The Role of Gut Microbiota Dysbiosis in the Pathogenesis and Management of Diabetes Mellitus

TAMANNA AKTER[1], BIBI AYESA[2], MST SHAHINUR BEGUM[3], FARHEEN IQBAL[4], BANASREE ROY URMI[5], ADITTA DAS[6], SAYED HOSSAIN[7], MD. JOBAER RAHMAN RASHED[8]
[1, 2, 3, 4, 5, 6, 7, 8] *Tairunnessa Memorial Medical College*

Abstract- ***It has been found that diabetes mellitus a worldwide metabolic dilemma characterized by persistent hyperglycemia is progressively linked to changes in the intestinal microbiome. The gut microbiota, a complex ecosystem of microorganisms found in the gastrointestinal tract, plays a crucial role in maintaining metabolic homeostasis. New evidence has also emphasized the role and importance of the gut-pancreatic axis in regulating glucose homeostasis with dysbiosis leaving the ability to secrete and act on insulin compromised due to inflammatory mechanisms, aberration of incretin response, and changes in short-chain fatty acid production. This review summarizes the existing data associating the gut microbiota disproportion with the pathophysiology of diabetes mellitus (DM) and discusses the potential of restoring a microbiota balance using therapeutic options. Probiotics, prebiotics, diet, and fecal microbiota transplantation have demonstrated the potential to affect glycemic control by improving insulin sensitivity and affecting host metabolism. Along with these encouraging results, it is necessary to conduct additional studies to understand the causal links and lay a foundation for understanding personalized, microbiota-directed treatment. This literature review underlines the topicality of manipulation of gut microbiota in diabetes management and proposes further directions for microbiome-guided interventions.***

Indexed Terms- ***Gut microbiota, Gut–pancreas axis, Glycemic control, Diabetes mellitus, Dysbiosis***

I. INTRODUCTION

Diabetes is a life-long form of metabolism in which there is persistent hyperglycemia due to inadequate secretions of insulin or lack of effectiveness of the insulin or both. There are two types of diabetes namely: Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). T1DM is an autoimmune disease in which there is the destruction of pancreatic B-cells resulting in an absolute insulin deficiency, which is mostly expressed during childhood or adolescence. On the contrary, T2DM is mainly linked to insulin resistance and the presence of relative insulin deficiency frequently connected with obesity, sedentary behavior, and genetic factors. T2DM is considered to comprise more than 90 percent of all the cases of diabetes in the world and now it is on the rise among many developed and developing countries due to the alarming rate of obesity and an increasingly aging population. The International Diabetes Federation stated that over 537 million individuals lived with diabetes in 2021, and by 2030, the figure is expected to go beyond 640 million. This ominous increase in the prevalence of diabetes highlights the need to learn more about its complicated pathophysiology and investigate new management approaches. Within recent years scientific curiosity has been drawn to the pursuit of the purpose of a diverse but plentiful community of trillions of microorganisms known as the gut microbiota inhabiting the human gastrointestinal tract and its role in metabolic health and disease. The microbial communities play a significant role in a number of physiological functions such as digestion, immune regulation, production of nutrients, and maintenance of energy balance. The gut microbiota also participates in a two-way communication system with several organs and what are called the aforementioned, the gut-organ axes. Of these, the gut-pancreas axis has turned out to be very pertinent in relation to diabetes pathology and sugar control. Gut microbiota imbalance or perturbation which is referred to as dysbiosis has been associated with numerous metabolic dysfunctions such as obesity, insulin resistance, diabetes type II, and diabetes type 1 diabetes.

