



# Microbiomes and Diabetes: New Emerging Roles in Pathogenesis, Biomarkers, Complications and Therapeutic Perspectives

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Received Date: 26 Aug 2026

Accepted Date: 23 Sep 2026

Published Date: 25 Sep 2026

### Citation:

Johnkennedy N, Emenikeh KA, Chidozie NJ. Microbiomes and Diabetes: New Emerging Roles in Pathogenesis, Biomarkers, Complications and Therapeutic Perspectives. WebLog J Immunol. wji.2026.i2503. <https://doi.org/10.5281/zenodo.23297985>

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## Abstract

Diabetes mellitus is a complex collection of chronic metabolic illnesses characterised by sustained abnormalities in glucose regulation and linked with significant microvascular and macrovascular morbidity. Growing data suggests that diabetes is not just a disease of host metabolism but also that complex relationships exist between the human microbiome and pathways of metabolism, immunity and endocrinology. Of particular interest has been the gut microbiome because of the effect of microbial communities and their metabolites on intestinal barrier integrity, inflammation, energy metabolism, bile-acid signalling, incretin secretion, and insulin sensitivity. Alterations in the composition and function of gut microbes have been seen in people with Type 2 Diabetes Mellitus (T2DM) including the loss of some short-chain fatty acid-producing organisms and an increase in the number of potentially pro-inflammatory or opportunistic microbes. In addition, antidiabetic treatments, including metformin, can affect the gut microbiota and hence pharmacological treatment is an important confounding factor in microbiome investigations. There is now growing evidence for the role of oral, urine and other microbiomes in diabetes and associated consequences. Dysbiosis in Type 1 Diabetes Mellitus (T1DM) may play a role in intestinal permeability and mucosal immune response, possibly resulting in autoimmune  $\beta$ -cell death. Changes in the microbiome have also been linked to diabetic kidney disease and associated consequences through inflammatory, metabolic and gut-organ-axis pathways. Therapeutic options include dietary modification, probiotics, prebiotics, synbiotics, faecal microbiota transplantation, microbial metabolites, and microbiome-guided precision medicine. However, the large variation among patients and research, and the uncertainty about the causality prevents the fast clinical translation. In this review, we discuss the present state of knowledge regarding microbiomes in diabetes, with an emphasis on biological mechanisms, diagnostic potential, consequences, therapeutic prospects, and objectives for future study.

**Keywords:** Microbiome; Gut Microbiota; Diabetes Mellitus; Type 2 Diabetes; Type 1 Diabetes; Dysbiosis; Insulin Resistance; Microbial Metabolites; Probiotics; Precision Medicine

## Introduction

Diabetes mellitus is one of the most important chronic metabolic diseases worldwide. Well-known determinants of diabetes include genetic susceptibility, obesity, diet, physical inactivity, inflammation, and environmental exposures. In the past decade, research has established the human microbiome as a significant component of the metabolic ecosystem which can impact disease development and progression. The microbiome refers to the collection of all microorganisms that live in or on the human body, including their genes and products. These communities are present in several anatomical places such as the gastrointestinal tract, mouth cavity, skin, urogenital tract and other body niches [1].

Among these microbial communities, the gut microbiome is the one most studied in diabetes. Early metagenomic studies have revealed that T2DM is linked to alterations in the microbial composition, such as a reduced abundance of certain butyrate-producing bacteria and an increased abundance of opportunistic organisms and microbial functions associated with oxidative stress and sulphur metabolism. Later research has suggested that the association is even more intricate than presence or absence of certain bacterial species [2]. Diet, obesity, ethnicity, age, lifestyle, medication

exposure and other host characteristics shape the diabetes-associated microbiome profiles.

Importantly, the microbiome-diabetes association is expected to be bidirectional. Hyperglycaemia, changed intestinal physiology, medicines, dietary modifications and immunological dysfunction may alter microbial populations. Conversely, microorganisms and their metabolites may influence inflammation, glucose homeostasis, insulin signalling and host energy metabolism. Recent reviews have characterised diabetes as a “condition of interconnected disturbances of intestinal integrity, immune regulation, microbial metabolism and insulin signaling”, not as an isolated anomaly of glucose metabolism [3].

