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Review of the Microbiome in Diabetes

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ABSTRACT

Diabetes mellitus is a rapidly expanding global health challenge driven by complex interactions between genetic, environmental, metabolic, and immunological factors. Growing evidence highlights the gut microbiome as a critical regulator of glucose homeostasis, insulin sensitivity, immune modulation, and pancreatic β-cell function. This narrative review synthesizes current knowledge on the role of the human microbiome in the pathophysiology of both type 1 and type 2 diabetes. It examines how early-life microbial exposures influence immune tolerance and autoimmunity, how gut dysbiosis contributes to β-cell destruction, insulin resistance, and metabolic inflammation, and how microbial metabolites such as short-chain fatty acids, bile acids, and lipopolysaccharides mediate host–microbe interactions along the gut–liver–pancreas axis. The review further evaluates emerging therapeutic strategies, including dietary modulation, probiotics, prebiotics, synbiotics, and fecal microbiota transplantation, alongside methodological challenges inherent in microbiome research. While microbiome-targeted interventions hold considerable promise, significant gaps remain regarding causality, reproducibility, and long-term clinical efficacy. Addressing these challenges through well-designed longitudinal and multi-omic studies will be essential to translating microbiome science into effective preventive and therapeutic strategies for diabetes.

Keywords: Gut microbiome, Diabetes mellitus, Gut dysbiosis, Short-chain fatty acids, and Microbiome-based therapies.

INTRODUCTION

The rising prevalence of diabetes mellitus represents a worldwide healthcare crisis. A complex constellation of risk factors drives its emergence, amplifying the need for innovative therapeutic strategies [2]. In recent years, mounting evidence has revealed the considerable influence of the gastrointestinal microbiome on glucose homeostasis and energy metabolism and, conversely, how perturbations in metabolism shape the microbiome. While the microbiome-gut-brain axis has received increasing attention from the research community [1], the connections between microbial communities, their metabolites, and pancreatic islet cells merit deeper exploration. New insights into these interactions hold promise for advancing mechanistic understanding and guiding novel therapies targeting the gut microbiome approaches that warrant urgent research attention [3].

Overview of the Human Microbiome

The term microbiome encompasses all microorganisms, bacteria, viruses, fungi, and protozoa and their genetic material at a given location [1]. A particular focus is the gut microbiome, which includes both luminal microorganisms and those associated with gut epithelial cells [2]. Microbial communities vary according to body site, individual, and environmental factors; dimensions of community structure include species richness (the number of species) and relative abundance (the proportion of each species) [8]. Core taxa are widely shared among healthy individuals at a given body site. Computational tools for sequencing analysis enable the characterization of microbial diversity and metabolic potential [5]. Sequencing approaches vary in throughput, read length, and taxonomic resolution and include targeted bacterial 16S ribosomal RNA gene amplicon sequencing and shotgun metagenomics [4]. The microbiome varies over time; some biofluids show rapid shifts, whereas others are stable over months or years [1]. Major early-life factors shaping the gut microbiota include delivery mode, diet,

antibiotics, medications, and hygiene practices. Interplay between the gut microbiome and the immune system occurs during early life, representing a critical window for intervention in type 1 diabetes [3].