Dysbiosis entails loss of beneficial species of microbes, an excess of disease-causing bacteria, or lowered numbers of microbial diversity. In diabetic patients, dysbiosis is linked to a person having enhanced intestinal permeability (leaky gut), translocation of bacterial endotoxins, especially lipopolysaccharides (LPS) into the blood, and consequent low-grade systemic inflammation. Such alterations may hamper the insulin-signaling process as well as the glucose metabolism. Additionally, dysbiosis impacts short-chain fatty acids (SCFAs) synthesis, biliary acids metabolism, and release of gastrointestinal (GI)-produced hormones such as glucagon-like peptide-1 (GLP-1), which all regulate insulin discharge and responsiveness. Dysbiosis is also considered to contribute to the occurrence of autoimmune reactions in T1DM, which are focused on the pancreatic beta-cells. In this way, the disturbance of the microbiota of the gut is considered not only as a product of the occurrence of metabolic disease but also as a cause of its development and progression.

The secret of this relationship is the gut-pancreas axis: a type of communication path between microbial interactions in the intestines and the functional mechanics of the pancreas. The microbiota of the gut may affect the production of insulin, the absorption of glucose, and the inflammation of the pancreatic tissue through neural, immune, and hormonal routes. As an example, GLP-1 secretion can also be stimulated by SCFAs that are produced by fiber-fermenting bacteria and lead to increased insulin secretion, as well as the regulation of postprandial blood glucose levels. Gut microbiome On the contrary, these good signals can be diminished by the existence of pro-inflammatory bacteria in the gut, and worsen the pancreatic dysfunction. Knowing this axis creates opportunities to intercede therapeutically, in which it is possible that regulating the gut microbiota can enhance glucose control and possibly retard or prevent development of diabetes. In this literature overview, the role in diagnosis and therapy of the dysbiosis of the gut microbiota in diabetes mellitus, in particular, the gut-pancreas axis and regulation of glycemic processes, will be considered. It also discusses the pathways through which the imbalance of the microbiota can lead to an alteration in metabolism and reviews the available evidence to support the use of microbiota-based interventions (i.e., probiotics, dietary management, fecal microbiota transplantation). This review and synthesis of current literature aim to address the treatment potential of the manipulation of gut microbiota and its deficiency in the body, as well as the determination of new research gaps to fill in the achievement of effective, individualized measures of diabetes treatment.

II. THE GUT–PANCREAS AXIS: BIOLOGICAL LINK TO GLYCEMIC CONTROL

The gut-pancreatic axis is a stimulation-response axis between enterocyte microbiota and pancreatic endocrine cells that runs through nerves, immune cells, and metabolic hormones. This axis is very vital in controlling glucose metabolism and the secretion of insulin and, recent research has managed to prove that it is highly related to the onset of diabetes mellitus. Among the most important parts of this axis is the release of incretin hormones, mainly glucagon-like peptide-1(GLP-1) and glucose-dependent insulinotropic peptide (GIP) that happens within the enteroendocrine cells due to the consumption of nutrients. The actions of these hormones are to stimulate the release of insulin, inhibit the release of glucagon, and enhance glycemic control. Short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate made by the intestine also activate free fatty acid receptors FFAR2 and FFAR3 to secrete GLP-1 and GIP by gut-specific L-cells and K-cells [1],[14]. The presence of a healthy gut microbiome will boost this signaling effect which helps in regulating postprandial glucose and responsiveness within the pancreatic β-cell.

Table 1: Mechanisms Linking Gut Microbiota to Pancreatic and Glycemic Function via the Gut–Pancreas Axis

Mechanism	Key Players	Effect on Glycemic Control
Incretin Hormone Secretion	GLP-1, GIP (via L-cells & K-cells), SCFAs (via FFAR2/3)	↑ Insulin secretion, ↓ glucagon, and improved postprandial glucose control

SCFA-Mediated Signaling	Acetate, Propionate, Butyrate	↑ GLP-1/GIP, ↑ insulin sensitivity, ↓ appetite, ↑ mitochondrial function
Immune Modulation & Inflammation	LPS (from Gram-negative bacteria), TLR4, TNF-α, IL-6, NF-κB, Regulatory T cells	Dysbiosis → ↑ inflammation → β-cell damage, ↓ insulin signaling
Gut Barrier Integrity	Tight junctions, SCFAs (especially Butyrate), LPS leakage	Intact barrier → ↓ LPS translocation; Dysbiosis → ↑ systemic inflammation
Peripheral Tissue Effects	SCFAs acting on the liver, adipose tissue, and muscle (via GPR41/43), and acetate on brain appetite centers	↑ Glucose uptake, ↓ gluconeogenesis, ↓ lipogenesis, ↓ and insulin resistance