So, this growing discipline is moving from descriptive studies of ‘which bacteria are there?’ to functional microbiomics, metagenomics, metabolomics and studies of microbiome-host interactions. Such techniques may potentially yield novel biomarkers and therapeutic solutions for diabetes, while some key translational obstacles remain.

## The Gut Microbiome and Type 2 Diabetes

T2DM has the strongest evidence base linking diabetes with microbial dysbiosis. Early metagenomic studies identified a characteristic pattern of altered microbial abundance and function in T2DM. It was reported that a reduction in several butyrate-producing bacteria and an increase in opportunistic pathogens in individuals with T2DM. More recent reviews similarly describe a pattern characterized, in many populations, by depletion of short-chain fatty acid-producing taxa and enrichment of potentially pro-inflammatory microorganisms [4].

However, the microbiome signature of diabetes should not be interpreted as a single universal microbial profile. Microbial diversity varies substantially among geographical populations and individuals. Dietary habits, cultural practices, medication exposure, obesity, and methodological differences may all contribute to variation between studies [5]. Consequently, it is more appropriate to consider diabetes-associated dysbiosis as a functional disturbance involving microbial pathways and host-microbe interactions rather than a single diagnostic “diabetes microbiota.”

One of the most important discoveries has been that antidiabetic drugs themselves can modify the microbiome. It was demonstrated that metformin can produce substantial changes in microbial composition and function and that medication effects can confound attempts to distinguish diabetes-related microbial alterations from treatment-related changes [6]. Another randomized study involving treatment-naïve patients confirmed that metformin alters the gut microbiome and suggested that these changes may contribute to some of the drug's metabolic effects. Thus, future microbiome research in diabetes must carefully account for medication use [7].

## Mechanisms Connecting the Microbiome and Diabetes

The intestinal epithelial barrier separates the luminal microbial ecosystem from systemic tissues. This barrier can be compromised by dysbiosis, resulting in increased intestinal permeability and translocation of microbial products such as Lipopolysaccharide (LPS) into the blood. Systemic exposure to microbial compounds activates innate immune pathways and promotes chronic low-grade inflammation [8].

Insulin signalling in liver, skeletal muscle and adipose tissue may be disrupted by inflammatory signalling through toll-like receptors, nuclear factor- $\kappa$ B, c-Jun N-terminal kinase and other pathways. Recent reviews suggest that increased intestinal permeability, exposure to microbial endotoxins and inflammatory signalling are interlinked pathways that contribute to insulin resistance [9].

The primary products of microbial fermentation of dietary fibre are Short-Chain Fatty Acids (SCFAs) such as acetate, propionate and butyrate. They are not just metabolic waste products but act as signalling molecules impacting intestinal epithelial integrity, immunological function, glucose metabolism and energy balance [10].

For example, butyrate is involved in the maintenance of the epithelial barrier and can affect the host metabolism via G-protein-coupled receptors and epigenetic pathways. Reduced abundance of SCFA-producing organisms has been described repeatedly in T2DM-associated dysbiosis. Reduced SCFA synthesis may consequently lead to reduced barrier function, altered enteroendocrine signalling and metabolic inflammation.

The gut microbiota extensively transforms primary bile acids to secondary bile acids. These chemicals participate in host metabolic signalling via receptors such as the farnesoid X receptor and the Takeda G-protein-coupled receptor 5. Thus, microbial change may influence bile-acid pools and signalling pathways associated with glucose, lipid and energy metabolism.

Recent therapy investigations have shown alterations in bile acids and microbial metabolites as the underlying mechanisms for the improvements in glycaemic management following microbiome-targeted treatments, while the precise causal linkages are still under research [11].

Chronic low-grade inflammation is a known characteristic of insulin resistance. Altered bacterial products, decreased barrier integrity and alterations in microbial metabolites might promote inflammatory signalling via microbial dysbiosis. Increased LPS exposure and activation of inflammatory signalling pathways are identified in recent work as putative mechanisms by which dysbiosis may be linked to impaired insulin signalling and  $\beta$ -cell dysfunction.

The microbiome also intimately interacts with intestinal and systemic immune cells. Changes in the microbial makeup may affect regulatory T cells, macrophages, cytokine production and innate immune activation [12]. These pathways mechanistically link microbial imbalance to chronic inflammation that is associated with metabolic illness.