The Pancreatic Islet Microenvironment and Microbiome Interactions

Postnatal development of pancreatic islets is characterized by a two-tiered approach, starting with the establishment of a functional islet-specific architecture followed by the regulation of islet size and function [7]. The pancreatectomized rat model helped to delineate the existence of a secondary wave of growth-promoting signals that was mediated by thoracic duct lymph, with the pleural cavity serving as an accurate in vivo compartment to study this phenomenon [4]. Di- and trihydroxy lipids constitute the lipophilic activity present in pleural cavity reservoir water and have been identified, together with phosphocholine, as potential candidates responsible for the islet mass-stimulating activity [3]. There is a growing appreciation of pancreatic islets as functioning organs comprising a variety of cells, each providing a distinct subset of signals to define overall function. The balance of these signals is of critical importance for the proper setting of the islet activity. Weight of evidence from numerous diabetic models indicates that disorganization of the signalling network that defines islet activity is the common final pathway leading to deranged glucose homeostasis [3]. The pancreas possesses protective mechanisms that form a barrier to pathogenic agents. In the islet, the endocrine cells are spaced apart by matrix and cadherin-based junctions that limit uncontrolled hormone diffusion to the blood. The islet-endothelium interacts via a variety of signalling molecules, including morphogens that provide critical functional information to the islet [6]. Despite these protective mechanisms, the islet is both a target and modulator of systemic immune responses and can therefore be a portal of entry for pathogenic micro-organisms [2]. Specific β-cell GRK2 overexpression results in increased: (i) systemic and local inflammatory cytokines, (ii) vascular leak and accumulation of second messengers, (iii) β-cell loss and reduced islet mass associated with the diabetic phenotype at a pre-symptomatic stage, (iv) amplifying and attracting functions on multiple immune cell subtypes at an early stage that subsequently becomes complicated by insulin-secretory down-regulation on β-cells during advanced diabetic phases. Over-activation of the β-cell microenvironment is associated with type 2 diabetes [3].

Early-Life Factors and Autoimmunity

The early-life period is critical for the establishment of microbial communities in the infant gut, and this is particularly true in type 1 diabetes (T1D). Changes in microbial community composition have been shown to contribute to the onset of the disease [2]. The interaction of microbial and autoimmunity-related genes in the microbiome can be modulated by external environmental factors such as birth mode, breastfeeding or formula feeding, the use of antibiotics and/or proton-pump inhibitors (PPIs), and early-life hygiene conditions [2]. For instance, when an infant is born via cesarean section, the microbial colonization that occurs is significantly different from that of infants born naturally [5]. These bacteria can have both pro-inflammatory and protective roles. Specific microbial compositions can modulate host inflammation, like TNFα, IL-6, and IL-18, to prevent T1D onset. Germ-free studies indicate that the early-life gut microbiome has a substantial influence on the host immune system [6]. Germ-free conditions during pregnancy lead to inhibition of β-cell autoimmunity and T1D in the offspring, indicating that it is possible to suppress such autoimmunity in the offspring by performing environmental modifications [7]. The first few months preceding the onset of T1D are considered a critical window of susceptibility to the development of T1D in predisposed individuals. Similarly, the gut microbiome shifts rapidly in infants and is maintained before any other major alterations for about 2 years. Likewise, during the first 12 months of life, the microbiota composition is heavily influenced by the mode of delivery [8].

Mechanistic Links between Gut Dysbiosis and Beta-Cell Destruction

Alterations in the gut microbiota termed gut dysbiosis have been implicated in the epidemiological link between the gut microbiome and type 1 diabetes (T1D). Gut dysbiosis potentiates β-cell destruction during the prediabetic phase of T1D [1]. Mathematical modeling predicts that gut dysbiosis causes high intestinal permeability and translocates gut-derived microbial products into the systemic circulation, triggering an increase in lipopolysaccharide (LPS)-induced inflammation in the islets of Langerhans during the prediabetic phase. Consistent with this prediction, α-GalCer, which induces Th2 cytokines and inhibits the Th1 response, diethylene triamine penta-acetic acid (DTPA), an intestinal peristalsis inhibitor, and bovine colostrum with lactoferrin supplementation have been shown to prevent gut dysbiosis and hyperpermeability, leading to the prevention of diabetes onset [5]. Both gut-derived LPS and interleukin-1β (IL-1β), produced in the intestine by vancomycin-sensitive Lactococcus piscium or induced by dietary butyrate in gut-educated T cells, have been implicated in β-cell destruction [3]. Therefore, changes in the gut microbiota may enhance the intestinal permeability and capacity of microbial antigens to penetrate the systemic circulation and promote diabetes progression by amplifying ongoing inflammation in the pancreatic islets driven primarily by the microbiota-dependant lysosomal LPS, possibly in conjunction with IL-1β production, Spontaneously-diabetic non-obese mice bear a microbiota

with low capacity to facilitate β-cell destruction, suggesting that the link between gut microbiota and β-cell destruction may exist even in the absence of overt T1D[4].

