metabolic Dysregulation

Gut microbiome dysbiosis, an imbalance in the microbial population of the gastrointestinal tract, has been increasingly linked to metabolic dysregulation. This relationship is mediated through mechanisms involving inflammation, oxidative stress, and altered metabolic pathways (Ma *et al.*, 2025). Dysbiosis plays an important role in developing insulin resistance in type 2 diabetes through various mechanisms, such as intestinal barrier dysbiosis, which can increase lipopolysaccharides (LPS) levels in the systemic circulation. Among these various mechanisms, intestinal barrier dysfunction is the most significant (Sharma & Tripathi, 2019). Gut dysbiosis, characterized by an imbalance in the composition and function of gut microbiota, is strongly associated with T2DM. Studies have shown that individuals with T2DM exhibit reduced microbial diversity and altered abundances of specific bacterial taxa compared to healthy individuals (Letchumanan *et al.*, 2022; Chong *et al.*, 2025). For instance, genera such as *Akkermansia*, *Bifidobacterium*, and *Faecalibacterium* are often reduced in T2DM patients, while pro-inflammatory taxa like *Escherichia-Shigella* and *Streptococcus* are increased (Letchumanan *et al.*, 2022; Chong *et al.*, 2025).

Inflammation and Immune System Activation

Dysbiosis disrupts gut barrier integrity, increasing intestinal permeability. This allows microbial products like lipopolysaccharides (LPS) to enter systemic circulation, triggering chronic low-grade inflammation. This inflammation is a hallmark of metabolic disorders such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) (Mostafavi Abdolmaleky, and Zhou, 2024). Gut-derived metabolites can modulate immune responses, either promoting or alleviating inflammation, depending on the microbial composition (Bandopadhyay and Ganguly, 2022; Hrnccir, 2022).

Oxidative Stress

Dysbiosis induces excessive production of reactive oxygen species (ROS), which damages cellular components and exacerbates

inflammation. ROS also disrupts the gut microbiota further, creating a feedback loop that worsens metabolic dysfunction (Mostafavi Abdolmaleky and Zhou, 2024).

Metabolic Pathway Alterations

Metabolic pathway alterations in the gut microbiome are a key mechanism linking dysbiosis to various diseases, including metabolic disorders, inflammatory conditions, and cardiovascular diseases. These alterations are driven by changes in microbial composition and function, leading to shifts in the production of metabolites that influence host physiology (Wu *et al.*, 2021). Gut microbes produce metabolites like short-chain fatty acids (SCFAs), bile acids, and trimethylamine (TMA), which regulate host glucose and lipid metabolism. Dysbiosis often reduces the production of SCFAs like butyrate, acetate, and propionate, which are crucial for maintaining gut barrier integrity, regulating glucose metabolism, and modulating immune responses. Decreased butyrate levels, for example, are associated with type 1 diabetes (T1D) and impaired insulin sensitivity (Yuan *et al.*, 2022). Alterations in these pathways contribute to insulin resistance, dyslipidaemia, and other features of metabolic syndrome. Dysbiosis disrupts bile acid metabolism, leading to changes in the synthesis and conversion of bile acids. This affects lipid digestion, cholesterol homeostasis, and glucose regulation (Singh *et al.*, 2021; Hrnccir, 2022; Mostafavi Abdolmaleky and Zhou, 2024). Reduced bile acid metabolism has been observed in T1D and post-stroke depression (PSD) (Jiang *et al.*, 2021; Yuan *et al.*, 2022).