Along with the hormonal signaling, the microbiota of the gut has certain effects on the immune system, which makes an impact on the functioning of the pancreatic system. In dysbiosis, Gram-negative pro-inflammatory bacteria overgrow producing more lipopolysaccharides (LPS) that impair the integrity of the intestinal barrier. This enables LPS to diffuse into the systemic circulation system where it interacts with Toll-like receptor 4 (TLR4) located in immune cells causing an activation of inflammatory cascades [22]. The low-grade systemic inflammation causes poor insulin receptor signaling as well as leads to the destruction of the beta cells in the pancreas, which eventually leads to insulin resistance and intolerance of glucose. Conversely, SCFAs, particularly butyrate, encourage gut barrier capacities and the growth of regulatory T cells, which assist in inhibiting inflammation and upholding endocrine pancreas level [1], [15]. Maintenance of the gut barrier insulin immunometabolic health is thus critical in the prevention of inflammatory-mediated deterioration of the functions of β-cells.

The peripheral insulin sensitivity is also contributed to by SCFAs. These metabolites of microbes raise or lower energy utilization, fat generation, and glucose uptake into the adipose tissue, liver, and skeletal muscle by their effect on the corresponding receptors. Hypothalamic pathways of appetite regulation are affected through acetate whereas propionate has been found to impact hepatic gluconeogenesis and glucose production [15]. Butyrate is an anti-inflammatory that promotes effects on insulin sensitivity and mitochondrial health. The loss of production of SCFAs made in dysbiosis interferes with this process and leads to hyperglycemia. In addition, a persistent LPS-driven activation of the nuclear factor kappa B (NF-KB) signaling pathway elevates the level of circulating cytokines, including TNF-a as well as IL-6 which interfere with the insulin receptor signaling to aggravate the metabolic disease [22],[1]. Collectively, the gut-pancreas axis acts as an important connection to gut microbiota and glycemia. The well-orchestrated action of microbial metabolites, enteric hormones, and immune mediators favors the β-cell pancreatic function and insulin action. The changes in this axis by way of dysbiosis have the capability of triggering and maintaining the metabolic imbalances that accompany diabetes mellitus. The awareness of these mechanisms pinpoints the therapeutic value of microbiota-based interventions-e.g., probiotics, diet interventions, and SCFA-promoting therapies the restoration of glycemic harmony and prevention of diabetes.

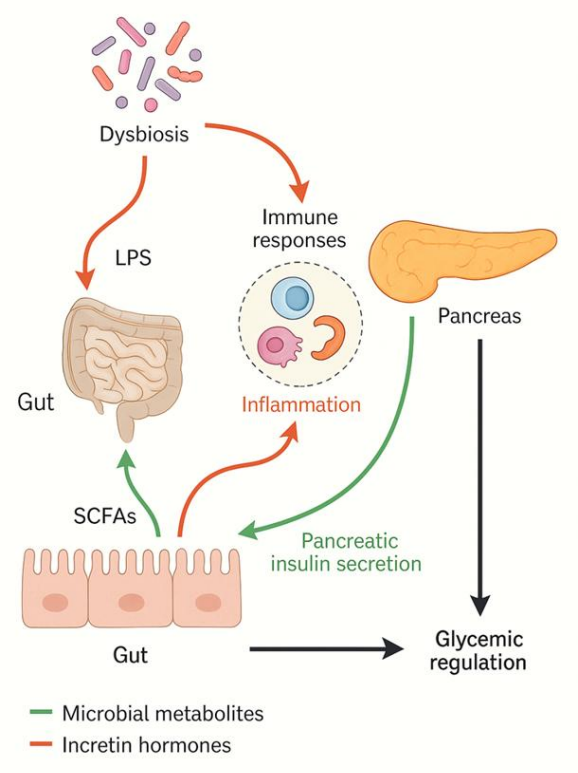

Figure 1: Gut–pancreas axis connecting microbiota signals to insulin secretion and glucose control