Gut Microbiota Alterations in Type 2 Diabetes

The term 'microbiota' refers to all microbial communities in the human body. The microorganisms of the human gut microbiota contribute to the digestion of human food, provide essential metabolites, and protect against pathogens [1]. Type 2 diabetes mellitus is a metabolic disorder characterized by altered glucose and fat metabolism due to insulin resistance or the decreased ability of insulin secretion [8]. The pathophysiology of type 2 diabetes mellitus is highly interconnected with the gut microbiota, and many researchers worldwide are investigating the exact mechanism of interaction between them [7]. The gut microbiota of type 2 diabetes patients is notably characterized by the increased abundance of pro-inflammatory microbes such as Firmicutes and Proteobacteria, and a decreased presence of beneficial microbes such as Bacteroidetes [14]. It has been shown that the gut microbiota composition and its metabolites contribute to many critical alterations responsible for inducing and progressing insulin resistance, increased inflammatory response, and imbalance of the gut metabolism of glucose and lipids [16]. Therefore, an improved grasp of gut microbiota dysbiosis in type 2 diabetes and its respective pro-diabetic pathophysiological mechanisms can provide much insight into potential therapeutic approaches targeted at curtailing diabetes development and progression [15].

Dysbiosis, Metabolic Inflammation, and Insulin Resistance

The gut microbiota is a complex and variable environment, where an imbalance of bacterial populations, called dysbiosis, often occurs [2]. Dysbiosis leads to the overgrowth of pathobionts, the depletion of commensals, or a reduction in overall bacterial diversity. Diet and antibiotics heavily influence the gut microbiome and are known to promote alterations associated with obesity and type 2 diabetes (T2D) [5]. Obesity-related microbiomes extract greater caloric energy from complex polysaccharides, resulting in substantial energy surplus and, consequently, excessive fat storage [3]. The loss of anti-inflammatory bacterial genera, such as Faecalibacterium prausnitzii and Akkermansia muciniphila, reduces the biosynthesis of short-chain fatty acids (SCFAs), which are crucial mediators of energy metabolism. Interestingly, obesity is associated with increased SCFA production, favouring enhanced energy extraction under dietary control. Early findings linking enhanced butyrate production to improved insulin sensitivity suggest a direct metabolic role for this SCFA in T2D pathogenesis [7]. Moreover, defective propionate production and/or absorption have been implicated in elevated T2D risk. Although >80% of colonic SCFAs are absorbed by colonic epithelial cells, this microbial-derived energy source supports metabolic health in these individuals [8]. Diabetes Mellitus (DM) constitutes a worldwide socio-economic health threat. Data indicate that the disease is steadily increasing, with type 2 diabetes (T2D) accounting for the higher proportion [1]. DM is an inflammatory disease at its core, comprising multifactorial components, e.g., gut microbiota dysfunction [9]. At an early instrumental stage of DM pathogenesis, gut microbiota dysbiosis develops, altering normal bacterial composition [9]. Disturbed gut microbiota causes the release of elevated levels of lipopolysaccharides (LPS) via the gut–liver circuit, which compromises the gastrointestinal barrier. Once the intestinal barrier is damaged, LPS keeps entering the bloodstream, creating a pro-inflammatory environment [2]. The excess of pro-inflammatory mediators affects the insulin receptor signal transduction pathway, provoking insulin resistance and hyperglycemia. Conversely, gut commensals present in an eubiotic state attenuate the intestinal barrier with the help of short-chain fatty acids (SCFAs). Various SCFAs (butyrate, propionate, and acetate) not only protect against the LPS induced damage but also favour the metabolic outcomes of eubiotic gut flora [3]. The human gut harbours trillions of microorganisms, with 70–90% being uncharacterised and culture intractable. Systematic studies applying dietary lifestyle modifications, probiotics, prebiotics, synbiotics, and dietary supplements as gut microbiota-modulating agents could yield soluble solutions for managing the diabetes-induced inflammatory vicious cycle [6].

