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Role of the Gut Microbiome in Type 1 and Type 2 Diabetes Pathogenesis

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ABSTRACT

Diabetes mellitus, encompassing type 1 (T1D) and type 2 (T2D), has traditionally been viewed through lenses of genetics, autoimmunity, insulin resistance, and environmental risk factors such as diet and obesity. Recent advances in microbiome research have identified the gut microbiome as a potentially pivotal player in the pathogenesis of both forms of diabetes. In T1D, alterations in the early-life microbiota, impaired intestinal barrier function, dysregulated immune development, and specific microbial taxa shifts precede or accompany islet autoimmunity. In T2D the gut microbiome influences metabolic regulation through modulation of energy harvest, short-chain fatty acid (SCFA) production, bile acid metabolism, lipopolysaccharide (LPS)-driven endotoxemia, inflammation, and insulin sensitivity. This review surveys the current evidence linking gut microbial composition and function to both T1D and T2D pathogenesis, explores mechanistic studies elucidating causal pathways, examines how modifiable factors (diet, antibiotics, mode of birth, probiotics/prebiotics) might influence risk, and evaluates translational prospects for microbiome-based interventions. We emphasize that while cross-sectional human studies are abundant, prospective cohort, mechanistic animal, and intervention studies are fewer, leaving gaps in the understanding of causality and heterogeneity among individuals. Ultimately, harnessing the gut microbiome may enable novel prevention or therapeutic strategies, but rigorous trials, better biomarkers, and understanding of host-microbiome interactions remain essential.

Keywords: gut microbiome; type 1 diabetes; type 2 diabetes; dysbiosis; metabolic inflammation

INTRODUCTION

Diabetes mellitus affects hundreds of millions of people worldwide, imposing a heavy burden in terms of morbidity, mortality, and healthcare costs[1–3]. In its two major forms, type 1 diabetes (T1D) and type 2 diabetes (T2D), distinct etiologies converge on the failure of regulated glucose homeostasis[4, 5]. T1D is classically an autoimmune disease, characterized by destruction of the pancreatic islet β-cells, commonly in childhood or adolescence, often leading to life-long insulin dependence[6–8]. T2D, more prevalent globally, arises largely through insulin resistance, with β-cell dysfunction developing over time, often associated with obesity, sedentary lifestyle, and diet. Genetic predisposition plays an important role in both, but for neither disease does genetics fully explain the rising incidence over recent decades. Environmental factors are increasingly recognized as critical[6, 9, 10]. Among these factors, the gut microbiome, the trillions of microorganisms inhabiting the gastrointestinal tract, is emerging as a potentially major mediator of environmental influence on disease risk, offering both mechanistic insights and therapeutic promise [11].

The gut microbiome is a dynamic ecosystem that establishes early in life and is influenced by mode of delivery, infant feeding, antibiotic exposures, diet, geography, and host genetics[12–14]. It contributes to nutrient metabolism, immune system education, maintenance of barrier integrity, regulation of inflammation, and production of microbial metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, and other bioactive compounds. Dysbiosis or perturbation of microbial community structure, function, or both has been linked to multiple diseases, including obesity, inflammatory bowel disease, metabolic syndrome, and autoimmune disorders[15–17]. In the case of diabetes, an expanding body of epidemiological, clinical, and preclinical evidence suggests that changes in the gut microbiome precede or accompany both T1D and T2D onset, implicating mechanisms that span immune dysregulation, metabolic endotoxemia, barrier dysfunction, and altered host-microbial metabolic crosstalk[18].