Increased Lipopolysaccharide (LPS) production in dysbiotic conditions triggers systemic inflammation by activating immune responses. Elevated LPS levels are linked to metabolic dysregulation and pancreatic inflammation in T1D (Yuan *et al.*, 2022). Dysbiosis alters the metabolism of amino acids and nucleotides, affecting energy production processes and protein synthesis. For instance, disturbances in glutamate and histidine metabolism have been observed in heart failure and PSD (Jiang *et al.*, 2021; Wang *et al.*, 2024). Gut microbes convert dietary choline and carnitine into

Trimethylamine (TMA), which is further oxidized in the liver to Trimethylamine N-Oxide (TMAO), through the TMA and TMAO pathways. Elevated TMAO levels are associated with cardiovascular diseases and chronic heart failure (Chen *et al.*, 2019). Dysbiosis affects vitamin B salvage and biosynthesis pathways, which are critical for energy metabolism and immune function. These

changes are observed in inflammatory arthritis (Thompson *et al.*, 2023). Altered carbohydrate metabolism, including fructose, mannose, and galactose pathways, has been linked to T1D and other metabolic disorders. These changes influence glucose homeostasis and insulin sensitivity (Yuan *et al.*, 2022).

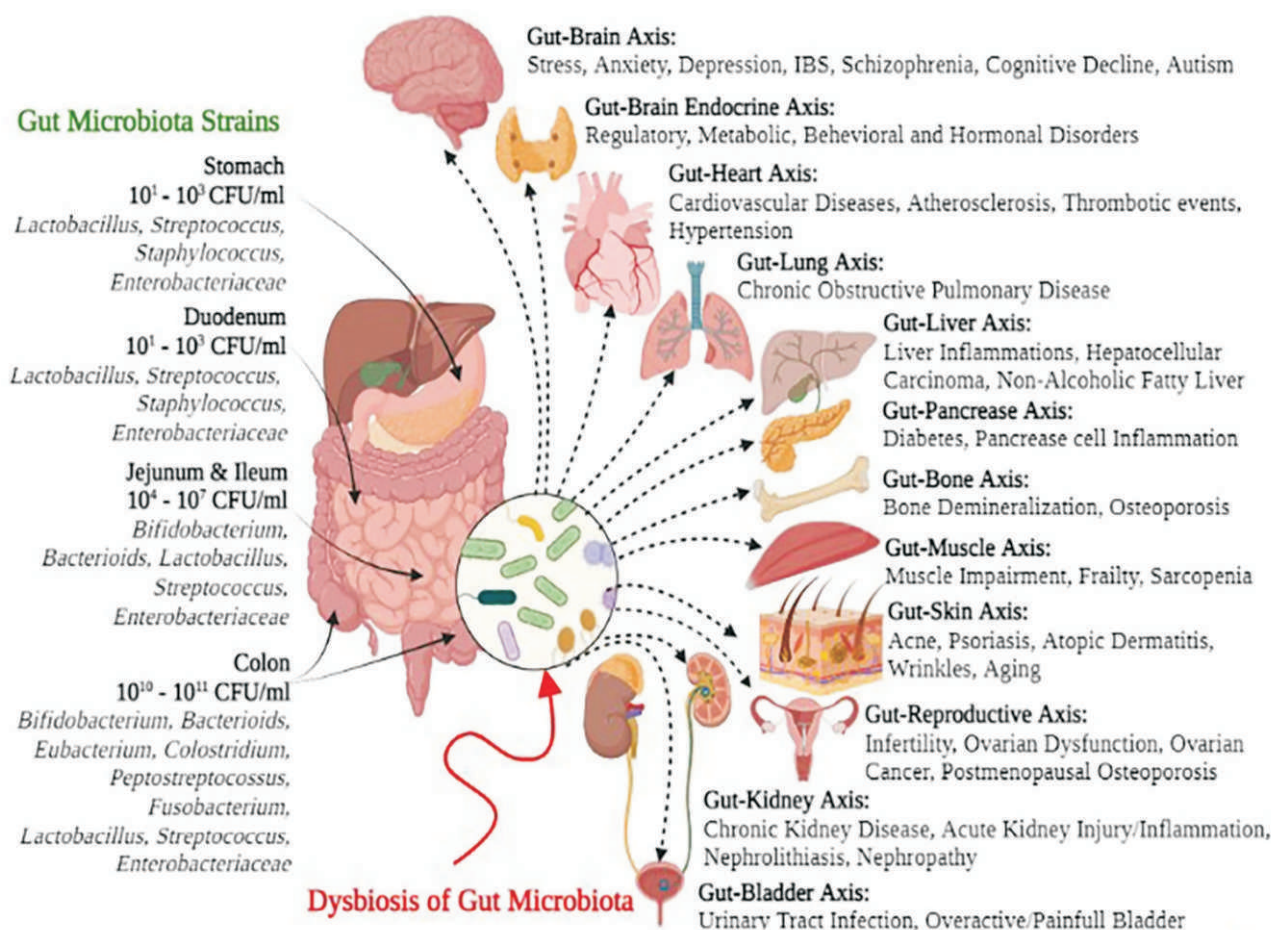


Figure 1. Gut microbiota strains and the negative health outcomes of gut microbiota dysbiosis. (Afzaal *et al.*, 2022).

Epigenetic Modifications

Epigenetic changes driven by gut microbial metabolites influence gene expression in metabolic pathways (Mostafavi Abdolmaleky and Zhou, 2024). Short-Chain Fatty Acids (SCFAs) like butyrate, propionate, and acetate are produced by gut bacteria's fermentation of

dietary fibers. These metabolites can influence epigenetic modifications by inhibiting HDACs and altering DNA methylation patterns, or modulate histone acetylation, directly impacting metabolic regulation, thereby regulating genes involved in inflammation, metabolism, and immune responses (Tan and Chen, 2024).

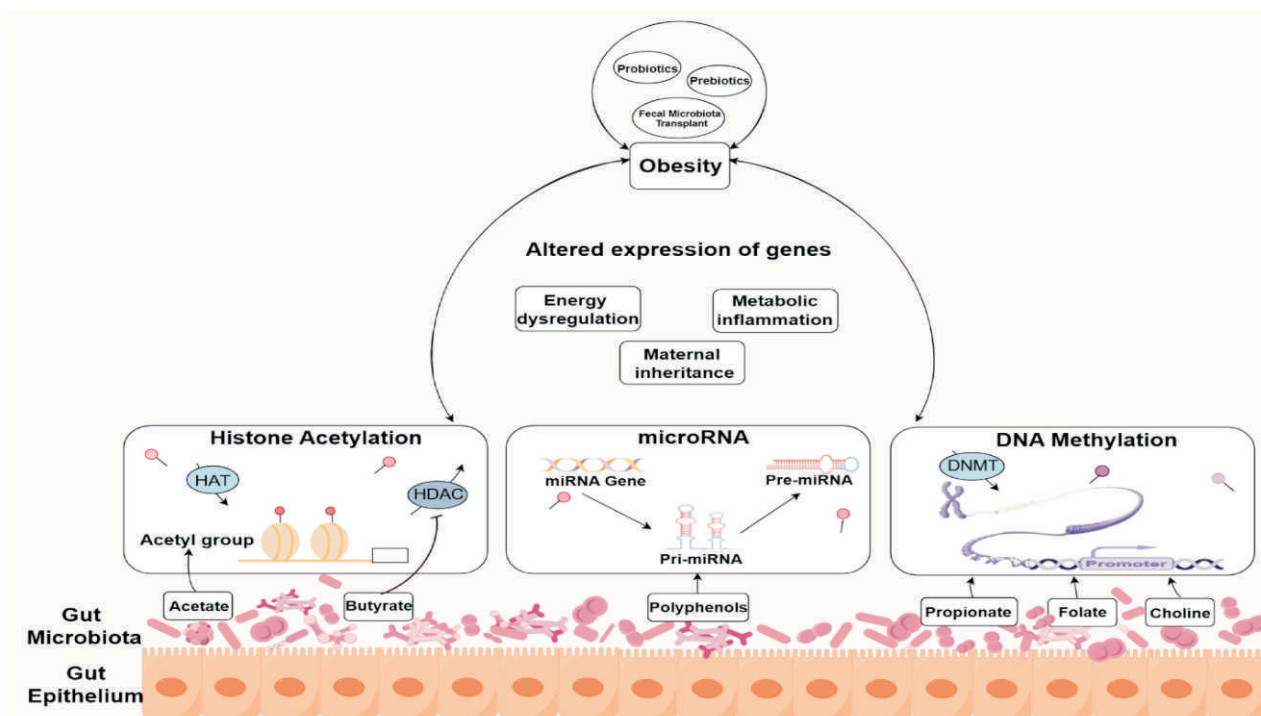


Figure 2: Interplay between gut microbiome, host genetic and epigenetic modifications (Ha, et al., 2024)