III. GUT MICROBIOTA DYSBIOSIS IN DIABETES PATHOGENESIS

Changes in the intestinal microbiome-more commonly known as dysbiosis-are becoming associated with the pathogenesis of both Type 1 and Type 2 diabetes mellitus. Diabetic prevalent patients have differences in microbial signatures with healthy patients. Research has reported a decline in the presence of favorable bacteria genera such as Faecalibacterium, Bifidobacterium, and Roseburia with a boost in the presence of opportunistic pathogens like Ruminococcus and Desulfovibrio [19]. Such changes in microbial community interfere with gut metabolic performance, immune system, and hormonal messages, which are crucial aspects of glucose homeostasis maintenance. One of the main pathological conditions associated with gut dysbiosis is the decrease in intestinal permeability that may be referred to as a leaky gut. The mucosal barrier in this state is altered and bacterial endotoxins including lipopolysaccharides (LPS) translocate to the systemic circulation. Chronic low-grade inflammation is induced by the stimulation of toll-like receptor 4 (TLR4) by LPS within immune cells that alters insulin signaling through interference with the insulin receptors in the periphery leading to insulin resistance. When microbial imbalances sustain such an inflammatory environment, it is at the centre of the metabolic dysfunction in Type 2 diabetes.

The role of gut dysbiosis in Type 1 diabetes is that it mediates autoimmune-related reactions against pancreatic β-cells. Data on longitudinal studies of children with genetic risk of T1DM demonstrate that autoantibodies precedence is succeeded by microbiota alterations, especially a low microbial diversity [16]. Dysbiosis interrupts antigen presentation and the intestinal barrier, contributing to immune activation and cross-reactivity with cell-cell antigens. These results have also been confirmed by animal experiments, with germ-free or antibiotic-treated mice inoculated with fewer cases of autoimmune diabetes, presumably because of fewer gut-sourced inflammatory mimics. Modulation of incretin hormone secretion is one of the main pathways whereby the microbiota of the bowel influences glucose metabolism in Type 2 diabetes. Enteroendocrine cells release incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that in turn trigger an insulin release by the pancreas in response to food consumption. Alteration of the composition of dietary fibers by dysbiosis alters fermentation to short-chain fatty acids (SCFAs) which include butyrate and propionate essential in sustaining the activity of these incretin pathways. The low level of GLP-1 is associated with reduced SCFA production hence poor glycemic control.

The involvement of gut dysbiosis in diabetes is supported by an increase in the literature of human and animal studies. The metagenomic studies have supplied specific details concerning the structure and the performance of the microbiome in diabetic patients demonstrating serious impediments at the abrogated pathways of the amino acid metabolism, oxidative stress, and lipid generation [12]. Mouse experimental models revealed that administration of the microbiota of diabetic donors makes the germ-free mice unable to tolerate glucose, further showing that microbial imbalances are the cause of metabolic dysfunction.