Short-Chain Fatty Acids and Glucose Homeostasis

Gut microbiota-derived short-chain fatty acids (SCFAs) produced by fermentation of indigestible dietary fiber affect glucose homeostasis and metabolic regulation [10]. Acetate, butyrate, and propionate, generated in the colon and transported into the circulation, are major SCFAs that can regulate glucose metabolism, fat metabolism, and energy expenditure [9]. SCFAs improve glucose intolerance and insulin sensitivity during high-fat diet (HFD) or diabetic model feeding. Acetate alone ameliorates obesity, glucose intolerance, and animal longevity in an HFD-fed diabetic model [6]. SCFAs exert their effects through the SCFA receptor free fatty acid receptor 2 (FFA2 or GPR43) in pancreas β-cells, positively regulating glucose-activated insulin secretion [12]. Abundance and composition of gut microbiota show differences in type 2 diabetes (T2D), obesity, and metabolic syndrome. SCFAs, as key microbial metabolites linking dietary fiber intake to host physiology, possess beneficial effects on metabolism. They exert important metabolic regulatory roles in T2D, obesity, and other metabolic disorders [8].

Mechanisms Linking Microbiome to Diabetes Pathophysiology

Although type 1 and type 2 diabetes arise from distinct pathophysiological mechanisms, they share common features at the microbiome–host interface [11]. Increased gut permeability and elevated plasma levels of the bacterial lipopolysaccharide component endotoxin drive metabolic dysregulation and autoimmune pathologies in both disorders [10]. In type 2 diabetes, the gut microbiota induces the synthesis of bile acid intermediates (via the gut–liver–portal axis), as well as gut-derived incretin hormones that increase hepatic glucose output. Moreover, the efficacy of metformin, a first-line drug for type 2 diabetes, depends on a functional microbiota [1]. The cross-talk between the microbiota and pancreatic islets remains an intriguing area of investigation. Microbial metabolites that produce gut–brain axis signaling or the immunogenicity of exogenous insulin may influence islet health [5]. Further efforts are required to establish causal relationships and elucidate the underlying mechanisms connecting gut dysbiosis to the onset of diabetes mellitus [6].

Immune Modulation and Endotoxemia

The human gut harbors 1014–1015 bacteria comprising more than 1000 different species and a total of >10,000 different strains that constitute the gut microbiota [9]. The functional capacity of any single species from the thousands present in a given individual is limited, yet the overall capability derived from the gut microbiota is immense, permitting a much broader range of metabolic activities than the individual host possesses [8]. Through these metabolic activities, the gut microbiota exerts pleiotropic effects on the host and contributes to the development of many diseases, including diabetes [5]. Short-chain fatty acids (SCFAs), of which acetate, propionate, and butyrate are the most abundant, are produced from the fermentation of non-digestible carbohydrates and dietary fibers by gut bacteria. They are the only microbial metabolites that can efficiently modulate several metabolic pathways in the mammal gut in a host-specific manner. SCFAs are implicated in the regulation of glucose homeostasis; recruitment of immune cells, especially regulatory T cells; modulation of inflammation; and alleviation of metabolic disorders [9]. In addition to SCFAs, bile acids and metabolites of the tryptophan, branched-chain amino acid, phenylalanine, and polyunsaturated-fatty-acid pathways have been recognized to actively shape glucose homeostasis and the host-microbiome interaction [8]. The gut microbiota disturbs the glucose-lipid metabolism system, and uncontrolled glucose and lipid metabolism alter gut-microbiota composition [4]. Host metabolic-factors modulating gut-microbiota composition have been extensively investigated to explicitly clarify the gut microbiota's role in metabolic disease development. Host environmental factors such as medication, supplemental nutrition, and diet plan also influence gut microbiota composition to restrict metabolic syndrome [9].

Metabolic Signaling and Gut-Liver-Portal Axis

The gut microbiome contributes to the pathogenesis of diabetes not only through immune modulation but also via metabolic signaling that alters nutrient metabolism [11]. Primary bile acids undergo microbial transformation and thus confer a strong link between the gut microbiota and diabetes. Bile acids influence glucose and lipid metabolism by activating farnesoid X receptors (FXR) and G protein-coupled bile acid receptor (TGR5) in the liver and adipose tissue, respectively [4]. Increased circulating bile acids are found in both insulin-resistant and diabetic individuals, and the gut microbiota composition is associated with bile acid profiles [8]. The pancreatic β-cell incretin glucagon-like peptide-1 (GLP-1) is produced in response to glucose ingestion and is an important regulator of glucose homeostasis. Oral administration of glucose stimulates more GLP-1 secretion in both non-diabetic and type 2 diabetic humans than intravenous glucose infusion. Incretin-producing intestinal L cells are stimulated by microbiome-derived metabolites. All these factors indicate an important role of the gut microbiota in metabolic signaling and in regulating the gut-liver-portal axis of glucose metabolism [7]. The gut microbiome continues to shape bile acid metabolism throughout life, and shifting the gut microbiome composition through dietary interventions modifies bile acid profiles and improves glucose homeostasis. Despite the increasing evidence linking bile acids and diabetes, the underlying mechanisms remain largely unknown [5]. Microbiome analyses have demonstrated that an enteric strain of bacteriophage can translocate into the pancreas and interfere with β-cell function, highlighting an alternative microbial route that may directly impact the pancreas [8].

