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Review

Gut Microbiota and its Role in Enhancing the Efficacy of Diabetes Therapies

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ABSTRACT

Multiple studies show gut microbiota modulation represents a vital method for diabetes mellitus treatment which strengthens therapeutic performance. The metabolic functions and immune regulation and gut barrier maintenance capabilities of gut microbiota contribute to the development of type 1 and type 2 diabetes. The process of dysbiosis which generates improper microbial composition creates long- lasting inflammation and results in insulin resistance and glucose intolerance. The article reviews the effects of gut microbiota on diabetes Mellitus medicine treatments by examining oral hypoglycemic agents and insulin sensitivity methods and non-drug interventions such as dietary adjustments and probiotics usage. Premise-based therapy and FMT interventions demonstrate strong potential in both restoring microbiome equilibrium and enhancing blood sugar control. Research should continue because the individual differences in microbiota shapes need additional study as do safety risks when using these interventions. The optimization of microbiome-based approaches will be possible with emerging technology in metagenomics alongside advances in artificial intelligence and precision medicine. In this review, we explore the intricate relationship between gut microbiota and diabetes therapies, emphasizing its potential to enhance treatment efficacy and improve patient outcomes. Future research should focus on developing targeted microbiota-based interventions and ensuring their long-term safety to fully harness their therapeutic potential in diabetes care.

Keywords: gut microbiota, diabetes, dysbiosis, oral hypoglycemic agents, pre & probiotics, personalized medicine.

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1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from either insufficient insulin production or the impaired ability of body cells to utilize insulin effectively. Type 1 diabetes mellitus (T1DM) arises from autoimmune-mediated destruction of pancreatic β-cells, leading to absolute insulin deficiency, whereas type 2 diabetes mellitus (T2DM) is primarily driven by insulin resistance and progressive β-cell dysfunction. Both forms of diabetes are associated with severe complications, including cardiovascular diseases, neuropathy, and retinopathy, contributing significantly to morbidity and mortality.

The global prevalence of diabetes continues to rise at an alarming rate, with an estimated 537 million adults affected in 2021—a figure projected to reach 783 million by 2045. (1) This escalating burden underscores the urgent need for novel therapeutic strategies. Emerging evidence highlights the potential role of gut microbiota in modulating glucose metabolism and metabolic homeostasis, offering promising avenues for mitigating the

disease's impact. Further research is warranted to explore microbiome-targeted interventions as adjunctive therapies in diabetes management.

The gut microbiota is an intricate assembly of microorganisms that inhabit the gut, most of which are bacteria, though the members may include fungi, viruses, and archaea. This complex of microorganisms plays roles as diverse as degrading components of a diet, which are not utilizable by the host, synthesizing essential vitamins, and modulating immune reactions. Expansion of this role to systemic health allows the bacteria to directly impact metabolism and inflammation which powerfully regulate disease processes. (2) The relative novelty of gut microbiota research has revealed the complexity of the gut microbiome and identified over 1,000 bacterial species. Important phyla include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Disruptions in the balance of these microbial communities, known as dysbiosis, have been linked to metabolic diseases such as diabetes and obesity. (3) For example, higher Firmicutes Bacteroidetes ratio is associated with improved efficiency for extracting energy and obesity in both human and animals.

Gut microbiota plays a role in diabetes physiopathology. Abnormal gut microbiota has also been associated with the enhanced permeability of the gut lining, heightened inflammation and metabolic changes all of which fuel diabetes advancement. Lower level of *Bifidobacterium longum* and *Akkermansia muciniphila* was found to be associated with T2D development. Dysbiosis is also known to release lipopolysaccharides (LPS) from Gram-negative bacteria leading to low-grade chronic inflammation and insulin resistance in humans. On the other hand, some interventions which seek to modify the GIT microbiota hold potential for enhancing glycemic regulation and metabolic profile. *Akkermansia muciniphila* functions as a gut integrity-maintaining bacterium which degrades mucin to generate acetate and propionate at the same time supports gut barrier functions. Short-chain fatty acids that form from bacterial fermentation work as messengers to control glucose metabolism then support intestinal barriers and lower body-wide inflammation. Animal studies confirm that *Akkermansia muciniphila* achieves insulin sensitivity through two mechanisms which prevent endotoxemia and simultaneously control metabolic inflammation and create conditions for better glucose homeostasis. (4)

The human gut is home to a diverse and dynamic ecosystem of microorganisms, often referred to as the gut microbiota, that performs numerous vital functions for the host. Over the past two decades, research has illuminated the intricate relationship between the gut microbiota and host health, establishing a direct connection between microbial composition and various aspects of metabolic regulation. With more than 1,000 identified bacterial species in the human gut, the complexity of this microbial community is far greater than initially understood. Among these, major phyla include Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, each with distinct roles in digestion, immune modulation, and even central nervous system functioning through the gut- brain axis. Emerging evidence suggests that changes in the balance of these microbial populations can significantly impact the development of several diseases, including diabetes, by influencing inflammation, metabolism, and the gut's barrier function. This microbiota-gut- brain axis is particularly noteworthy, as it helps mediate systemic inflammation and metabolic processes that are linked to diseases like diabetes, obesity, and even neurodegenerative conditions. (5)

Research on the gut microbiota has been propelled by the advent of advanced sequencing technologies, which have enabled the identification of microbiota composition with unparalleled precision. The growing body of literature underscores how alterations in microbial diversity, often referred to as dysbiosis, are strongly associated with the onset and progression of metabolic disorders, including type 1 and type 2 diabetes (T1DM and T2DM). In particular, dysbiosis has been linked to insulin resistance, glucose intolerance, and chronic low-grade inflammation, all of which contribute to the pathophysiology of diabetes. In the case of T1DM, an autoimmune disorder characterized by the destruction of insulin-producing beta cells in the pancreas, the microbiota may play a role in modulating immune responses, influencing the onset of autoimmunity. In T2DM, a condition primarily driven by insulin resistance and pancreatic beta-cell dysfunction, gut microbiota imbalances may further exacerbate metabolic dysfunction and contribute to the progression of the disease.