In T1D, children who later develop islet autoantibodies often show altered microbial diversity, reduced abundance of certain taxa thought to be beneficial, and altered microbial metabolic output. Early life

perturbations such as antibiotics, cesarean section, low fiber diet, or other environmental exposures appear to increase risk, possibly via effects on mucosal immunity, regulatory T cell induction, and intestinal permeability[19, 20]. While autoantibodies and genetic susceptibility (for example, HLA loci) are established markers of risk, they do not fully predict who will develop T1D, and microbiome variation may help explain additional inter-individual differences. In adults with longstanding T1D, studies have shown differences in microbial taxa compared to healthy controls, associations between microbial pathways and measures such as HbA1c, disease duration, and presence of vascular complications, though the direction of causality remains uncertain[21]. The literature is enriched by recent metagenomic shotgun sequencing which enables deeper taxonomic and functional profiling.

In T2D, the relationship between gut microbiome and pathogenesis is arguably more multifaceted owing to interactions among diet, obesity, metabolic inflammation, insulin resistance, and hepatic metabolism. Observational studies have shown that individuals with T2D often display reduced microbial diversity, decreased abundance of SCFA-producing bacteria (such as *Faecalibacterium prausnitzii* and Roseburia spp.), altered bile acid composition, and increased proportions of opportunistic or pro-inflammatory taxa. Animal experiments have demonstrated that transferring microbiota from T2D donors into germ-free or antibiotic-treated mice can reproduce features of insulin resistance or altered glucose metabolism[22]. Mechanisms proposed include increased gut permeability enabling translocation of bacterial components such as lipopolysaccharide (LPS), triggering systemic low-grade inflammation; impaired production of microbial metabolites that modulate glucose and lipid metabolism; and altered bile acid signaling affecting host receptors that regulate metabolic homeostasis.

Despite accumulating data, important gaps remain. Many human studies are cross-sectional and thus cannot establish temporal order or rule out reverse causation. There is substantial heterogeneity in results across different populations, methods, sample sizes, sequencing approaches, and definitions of dysbiosis. [15, 16, 23]. Whether there are shared microbial features between T1D and T2D pathogenesis, or whether they are distinct, remains unsettled. Understanding how environmental modifiers (diet, prebiotics, probiotics, antibiotics, lifestyle) interact with host genetics and early immune development is crucial. Moreover, translating microbiome findings into therapeutics or biomarkers demands mechanistic studies and clinical interventions. This review will first summarize what is known about the gut microbiome in T1D, then review data for T2D, then examine mechanistic pathways common and distinct between them, consider modulators of the microbiome, evaluate therapeutic implications, and finally consider methodological and translational challenges and future directions. Through this, we aim to clarify where the field is, what it meaningfully suggests about pathogenesis, and what needs to be done before microbiome-based strategies can be reliably deployed in diabetes prevention or treatment.

Gut Microbiome in Type 1 Diabetes Pathogenesis

Type 1 diabetes is initiated by autoimmune destruction of insulin-producing β-cells, commonly preceded by a preclinical phase marked by islet autoantibody development. Recent evidence supports that perturbations in the gut microbiome may precede or accelerate this sequence. Studies of children at high genetic risk show altered microbiome diversity and taxonomic shifts before seroconversion[24, 25]. Taxa producing short-chain fatty acids are often lower in abundance; for example, butyrate producers tend to be depleted. Reduced levels of SCFAs may compromise intestinal barrier integrity and reduce the induction of regulatory immune cell populations. Early-life exposures such as formula feeding, antibiotic treatment, or cesarean section, which influence initial microbiota colonization, are correlated with a higher risk of autoimmunity[26]. Animal models, such as non-obese diabetic (NOD) mice, have shown that germ-free status or antibiotic manipulation can alter the incidence of insulitis or delay diabetes onset, suggesting causality[27].

Human studies in established T1D have shown consistent alterations in microbiome composition. For example, in adults with longstanding T1D, several bacterial taxa and metabolic pathways correlate with glycemic control metrics such as HbA1c, continuous glucose monitoring, and with disease duration. One recent large study of participants with T1D (average disease duration ~28 years) compared to matched healthy controls found that though α-diversity (a measure of species richness) was not significantly different, many bacterial taxa were significantly enriched or depleted in T1D; moreover, HbA1c and duration of disease explained part of the variation in microbiome composition[28]. Some taxa depletion has been associated with vascular complications, especially nephropathy. These findings indicate that the microbiome alteration is persistent and correlates with disease severity and complications[28].