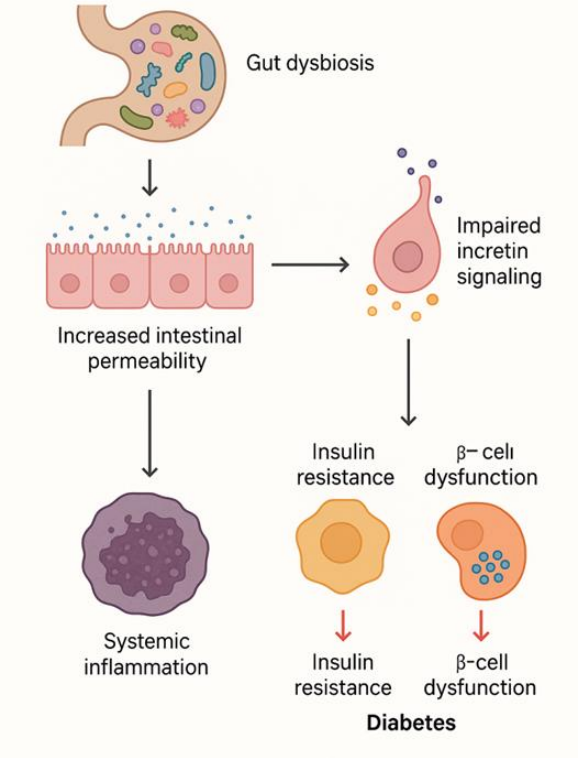

Figure 2: Gut Dysbiosis and Diabetes Mechanisms

IV. MANIPULATING THE GUT MICROBIOTA TO IMPROVE GLYCEMIC CONTROL

Manipulation of the gut microbiota has become an interesting add-on to therapeutic strategies to achieve glycemic control in diabetic patients with mellitus. Probiotics and prebiotics have been studied among the most active interventions, as they have been proven to positively influence the glucose metabolism level. Certain strains of bacteria including Lactobacillus acidophilus, Lactobacillus casei, and Bifidobacterium lactis that have been found to show positive effects in reducing fasting blood glucose and HbA1c levels, especially in Type 2 diabetes mellitus patients [6]. Recently, it was revealed by a meta-analysis that fasting plasma glucose and insulin resistance were significantly improved with probiotic supplementation, particularly, when a combination of several strains was used. Prebiotics are generally non-digestible fibers such as inulin and fructooligosaccharides that are used by beneficial bacteria in the gut as a nutrient source, and they increase short-chain fatty acids (SCFAs) synthesis which has positive effects of increasing insulin sensitivity and decreasing systemic inflammation.

A dietary practice that promotes microbial diversity has also been shown to be highly metabolically advantageous. Diets rich in fiber stimulate the production of SCFA, especially butyrate which facilitates better glucose control through the increased secretion of gastrointestinal peptide 1 and decreased gut permeability. Fermented foods (e.g. kimchi and yogurt), kimchi and yogurt fermented foods Low-glycemic index (GI) diets, mostly plant-based diets showed positive changes in microbial composition and metabolic outcome [25]. These diets not only decrease postprandial glucose peaks but also facilitate the increase of microbial populations with a positive effect on the gut pancreatic axis. The Fecal Microbiota Transplantation (FMT) is a new experimental treatment for the metabolic syndrome and T2DM. Transplantation of the microbiota of lean healthy subjects to insulin-resistant lean individuals has demonstrated positive but temporarily transient effects on insulin sensitivity, and glucose homeostasis. Nevertheless, the safety and effectiveness of FMT in metabolic disease need to be clinically confirmed in the long run.

The novel therapeutic opportunities are in the form of synbiotics, a combination of probiotics and prebiotics, and postbiotics as bioactive compounds created due to probiotic activity (e.g., SCFAs, enzymes, peptides). The latter interventions are geared towards stabilizing the intestinal microbiome and increasing the metabolic products produced by it without necessitating live bacterial enrollment. Early research suggests a possible synergistic effect or potential of synbiotics to increase the effect of lowering insulin resistance and systemic inflammation. The effects of pharmaceutical agents are also microbiota-related. Metformin is the initial option in T2DM not only due to insulin-sensitizing effects but also due to the changes in the composition of gut microbes involving the elevation of the availability of Akkermansia muciniphila and SCFA-producing bacteria [23]. Such bacterial alterations are assumed to assist in the portion of metformin to reduce glucose levels, and the drug-microbiome interface is a field of clinical interest. Collectively, it presents a multi-pronged type of modulating glucose homeostasis and controlling diabetes mellitus which involves microbiota-based interventions. Nevertheless, the unintended effects of

drugs on an individual basis and failure to standardise the administration processes emphasize the requirement of personalised, evidence-based approaches in microbiome-based therapies in the future.