Therapeutic Implications and Interventional Approaches

The therapeutic targeting of the microbiome holds promise for the prevention and treatment of diabetes. The use of probiotics (live beneficial microorganisms), prebiotics (substrates selective for beneficial microorganisms), and synbiotics (combined probiotics and prebiotics) has been proposed [6]. A range of experiments have been conducted to evaluate the use of probiotics and prebiotics in the prevention and/or management of T1D and T2D. Some taxa have been documented to confer beneficial effects. However, variation in study design makes it difficult to compare results [4]. The findings suggest additional interest in interventions that go beyond probiotics [1]. Dietary shifts can modulate the composition of the gut microbiota [2]. In particular, the incorporation of fiber into the diet is expected to elicit substantial changes in the microbiome and produce beneficial effects on metabolism. Of the seven commonly studied types of dietary fiber, all were noted to engender genus-level changes in the gut

microbiome associated with improvements in hyperglycemia. Such dietary alterations warrant consideration as adjunct or complementary interventions alongside the modulation of the gut microbiota [8]. Fecal microbiota transplantation (FMT) involves the transfer of stool from a healthy donor into the gastrointestinal tract of an individual seeking restoration of a stable microbiota. Evidence indicates that modulation of the microbiome following FMT has a favorable effect in diabetes. Safety concerns and regulatory uncertainties accompany the procedure, but FMT as therapy has been evaluated in clinical studies. Consideration of the microbiome is deemed warranted in T1D, T2D, and gestational diabetes, and the role of FMT as a means to restore a stable microbiota receives explicit attention [7].

Probiotics, Prebiotics, and Synbiotics in Diabetes

Probiotic treatment of diabetes has been studied since the 1990s, with more than forty clinical trials recorded. Such trials have examined strains with various properties, dosing regimens, and endpoints [8]. Despite efforts to standardize and rigorously implement the 2016 American Diabetes Association (ADA) guidelines, the aggregate quality remains low [9]. While various actors have begun to establish uniform protocols and essential clinical trial variables, methodology is still a fundamental limitation. Syllabic constructs of β-cells and improvements in blood glucose, glycated hemoglobin (HbA1C) level, and insulin requirement have been favored [12]. Metformin remains the most important drug for T2D. Globally, metformin is administered to around 130 million people, with around 270 million people suffering from diabetes [8].

Dietary Interventions and Dietary Fiber

Consumption patterns and fermentation of specific dietary fibers modulate the gut microbiome; transient but considerable changes in bacterial composition support fiber-prebiotic efficacy [6]. Fermentable fibers (inulin, resistant starch, pectin) alter microbiota by enhancing proportional representation of beneficial genera (Faecalibacterium, Roseburia, Bifidobacterium) that boost anti-inflammatory SCFAs [13]. Increased SCFA production slows type 2 diabetes and limits metabolic syndrome by stimulating GLP-1 secretion and the subsequent insulinotropic effect. Such mechanisms warrant consideration for type 1 diabetes. Scant work has explored direct dietary fiber influence on pancreatic islets, yet the correlation between gut microbiota and β-cell function suggests second-order involvement. Fiber exposure in preclinical models accelerates type 1 diabetes onset [12]. Dietary patterns additionally impact type 2 diabetes beyond modulatory microbiome influence [8]. Interventions incorporating multiple fiber-rich whole foods enhance metabolic benefits and gut-microbiome biomarkers over isolated fiber supplements. Vegetarian, Mediterranean, and modified Atkins dietary patterns positively affect type 2 diabetes, yet the vegan alternatives surpass with large reductions in HbA1c, CRP, fasting blood glucose, total cholesterol, and low-density lipoprotein and increases in SCFA producers, methylamines, and Clostridiales [9].