Mechanistically, the gut microbiome in T1D seems to influence disease via modulation of immune responses and intestinal barrier function. Gaps in the intestinal epithelium ("leaky gut") may allow microbial byproducts (e.g. lipopolysaccharide) or whole bacteria to translocate and activate innate immune pathways[29]. Microbial signals can affect antigen presentation, regulatory T-cell development, and the balance of pro- versus anti-inflammatory cytokines. Microbial metabolites such as SCFAs can influence epigenetic regulation of immune cells, promote mucin production, and modulate gut pH, which in turn affects which bacterial species flourish. Bile acid metabolism and microbe-derived tryptophan metabolites have also been identified as relevant[30].

However, limitations in human studies include reliance on cross-sectional designs, small sample sizes in many pediatric cohorts, variability in sequencing and bioinformatics pipelines, and confounding by diet, geography, antibiotic exposure, and other environmental exposures. While animal models provide strong causal hints, translating those findings into human risk prediction or prevention remains challenging[31]. Yet, microbiome modulation (via prebiotics, probiotics, synbiotics, or other agents) holds promise, and early trials have reported modest improvements in HbA1c, insulin usage, and C-peptide levels when microbiome-modulating agents are used in T1D.

Gut Microbiome in Type 2 Diabetes Pathogenesis

Type 2 diabetes pathogenesis involves a complex interplay of insulin resistance, obesity, hepatic metabolic dysfunction, and chronic low-grade inflammation[32]. The gut microbiome appears to participate integrally in this interplay through multiple pathways. Observational human studies have revealed that persons with T2D often have reduced microbial diversity and marked depletion of microbes that produce beneficial metabolites such as butyrate, propionate, and other SCFAs. There are increases in pro-inflammatory or opportunistic taxa, shifts in bile acid metabolism, and changes in the capacity for energy harvest from diet[33]. Fecal metabolome studies show altered SCFA profiles, differences in branched chain amino acid metabolism, and differences in gut microbial genes implicated in lipopolysaccharide (LPS) biosynthesis and endotoxin release[33].

Mechanistic and animal model work provides stronger evidence of causality. Transfer of microbiota from diabetic humans or mice into germ-free or antibiotic-treated rodents can transfer aspects of glucose intolerance, weight gain, and hepatic fat accumulation[34]. LPS translocation across an impaired intestinal barrier initiates toll-like receptor (TLR)-mediated innate immune activation, increasing systemic low-grade inflammation, which in turn impairs insulin signaling in adipose tissue, liver, and muscle[35]. SCFAs, particularly butyrate, play roles in maintaining intestinal epithelial health, promoting gluconeogenesis regulation, stimulating the release of gut hormones (such as GLP-1, PYY) via free fatty acid receptors, and modulating adiposity and satiety. Altered bile acid signaling via receptors such as FXR and TGR5 has been shown to affect glucose and lipid metabolism, with the microbiome influencing conjugation, deconjugation, and transformation of bile acids[36]. Microbial metabolites of tryptophan and others also appear to contribute to oxidant stress, immune modulation, and possibly β-cell dysfunction in T2D.

Host factors, including diet composition (fiber content, fat type), obesity, lifestyle patterns, medications (especially metformin), antibiotic use, and circadian rhythms, further modulate the gut community[37–39]. These factors may lead to microbial dysbiosis that amplifies metabolic perturbations. For example, high-fat or high-sugar diets reduce SCFA-producing organisms and increase gut permeability. As gut barrier function is compromised, endotoxemia increases, adipose and hepatic inflammation ensue, driving insulin resistance. There is evidence in human cohorts correlating LPS levels, markers of inflammation such as CRP or IL-6, and microbial profiles[40]. Interventions that alter the microbiome dietary fiber, fermented foods, metformin, and post/prebiotics, have shown associations with improved glucose homeostasis. Yet causality in humans remains less conclusively established than in animal studies. There is inter-individual variability, regional and dietary confounders, and difficulty in isolating microbiome effects from other metabolic risk factors[41].