Mechanisms Linking Gut Microbiota to T2DM

The mechanism through which gut microbiota influences glucose metabolism and insulin sensitivity is through various ways:

- 1. Short-Chain Fatty Acids (SCFAs):** Beneficial bacteria, such as *Roseburia* and *Faecalibacterium*, produce SCFAs (e.g., butyrate, propionate, and acetate), which enhance insulin sensitivity and improve glucose uptake in tissues (Garcia-Menéndez *et al.*, 2022; Idris, 2023).
- 2. Gut Barrier Integrity:** Dysbiosis can impair the gut barrier, leading to increased permeability and the translocation of lipopolysaccharides (LPS) into the bloodstream, promoting systemic inflammation and insulin resistance (Fliegerová *et al.*, 2025; Baars *et al.*, 2024).
- 3. Modulation of the Immune System:** The gut microbiota regulates immune responses, with dysbiosis contributing to chronic inflammation, a key driver of T2DM (Fliegerová *et al.*, 2025; Madej *et al.*, 2024).

Therapeutic Strategies Targeting Gut Microbiota

Several gut-targeted therapies have been developed to modulate the gut microbiota and improve glycaemic control in T2DM.

Researches, both clinical and experimental, indicates that altering gut microbiota via dietary strategies such as prebiotics, probiotics, and synbiotics can enhance glycaemic control and insulin sensitivity in patients with diabetes mellitus (DM), when administered in adequate amounts. Additionally, Faecal Microbiota Transplantation (FMT) has shown potential in reestablishing a healthy gut microbiome and mitigating metabolic issues associated with DM (Shakya *et al.*, 2025).

Probiotics and Synbiotics

Probiotics, live microorganisms that confer health benefits, have shown promise in managing T2DM. Certain strains, such as *Lactobacillus* and *Bifidobacterium*, improve glycaemic control by enhancing insulin sensitivity and reducing inflammation (Zainab *et al.*, 2022; Xu *et al.*, 2024). Synbiotics, combinations of probiotics and prebiotics, further enhance these effects by promoting the growth of beneficial microbes (Chen *et al.*, 2024).

Faecal Microbiota Transplantation (FMT)

FMT, the transfer of faecal material from a healthy donor to a patient, has been explored as a therapeutic option for T2DM. FMT has

demonstrated efficacy in treating *Clostridium difficile* infections and shows potential therapeutic benefits for metabolic disorders. Previous studies (Zainab *et al.*, 2022; Xu *et al.*, 2024) reported enhanced peripheral insulin sensitivity and an increased abundance of butyrate-producing bacteria following FMT from a lean donor to an adult male with metabolic syndrome, likely by restoring a balanced gut microbiota. Additionally, research on *db/fb* mice revealed significant improvements in intestinal microbiota composition and reductions in plasma glycolipid levels when FMT was performed using donors with normal glucose tolerance. Notably, an increased abundance of *Akkermansia muciniphila* was correlated with heightened expression of histone deacetylase 3 (HDAC3), suggesting a possible mechanistic link between microbial composition and metabolic regulation (Xu *et al.*, 2024; Shakya *et al.*, 2025).

Dietary Interventions

Dietary modifications, such as increased fiber intake and adherence to a Mediterranean diet, can positively alter gut microbiota composition, improving insulin sensitivity and glycaemic control (Farahbod *et al.*, 2024) (Dimba *et al.*, 2024). These interventions often increase the abundance of beneficial bacteria, such as *Bacteroidetes*, while reducing pro-inflammatory taxa (Dimba *et al.*, 2024).