The biological importance of the microbiome is not limited to the microbial taxonomy, as microbes create a wide variety of metabolites. These include SCFAs, bile acid derivatives, indole derivatives, LPS, trimethylamine, trimethylamine N-oxide and branched-chain amino acids.

These products may affect insulin sensitivity, lipid metabolism, inflammation, hunger, mitochondrial function, intestinal signalling and vascular function. Thus, metabolic phenotyping coupled with microbiome analysis might offer more clinically relevant information than bacterial composition alone [13].

## Type 1 Diabetes and the Microbiome

Although the gut microbiome has been more extensively

investigated in T2DM, there is increasing evidence implicating intestinal microbial abnormalities in T1DM. T1DM is an autoimmune illness characterised by immune-mediated death of the pancreatic  $\beta$ -cells resulting in absolute insulin insufficiency. Genetic predisposition alone cannot account for the full disease process and environmental factors are thought to be involved in the initiation and progression of autoimmunity.

Recent research indicates that gut dysbiosis may affect intestinal permeability and mucosal immune control and can promote aberrant immunological activation in genetically sensitive individuals. A systematic review on studies on T1DM showed differences in the gut microbial composition between T1DM and healthy persons and suggested potential links between changes in the microbiome, inflammation, intestinal permeability, metabolites and glycaemic management.

However, it is questionable whether specific microbial shifts are the cause of T1DM or are a consequence of autoimmune illness, dietary changes, insulin treatment, or other environmental factors. Therefore, microbiome research in T1DM is promising but has not yet identified a therapeutically relevant microbial profile [14].

## Oral Microbiome and Diabetes

The oral microbiome is another potentially essential component of the diabetes-microbiome connection. Diabetes is linked to enhanced vulnerability to periodontal disease and other oral problems. Chronic mouth inflammation may play a role in systemic inflammatory load.

A scoping analysis in 2025 reported major alterations in oral microbial communities of T2DM persons, although the findings were heterogeneous between studies. *Fusobacteria* were enriched in multiple investigations and taxa such as *Catonella*, *Leptotrichia*, *Prevotella* and *Rothia* were revealed to be more common in T2DM people. Another recent analysis indicated that there is a bi-directional association between oral microbial dysbiosis and T2DM involving inflammation, poor metabolic control and dental illness [14].

An integrated microbiome-metabolome study has also demonstrated that oral microbial changes may be related to glycaemic state, emphasising the necessity of functional rather than only taxonomic examination.

The oral microbiota consequently may be beneficial in assessing diabetes risk, not least because saliva is quite easy to collect. However, before oral microbiome-based indicators can be successfully employed in the clinical setting, standardisation of sampling, sequencing, periodontal health, dental hygiene, medication use, diet, and smoking exposure is necessary [15].

## Microbiome and Diabetic Complications

The gut-kidney axis has appeared as an essential field of research in diabetes. Diabetic Kidney Disease (DKD) is characterised by significant metabolic and inflammatory dysregulation and recent research suggests that abnormalities in gut microbiota may contribute to renal injury.

Dysbiosis may affect intestinal barrier function, enhance systemic inflammatory signalling, change SCFA synthesis, and induce formation or accumulation of microbial metabolites linked with renal failure. Recent reviews have identified links between changed gut microbial composition, inflammation, intestinal permeability, vascular dysfunction, and development of DKD.

The relationship might be bidirectional. Decreased kidney function can change the intestinal environment and microbial metabolism, and microbial products can then contribute to inflammation and kidney injury. This establishes a possible self-reinforcing gut-kidney cycle.

New research is studying the role of the microbiota in diabetic neuropathy, cardiovascular disease, retinopathy, foot issues and poor wound healing. These associations are medically feasible, as these consequences involve inflammation, vascular dysfunction, immunological abnormalities and altered tissue metabolism. However, evidence is highly heterogeneous by complication and causative pathways are less well established than those identified for insulin resistance and DKD [16].

## Diabetes Biomarkers from the Microbiome

The repeatable link between microbial abnormalities and diabetes opens the door to microbiome-based biomarkers. Metabolic phenotypes can be linked to microbial taxa, genes, pathways and metabolites using shotgun genome sequencing, 16S rRNA sequencing, metabolomics and multi-omics.