Cross-cutting Mechanistic Pathways & Comparison

Despite differences in etiology and clinical presentation, T1D and T2D share several mechanistic pathways through which the gut microbiome may influence disease, and also display unique features[42]. Both forms involve inflammation, immune regulation, microbial metabolite production, and intestinal barrier integrity, but the timing, relative importance, and downstream targets differ[42].

One shared mechanism is intestinal permeability. When the gut barrier is compromised, bacterial components such as lipopolysaccharide or flagellin may translocate into circulation, triggering innate immune activation[43]. In T1D, this may promote or accelerate autoimmune responses against islet antigens; in T2D, this contributes to systemic low-grade inflammation that worsens insulin resistance. Second, SCFAs (butyrate, propionate, acetate) appear to be protective in both contexts. In T1D, SCFAs seem to promote regulatory immune cell differentiation, maintain gut barrier function, and dampen autoimmunity. In T2D, they also help maintain the barrier, reduce adipose or hepatic inflammation, stimulate gut hormone release, and influence energy metabolism[44]. Third, bile acid metabolism, tryptophan metabolites, and other small molecules generated by gut microbes have roles in modulating immune responses and metabolic signaling in both types, though the specific metabolic pathways implicated differ.

However, there are important contrasts. The autoimmune destruction in T1D generally involves early life, with immune tolerance and antigen presentation being critical, whereas in T2D, the chronic metabolic burden and insulin resistance are key drivers, with inflammation being more sustained and metabolic rather than primarily antigen-driven[45]. In T1D, changes in microbial taxa often precede or accompany seroconversion; in T2D, microbiome shifts may largely follow or amplify metabolic dysregulation though some may precede overt disease. Also the roles of diet and obesity are much stronger in T2D, whereas in T1D factors such as genetic predisposition (e.g. HLA), early immune development, viral infections etc., feature more prominently[46]. Therapeutic interventions may also differ; for example, in T1D preserving residual β-cell function is critical, in T2D improving insulin sensitivity and reducing metabolic burden are major aims[46].

Moreover, host genetics and environmental exposures interact. Genetic risk loci in T1D may influence gut barrier or immune system that are modulated by microbiome exposures. In T2D there is evidence that host metabolic phenotype influences what microbes flourish (e.g. high fat diet favoring microbes that extract more calories), and in turn microbial metabolites feedback on host metabolism[46]. Medications such as metformin have effects on the gut microbiome (shifting populations, increasing SCFA producers, altering bile acids) which seem to contribute to their therapeutic effect in T2D; this is less well-studied in T1D though immunomodulatory drugs may also have indirect effects via gut flora.

Modulators of the Gut Microbiome, Therapeutic Implications, and Challenges

Multiple modifiable factors determine the composition and function of the gut microbiome, offering opportunities for prevention and therapy, but also presenting challenges in consistency, safety, and intended effects. Among modulators, diet is among the most powerful[47]. Dietary fiber, resistant starch, and diverse-plant diets foster SCFA producers, improve intestinal barrier function, and reduce markers of inflammation; diets high in saturated fats, ultra-processed foods, and low in diversity tend to promote dysbiosis, LPS-producers, and pro-inflammatory states[48]. Prebiotics, probiotics, synbiotics, and postbiotics have been trialed in both T1D and T2D. In T1D, several randomized controlled trials of microbiome-modulating agents (MMAs) including probiotics and synbiotics have shown modest but statistically significant improvements in HbA1c, lowered exogenous insulin requirements, and improved C-peptide retention, though effects on inflammatory markers are less consistent[49]. In T2D, several diet and probiotic/prebiotic interventions have improved insulin sensitivity or glucose control, often accompanied by shifts in microbial diversity or metabolite profiles.