Nonetheless, several challenges persist, including the necessity for tailored treatments due to the variability of individual microbiota and the uncertain long-term consequences of these interventions. Future investigations should aim to clarify the mechanisms through which gut microbiota affects metabolism and to develop personalized strategies to improve the management of diabetes mellitus (Shakya *et al.*, 2025).

Gut Microbiota as a Biomarker for Early Detection and Prevention

Gut microbiota composition and function are emerging as promising biomarkers for the early detection and prevention of type 2 diabetes mellitus (T2DM). Research highlights microbial signatures and metabolites that correlate with disease progression, offering potential for targeted interventions (Du *et al.*, 2022).

Microbial Signatures in Prediabetes (PreDM) and T2DM

Emerging evidence suggests that specific gut microbiota signatures may serve as early biomarkers for T2DM. Pre-DM and T2DM patients show decreased microbial diversity, with specific reductions in *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and *Bifidobacterium* (Zhang *et al.*, 2021; Barlow and Mathur, 2022), and increased levels of *Lactobacillus* (Letchumanan *et al.*, 2022). These microbial changes often precede clinical manifestations of the disease, offering a potential window for early intervention (Bednarska & Häberg, 2024). PreDM individuals exhibit intermediate microbial changes (e.g., reduced *Roseburia*), suggesting that early dysbiosis precedes T2DM onset (Cunningham *et al.*, 2021; Zhang *et al.*, 2021).

Gut microbiota dysbiosis in T2DM is also characterized by an enrichment of specific harmful bacterial taxa that correlate with metabolic dysfunction, inflammation, and disease progression. Increased abundance of *Ruminococcus*, *Fusobacterium*, and *Lactobacillus gasseri* correlates with insulin resistance and hyperglycaemia (Zhou *et al.*, 2022; Barlow and Mathur, 2022). *For example*, *Clostridium hathewayi* and *Clostridium symbiosum* levels are increased in T2DM patients, associated with reduced glucose tolerance and insulin resistance. *Escherichia coli* and *Escherichia-Shigella* abundance are elevated in T2DM and linked to intestinal barrier dysfunction and systemic inflammation. *Bacteroides vulgatus* and *Veillonella denticariosi* are enriched in refractory T2DM (poorly controlled cases) and correlate with elevated HbA1c1. *Prevotella_9* levels discriminate T2DM patients from healthy controls and are associated with diabetic nephropathy (DN) progression (Zhou *et al.*, 2022).

Predictive modelling: Predictive modelling of the gut microbiome has emerged as a critical tool for understanding microbial community dynamics and their implications for human health. These models integrate multi-omics data (genomic, transcriptomic, metabolomic) to forecast disease risks, optimize therapies, and

elucidate host-microbiome interactions (Song *et al.*, 2021). A microbiome-based risk score combining ten discriminant genera (e.g., *Acidaminococcales*, *Bacteroides plebeius*) improved T2DM prediction accuracy (AUC: 0.632 to 0.946) when added to clinical parameters like HbA1c and triglycerides (Vals-Delgado *et al.*, 2021). The predictive modelling key approaches includes

Mechanistic Model: Inspired by bioreactor engineering, generalized Lotka-Volterra equations simulate microbial growth, species interactions, and responses to perturbations (e.g., antibiotics, diet). The model is defined as:

$$\frac{dx_i}{dt} = \mu_i x_i + \sum_j M_{ij} x_i x_j + \sum_k \epsilon_{ik} u_k(t)$$

where x_i represents species abundance, μ_i is the growth rate, M_{ij} captures interspecies interactions, and ϵ_{ik} quantifies susceptibility to external factors (Bucci and Xavier, 2014). These models enable short—and long-term predictions of microbiome dynamics.

Data-Driven AI Models; Machine learning frameworks like MB-SupCon (Microbiome-based Supervised Contrastive Learning) combine gut microbiome and metabolome data to predict diseases. In trials, MB-SupCon achieved 84% accuracy in predicting insulin resistance and 80% accuracy for inflammatory bowel disease (IBD) (Yang *et al.*, 2022).

Metabolic Modelling: Flux balance analysis integrates metagenomic sequencing to predict metabolic interactions within microbial communities, offering insights into nutrient utilization and metabolite production (Song *et al.*, 2021).