Table 2: Summary of Gut Microbiota-Based Interventions and Their Effects on Glycemic Control

Intervention	Mechanism	Glycemic Effects
Probiotics	Modulate inflammation, ↑ SCFAs, ↑ and GLP-1	↓ FBG, ↓ HbA1c
Prebiotics	↑ Growth of beneficial bacteria, ↑ SCFAs	↑ Insulin sensitivity
High-Fiber Diets	↑ SCFAs (butyrate), ↓ gut permeability	↓ Postprandial glucose, ↑ GLP-1
FMT	Replace dysbiosis with eubiotic flora	↑ Insulin sensitivity (short-term)
Synbiotics/Postbiotics	Combine probiotic/prebiotic, deliver active compounds	↓ Inflammation, ↓ IR
Metformin	↑ Akkermansia alters gut ecology	↓ FBG, ↓ IR

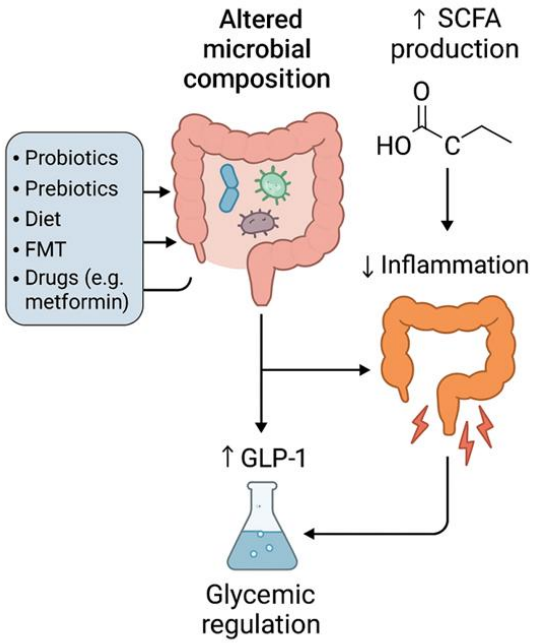

Figure 3: Gut microbiota interventions modulate SCFAs, inflammation, and hormones to improve glycemic control

V. RESEARCH GAPS AND FUTURE DIRECTIONS

Even though there have been tremendous developments explaining how the microbiota of the gut can interact with glucose metabolism, much is still lacking regarding the actual causal correlations at work. Although there are a lot of existing studies that have created correlations between microbiota composition and glycemic outcomes, well, not many studies have truly proven that there is a relationship that is causal relationship. These interactions between hosts and microbes are too complex and the gut ecosystem is dynamic and therefore it is not easy to tell whether dysbiosis is either a cause or an effect of metabolic diseases like diabetes mellitus. Indicatively, although insulin resistance and hyperglycemia have been associated with a reduction of potential microbes (e.g., Akkermansia muciniphila and butyrate-producing bacteria), there is still no mechanistic insight into the causality between the changes before or after metabolic impairment. The other shortcoming in the field is that most clinical trials are short-lived and targeted. Several interventions with probiotics, prebiotics, or dietary changes are usually conducted

for several weeks or months, yet it might be insufficient to induce or notice any long-term metabolic improvement or reconfiguration in sustainable microbiota. Also, the aspect of strain specificity is not much considered in trial design.

Variability in outcome Variously different bacterial strains even producing the same species may have significantly varied effects depending on metabolic capacity, colonization ability, and interaction with prevailing intestinal flora. However, several studies combine strains or do not identify strain identities, which makes reproducibility and clinical translation challenging. One of the main pitfalls of the existing therapeutic methods lies in their lack of personalization. The majority of the interventions that have mitigating effects on microbiota are homogenous without consideration of individual microbiome, genetic, lifestyle, or disease progression. This standardized model can be a part of the explanation for the variation of clinical outcomes in different patients with the same conditions. Recent studies further exemplify the heterogeneity of the gut microbial community structures and functional outputs between individuals across metagenomics and metabolomics. Consequently, individually adapted therapeutic strategies based on microbiota, i.e., specific to the microbial and metabolic peculiarities of individual patients, are sorely needed to boost their efficacy and minimize the chances of response failure.