Another therapeutic approach is fecal microbiota transplantation (FMT), which has shown efficacy in metabolic syndrome or insulin sensitivity in small trials in humans and more robust effects in animal models[49]. Also, small molecule or metabolite-based interventions (e.g., administering SCFAs, modulating bile acid signaling via receptor agonists) are under investigation. Drugs already used in diabetes treatment, such as metformin, may exert part of their effects via alterations to the gut microbiome; this suggests that understanding microbial contributions could allow for optimizing drug choice or developing adjunct treatments.

Challenges are substantial. Inter-individual variability in microbiome composition is high, influenced by geography, diet, age, genetics, prior antibiotic exposure and other environmental exposures, making generalization difficult[50]. Timing of interventions appears important: early life or even prenatal windows may be more malleable, especially for T1D, whereas later interventions may face more established pathological changes. Safety is a concern, especially for probiotics or FMT, including risks of infection or unintended metabolic effects[50]. Biomarker development is needed both to identify who may benefit most and to monitor effects. Standardization of methods (sampling, sequencing, bioinformatics) is weak in many studies, leading to heterogeneity in results. Longitudinal, carefully controlled human trials are fewer than necessary[51]. Also, distinguishing cause from consequence remains a central challenge: does the microbiome drive disease or does alter metabolism (or autoimmunity) drive microbiome changes (or both)?

Future Directions

The gut microbiome is now firmly established as a crucial environmental factor in the pathogenesis of both type 1 and type 2 diabetes. For T1D, evidence is mounting that early-life microbiome perturbations, impaired barrier function, and dysregulated immune responses play roles in initiating autoimmunity, and that in established disease microbial composition continues to correlate with glycemic control and complications. In T2D, microbial alterations appear interwoven with metabolic inflammation, insulin resistance, and diet, and both human cohort and animal transfer studies lend weight to the hypothesis that microbiota contribute causally to disease progression.

Looking ahead, several key priorities emerge. First, large prospective human cohorts are needed in both T1D and T2D that collect early life microbial data, dietary exposures, host genetics, immune markers, and longitudinal metabolic outcomes. These will help disentangle cause and effect, define temporality, and identify which microbial signatures best predict disease onset or progression. Second, mechanistic studies, especially in gnotobiotic or humanized animal models, must continue to clarify pathways SCFAs, bile acids, tryptophan derivatives, microbial cell wall components, immune training, epigenetic regulation, to understand which interventions are promising. Third, interventions must be designed with attention to timing, specificity, and host context. For example, for T1D preventive strategies, timing in infancy or even prenatally may offer greater leverage; for T2D, diet, lifestyle, and drug interactions will remain central. Tailored prebiotics, probiotics, synbiotics, or metabolite administration, maybe FMT in selected cases, deserve rigorous randomized controlled trials with adequate sample size, appropriate controls, long follow-up, and safety monitoring. Moreover, precision medicine approaches may be needed. Individuals differ in baseline microbiome, genetic risk, immune responsiveness, and environmental exposure; what works in one setting (e.g. a high-fiber diet) may not in another if the resident microbiome lacks necessary responder strains. Biomarkers that reflect microbial function (e.g. metabolite levels, barrier integrity measures, immune profiling) rather than only composition are likely to be more useful. Finally, regulatory, ethical, and logistical issues around microbiome modulation, especially interventions such as FMT must be addressed.

CONCLUSION

In summary, the gut microbiome occupies a central, though not fully mapped, role in the pathogenesis of both forms of diabetes. It offers both explanatory power for environmental contributions and promising targets for prevention or adjunctive therapy. Continued investment in prospective, mechanistic, and translational research will be essential for moving from association to impact, and for harnessing the microbiome to reduce the global burden of diabetes.

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