Fecal Microbiota Transplantation: Evidence and Considerations

Fecal microbiota transplantation (FMT) aims to modify the gut microbiota to improve clinical outcomes. It has been successfully used to treat recurrent Clostridioides difficile infection, which is characterized by severe gut dysbiosis [13]. Applications to other conditions, including obesity and metabolic syndrome, are under investigation. The contribution of gut microbiota to metabolic diseases remains debated. Several methodological approaches to FMT, as well as recent technological innovations, are being explored to restore microbial homeostasis in obesity and diabetes [14]. Fecal microbiota transplantation (FMT) shows promise for diabetes management, demonstrated by tolerance and intestinal microbiome changes in preliminary studies [5]. Nevertheless, these studies have small sample sizes and do not include children, intensive care unit patients, or other populations of particular interest [8]. Prebiotics, probiotics, and FMT are therefore plausible candidates for diabetes management, but existing evidence is still insufficiently clear and consistent to merit extensive clinical recommendations. Further well-designed interventional studies would help guide practical dietary therapies targeting the gut microbiota [1].

Methodological Considerations in Microbiome Research

Microbiome studies on diabetes exhibit considerable variation across several dimensions [1]. Diverse methodological strategies include differing study designs, data collection protocols, biological materials, experimental settings, time scales, and analysis pipelines [3]. Such heterogeneity complicates prediction of the consequences of specific alterations, impedes integration of independent observations, and poses challenges for reproducibility [6]. Decoupling confounding factors is therefore vital for understanding causative links between the microbiome and diabetes [2]. Bioinformatics methodologies and sequencing approaches diverge widely across microbiome studies on diabetes. Considerations include choice of primer sets, targeted hypervariable regions, quality-filtering thresholds, taxonomic classifiers, clustering algorithms, and distance metrics [1].

Study Design, Sequencing Technologies, and Data Analysis

The choice of sequencing technology, study design, and computational strategy is critical to understanding bacterial community structure and function, yet varies widely across studies of the microbiome and diabetes [16].

Insights into the types of data generated by different approaches can thus guide the interpretation of results and the identification of critical gaps in knowledge [15]. The choice of bacterial marker gene and the goals of the study determine the optimal sequencing platform to leverage the cost, taxonomic resolution, and biogeochemical information available from cultures. Amplicon sequencing of the 16S rRNA gene remains the most commonly used method for surveying taxonomic community structure, but metagenomic co-assembly of 16S genes is increasingly relied on to address the limitations of this widely adopted approach[15]. Metagenomes, metatranscriptomes, and shotgun sequencing, often considered together, provide mechanistic insight via functional, evolutionary, and biogeochemical information [13]. A core dataset of ten publicly available metagenomic sequencing characterized the differences in the gut microbiome of healthy individuals and people with type 2 diabetes [15]. A wider selection of datasets (fourteen total) was employed to reduce bias in the training of a machine-learning approach to the classification of diabetes-related species and antimicrobials [16]. A broader sampling of the gut microbiome dataset repository, including a range of diseases, was similarly targeted to assess insulin resistance and additional therapies confounding the population sampling [17].