The first metagenomic study and revealed that microbial indicators could discriminate between patients with T2DM and controls. More recent work has been in identifying functional signatures, rather than just individual organisms. Functional pathways related to SCFA generation, bile-acid transformation, inflammatory signalling, and other metabolic processes are likely to be more conserved across populations than specific bacterial species [17].

But it is premature for routine clinical use. Microbiome composition is correlated with geographical location, food, age, sex, drugs, obesity, antibiotics, sequencing platforms and analytical pipelines. Microbiome biomarkers should only be introduced into routine screening for diabetes or into clinical decision-making processes following standardisation and validation in large prospective cohorts [18].

## Therapeutic Modulation of Microbiome

Diet is one of the most powerful influences of gut bacteria makeup and function. High-fiber dietary patterns may improve fermentation and SCFA generation, but also possibly gut barrier function and metabolic health. Dietary interventions are thus potentially the easiest and most biologically based approach to manipulate the microbiota.

Importantly, microbiome responses to diet are personalised. The same dietary intervention can elicit distinct microbial and metabolic responses in different individuals, suggesting that future nutritional therapies may benefit from microbiome-guided personalisation.

The definition of probiotics is “live microorganisms which when administered in adequate amounts confer a health benefit to the host”. Prebiotics are substrates which are selectively used by beneficial microbes. Synbiotics bring together both techniques [19].

In 2025 a systematic review of 30 randomised controlled trials in T2DM and associated dysglycemia showed modest benefits in HbA1c, fasting glucose and HOMA-IR with many probiotic, prebiotic and synbiotic treatments, especially those lasting at least 12 weeks. The review also showed links with alterations in SCFAs, bile-acid metabolites, and endotoxemia.

These results are intriguing but clinical effects are usually small

and outcomes differ depending on the strain of micro-organism, dosage, duration of intervention, diet, other medicines and patient profile. Thus, probiotics should be evaluated as potential adjuncts, not alternatives, for evidence-based diabetic management.

Faecal Microbiota Transplantation (FMT) is an experimental procedure to transfer microbial communities from a screened donor to a recipient [20]. Microbial transfer can affect insulin sensitivity in some metabolic phenotypes, leading to increased interest in FMT for metabolic disorders.

Recent research suggests that FMT may enhance insulin sensitivity in certain persons with T2DM, although benefits on HbA1c are less consistent and may rely on donor features and recipient microbiome profiles. Important problems remain about donor selection, durability, safety, standardisation and how to identify responders. FMT is still being investigated for everyday diabetic management [21].

The interaction between the microbiome and therapy is not one-way. Drugs can alter microbial populations and microbial metabolism may influence medication efficacy and tolerance. Of them, the best studied is metformin. Metformin has been shown to alter the composition of the intestinal microbiome and some of its metabolic effects may be mediated via microbiome-dependent pathways.

The burgeoning discipline of pharmacomicrobiomics hints at the prospect that one day, treatments for diabetes might be personalised to the individual's microbial composition [22].

## Conclusion

The microbiome is becoming a key component of the biological network underpinning diabetes. The best evidence to date is for the gut microbiome and T2DM, where dysbiosis may be involved in insulin resistance, chronic inflammation, intestinal permeability, microbial metabolite production and glucose homeostasis. There is also increasing evidence of microbiomes in T1DM, oral health, diabetic kidney disease and other diabetes problems.

Alternatively, microbiome-directed therapies such as dietary modification, probiotics, prebiotics, synbiotics, FMT, and personalised nutritional strategies are promising but vary in clinical outcomes that are often modest. Crucially, the microbiome is not yet ready to be considered an alternative to proven approaches for preventing and treating diabetes. Rather it is a complementing biological system that may someday improve illness prediction, risk stratification, therapy selection and prevention.

The future of diabetic microbiome research will rely on progressing beyond descriptions of microbial “good” and “bad” bacteria and toward a systems-level knowledge of microbial roles, metabolites, host genetics, nutrition, medicines, and immune-metabolic interactions. Such an approach could potentially contribute to microbiome-informed precision medicine and open new avenues for alleviating the ever-growing global burden of diabetes.

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