Going forward, the future of microbiota-based glucose management will be in the context of precision medicine. New and improved probiotics--precision probiotics--with well-defined and function-specific bacteria strains are being designed to target certain metabolic pathways such as the production of SCFA, bile acid, and incretin signaling. Such strains may be selected in combination with companion diagnostics, using sequencing of the gut microbiome to determine compatibility and predict the use of response. Additionally, the field of bioengineering breakthroughs has made it possible to engineer bioengineered probiotics nowadays, which have the ability to sense and react to a glucose concentration or intestinal inflammation in real-time. Other innovations besides precision probiotics include microbial consortia (multi-strain cocktails), targeted postbiotics, and microbiota-derived metabolite therapies. They expect to get microbial balance, not by colonizing alone, and these approaches yield potentially more predictable and stable results. Long-term safety, host-microbe co-adaptation, and the possible combination of microbiota-modulation with established treatments (such as metformin or GLP-1 agonist) should also be studied in the future. Filling existing gaps and adopting a systems-level, personalised approach, gap microbiota interventions have the potential to usher in a paradigm shift in the management of diabetes, and instead of symptom control, metabolic reprogramming can be achieved.

CONCLUSION

The increased amount of evidence supports the centrality of gut microbiota dysbiosis in the pathogenesis of diabetes mellitus, in particular, Type 2 diabetes. Changes in microbial diversity and activities are strongly connected with metabolic defects like insulin resistance, constant inflammation, and poor glucose tolerance. Such fluctuations not only emerge as a byproduct of diabetes but also play a part in diabetes development and advancement through other mechanisms that include augmented intestinal permeability, endotoxemia as a result of lipopolysaccharide, and alteration of energy homeostasis. The metabolic profile and activity of gut microbiota shape the systemic glucose control, which is why the gut ecosystem has a much wider effect on endocrine health, which has not been recognized earlier. The most important part of this dialogue is between the gut and pancreas, which has a bi-directional molecule pathway that either microbial metabolites, immune-modulator molecules, and hormonal signalings influence pancreatic p-cell activity and insulin sensitivity. Commensal bacteria produce short-chain fatty acids (SCFAs), especially butyrate and propionate, via fermentation of dietary fibers and these have shown several positive effects in GLP-1 secretion, regulating appetite, and improving insulin sensitivity within glycemic control. On the other hand, dysbiosis characterized by the low prevalence of SCFA-producing bacteria and enrichment of opportunistic pathogens is capable of disrupting these regulation processes, facilitating hyperglycemia and systemic inflammation. This axis between the gut and the pancreas provides an exciting new avenue of therapy as there has been great promise

in correcting the metabolic disturbance by manipulating the gut microbiome.

Other interventions- such as probiotics, prebiotics, synbiotics, fecal microbiota transplantation (FMT), and pharmaceuticals, such as metformin, have been promising to realign microbial balances and enhance glycemic control. Nevertheless, among all these promising accomplishments, the bulk of these therapeutic approaches are either at early or experimental phases, and the transfer of these discoveries into conceptualized clinical practice is quite challenging. Variability in microbial ecology of the individual, the host, and the exposure to environmental factors makes it difficult to come up with universal treatment regimens. It is, therefore, timely to require sustained multidisciplinary studies into the mechanistic basis of microbiota-host interactions in diabetes. To help close the research-to-expanded-use gap, longitudinal human studies, personalized microbiome profiling, and integrative omics approaches will be needed to verify the results in the laboratory setting to achieve real-world success. As precision medicine takes shape, the exploitation of the gut microbiome might represent an explosive adjunctive or even preventative strategy in the management of diabetes. Full realization of its therapeutic potential may give rise to locally expedient types of microbial treatments that can not only treat but potentially alter the course of diabetes.

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