Lifestyle and Dietary Modifications for Prevention

Modifying lifestyle factors, such as diet and physical activity, can alter gut microbiota composition and reduce the risk of developing T2DM. For instance, high-fiber diets promote beneficial bacteria growth, improving insulin sensitivity and glucose metabolism (Farahbod *et al.*, 2024; Bednarska & Håberg, 2024).

Future Directions and Challenges

The gut microbiota's role in type 2 diabetes mellitus (T2DM) presents both promising therapeutic avenues and significant scientific challenges. While microbial modulation shows potential for personalized treatments, key hurdles must be addressed to translate findings into clinical practice.

Most gut microbiome interventions (e.g., probiotics, faecal microbiota transplantation [FMT]) remain in preclinical or observational stages, with limited high-quality human trial data (Baars *et al.*, 2024; Qin *et al.*, 2025). Studies often lack standardized protocols, long-term safety assessments, and diverse population representation (Wu *et al.*, 2023; Byndloss *et al.*, 2024). Linking microbiota composition, metabolites (e.g., short-chain fatty acids, bile acids), and host physiology requires advanced multi-omics approaches (Wu *et al.*, 2023; Jeyaraman *et al.*, 2024). The single-time sampling fails to capture dynamic ecosystems associated with microbial fluctuations influenced by diet, medications, and circadian rhythms (Byndloss *et al.*, 2024). There are methodological limitations with the current sequencing techniques (16S rRNA, metagenomics), which lack resolution for strain-level analysis, while metabolomic profiling struggles with low-abundance metabolites critical to T2DM pathways (Wu *et al.*, 2023; Jeyaraman *et al.*, 2024).

Personalized Therapies

The highly individualized nature of gut microbiota necessitates personalized therapeutic approaches. Future research should focus on developing tailored interventions based on an individual's microbial profile and clinical markers (Baars *et al.*, 2024; Byndloss *et al.*, 2024).

Mechanistic Insights and Causal Relationships

While observational studies have identified associations between gut microbiota and T2DM, establishing causal relationships remains a challenge. Mendelian randomization studies and longitudinal cohorts are needed to clarify the role of specific microbial taxa in disease pathogenesis (Sun & Huang, 2023; Liu *et al.*, 2024).

Integration of Multi-Omics Approaches

The integration of metagenomic, metabolomic, and clinical data will provide a more comprehensive understanding of the gut microbiota's role in T2DM.

Such approaches could uncover novel therapeutic targets and biomarkers (Byndloss *et al.*, 2024; Abdulhasan, 2024).

Table 1: Key findings on Gut microbiota and T2DM

Bacterial Taxa	Effect on T2DM	Citation
<i>Faecalibacterium</i> <i>Duncaniae</i>	Protective effect due to high butyrate production, which fights inflammation.	(Letchumanan <i>et al.</i> , 2022; Chong <i>et al.</i> , 2025).
<i>Coproccocus</i>	Associated with higher insulin sensitivity and lower dysglycaemia	(Idris, 2023)
<i>Flavonifractor</i>	Linked to lower insulin sensitivity and higher prevalence of dysglycaemia	(Idris, 2023; Sun & Huang, 2023).
<i>Lactobacillus</i>	Mixed effects: some strains improve glycaemic control; others correlate with insulin resistance	(Letchumanan <i>et al.</i> , 2022; Zainab <i>et al.</i> , 2022).
<i>Akkermansia</i>	Reduced abundance in T2DM; associated with improved metabolic health	(Letchumanan <i>et al.</i> , 2022; Chong <i>et al.</i> , 2025).

Conclusion

The gut microbiota is a critical factor in the pathogenesis and management of T2DM. Dysbiosis contributes to insulin resistance and metabolic inflammation, while therapeutic strategies targeting the gut microbiota, such as probiotics, FMT, and dietary interventions, offer promising avenues for disease management. Further research is needed to elucidate the causal relationships between specific microbial taxa and T2DM, paving the way for personalized and effective treatments.

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