Confounding Factors and Reproducibility

Gut microbiota composition is influenced by host genetics, biogeography, geographical locations, environmental factors, early-life exposures, and lifestyle-related factors [16]. The gut microbiome undergoes dynamic temporal shifts over the lifespan, which is modulated largely by environmental factors and, to a lesser extent, by host genetics. The human gut microbiome is generally composed of approximately 1000 species from around 1200 different genera [14]. Therefore, sequencing the 16S amplicons from the V3–V4 region can derive the highest coverage of taxa at different phyla and genus levels. Consistently, geographical location, particularly urban versus rural, shaping microbial composition in both healthy and overweight populations, is transferable in metabolome and gut microbiome and exerts significant influence on the response to environmental exposures, immunity development, diseases, and metabolism throughout life[13]. In addition, smoking status, drinking behavior, dietary intake, medication history, seasonal changes, sex, age, socio-economic status, and body mass index were also reported to be associated with the variation of gut microbiome [12]. Diet remains the most important factor shaping the gut microbiome [11]. The diet–microbiome interaction is highly dynamic, often changing within a few hours after a meal. Unfortunately, precise dietary information is usually lacking in population-based cohort studies on the gut microbiome. Since body-site variability, cohabiting partners, medication history, fitness level, and dietary intake were not recorded in detail, the influence of time-varying confounding factors, seasonal or temporary effects, and gut microbiome analysis across distinct populations was neglected in the previous study [11]. Nevertheless, the host genetics, including the MODY, T1D, T2D, and location-specific genes such as 1, and the gut microbiome genotype could be acquired through the integration of WGS and metagenomic data, and diverse metabolic health indicators from GIGH and HZG biobanks would allow subtype analysis of diabetes-associated microbiome [12]. The multi-omic data on population and clinical cohorts are valuable to characterize the dynamics of the gut microbiome with their corresponding metabolome and other molecular layers, such as virome, mycobiome, resistome, and plasmidome, which contribute to the understanding of gut microbiome involvement in diabetes susceptibility and can be integrated to explore the cross-omics interactions [10]. Combining the long-term time-series microbiome data with untargeted multi-omic data and further joint analysis on microbial community structure, metabolic network, and temporal multi-omics shift would deepen the insights into diet-associated functional capability shift and underlie the scientific basis for diurnal microbiome modulation strategy towards optimal health [9]. Additional dietary interventions with imposable and trackable alteration on individuals' food ingredients and external exposure to biota are anticipated to refine the precision diet intervention, and supplementing clinical analyses at distinct pathophysiological statuses offers an opportunity to capture the microbiome status transition [9]. Tracking oral-caecal microbiome transition under dietary modification or other external exposure would refine the understanding of the alteration in microbiome exposure associated with biogeographically distributed pathogens [8].

Gaps in Knowledge and Future Directions

Among the many gaps in the literature, several important topics require further research. Although gut microbiome shifts are extensively documented in diabetes, the understanding of the underlying mechanisms remains patchy [17]. Potential areas of investigation include cross-feeding networks, microbiome metabolism of currently undescribed substrates, and microbial modulation of the intestinal immune system. Further long-term longitudinal studies are warranted to complement existing cross-sectional analyses, especially on early-life factors implicated in diabetes pathways [16]. Explore whether off-target metabolic effects caused by probiotics or prebiotics could inadvertently induce some metabolic disorders in predisposed individuals. The emerging association between host genetics and the microbiome suggests these might modulate responses to lifestyle or microbial interventions in diabetes [1]. Comprehensive environmental factors have not been systematically

reviewed, evaluating factors like lifestyle, disorder, medication, travel, and stress, desirable in future studies [18-21].

CONCLUSION

The gut microbiome has emerged as a central player in the development and progression of diabetes mellitus, influencing metabolic regulation, immune responses, and pancreatic β-cell function. Evidence from experimental models and human studies demonstrates that microbial dysbiosis contributes to autoimmune processes in type 1 diabetes and promotes metabolic inflammation, insulin resistance, and impaired glucose homeostasis in type 2 diabetes. Microbial metabolites, including short-chain fatty acids, bile acids, and endotoxins, serve as key mediators linking dietary patterns and environmental exposures to host metabolic and immune pathways. Despite substantial advances, important challenges persist. Most studies remain associative, with limited ability to establish causality, and are complicated by methodological heterogeneity, population-specific effects, and confounding lifestyle and environmental factors. Moreover, the long-term safety, efficacy, and scalability of microbiome-targeted interventions such as probiotics, dietary fiber supplementation, and fecal microbiota transplantation are not yet fully established. Future research should prioritize longitudinal, multi-omic, and interventional studies that integrate host genetics, immune profiling, metabolomics, and environmental exposures. Such approaches will be critical for identifying robust microbial signatures, clarifying mechanisms, and developing personalized microbiome-based therapies. Ultimately, advancing understanding of microbiome–host interactions holds significant potential to improve diabetes prevention, refine treatment strategies, and reduce the global burden of this multifaceted disease.

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