As research continues to unravel the complex interactions between the gut microbiota and host metabolism, scientists are increasingly exploring strategies to manipulate the microbiome as a

potential therapeutic approach for managing diabetes. The concept of microbiome modulation holds promise for improving the efficacy of existing diabetes treatments, such as metformin, by enhancing the microbiota's ability to support metabolic processes. For instance, it has been shown that *Akkermansia muciniphila*, a bacterium that thrives in the gut mucosal layer, may enhance the effects of anti-diabetic drugs like metformin by promoting gut barrier integrity and increasing the production of beneficial SCFAs. This bacterium plays a critical role in preventing insulin resistance, regulating inflammatory pathways, and improving glucose metabolism. Furthermore, clinical studies have shown that the abundance of *Akkermansia muciniphila* correlates with improved insulin sensitivity and lower blood glucose levels in individuals with T2DM.

The growing interest exists in microbial-based interventions which include probiotics together with prebiotics and fecal microbiota transplantation (FMT) for diabetes management as supportive treatments. Research now demonstrates that gut microbiota function as critical controllers of metabolism while changing their composition in the gut can lead to improved treatment outcomes for patients with type 2 diabetes mellitus (T2DM). Extended research exists on probiotics as interventions for metabolic health improvement because these live microorganisms provide health benefits to the host when administered at proper dosage levels. Multiple studies both in clinical practice and research labs show probiotics benefit glucose control and insulin response as well as reduce inflammation within the bodies of individuals with T2DM. Studies have revealed that prebiotics help improve metabolism because these non-digestible food elements boost beneficial gut bacteria. Prebiotic supplementation enhances gut homeostasis maintenance by stimulating the growth of bacteria that produce short-chain fatty acids (SCFAs) while simultaneously decreasing intestinal permeability together with the normalization of immune responses that frequently break down in diabetic contexts.

The microbial therapy of Fecal Microbiota Transplantation (FMT) includes the moving of healthy donor fecal microbiota into an individual with dysbiosis as a potential invasive clinical approach. The treatment procedure seeks to balance microbial populations in the gut which researchers believe may cancel out the metabolic problems that result from gut dysbiosis in T2DM patients. Current studies indicate that fecal microbiota transplantation could represent a potential diabetes treatment method even though research remains at an investigative experimental stage. More extensive large-scale clinical trials with well-defined protocols need to prove both the long-term safety along with effectiveness of FMT as a diabetic treatment. (6)

The clinical use of diabetes approaches based on microbiome therapy remains limited because of existing obstacles in their implementation. The major hindrance arises from the sizable differences in gut microbial profiles among people because multiple lifestyle elements like nutrition and genetics and environmental influences impact microbiome composition. Studies demonstrate that gut microbiota serves as a fundamental element which influences diabetes medication results because they control drug breakdown mechanisms and control insulin resistance and blood sugar regulation. The identification of these mechanisms permits the development of better individualized strategies that utilize microbiome data for therapeutic decision-making. Through its partnership with all human microbiota groups the gut microbiota leads the process of digesting complex carbohydrates and fibers which human enzymes cannot break down on their own. The gut microbiota produces short-chain fatty acids (SCFAs) during microbial fermentation primarily comprising acetate, propionate, and butyrate that create substantial impacts on gut condition and systemic metabolism. Short-chain fatty acids act as fundamental agents that control blood sugar metabolism and improve insulin effectiveness and adjust inflammatory responses which sustain metabolic equilibrium. The SCFAs support beneficial bacterial growth while restricting pathogenic species population in the gut microbial ecosystem. The energy source for colonocytes requires SCFAs while these metabolites protect the gut barrier integrity to stop intestinal permeability dysfunction. The physiological state referred to as dysbiosis results in reduced SCFA production which leads to diminished gut barrier strength so endotoxins including lipopolysaccharides (LPS) become able to cross into the bloodstream. The transition of endotoxins into systemic blood circulation through intestinal walls establishes metabolic endotoxemia as a condition which leads to persistent low-grade inflammation. The delicate relationship between microbial SCFAs produced by the gut microbiota and human metabolic pathways

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reveals promising opportunities for modifying the diabetes management through microbiome-directed strategies. A larger clinical study with extensive data collection will help scientifically prove the permanent effectiveness and safety of these therapeutic methods.

2. Composition and Functions of Gut Microbiota

The gut microbiota, found in the human gastrointestinal tract, harbors a complex and dynamic community of microorganisms. This ecosystem is crucial for maintaining host health, supporting physiological functions like digestion, metabolism, and immune regulation. Changes in the gut microbiota, which may be linked to metabolic disorders like diabetes, have been observed in animal studies. These alterations affect the normal functioning of the gastrointestinal system, and many of these findings have been applied to human health research. (7-8)

Gut Microbiota: Composition and Functions

The gut microbiota consists of trillions of microorganisms, including bacteria, viruses, fungi, and archaea. Among the bacteria, two main groups are Firmicutes and Bacteroidetes. Bacteria like *Clostridium* and *Lactobacillus* are part of Firmicutes, while *Bacteroides* belongs to Bacteroidetes. Other important groups include Actinobacteria (e.g., *Bifidobacterium*) and Proteobacteria. (9) Healthy individuals balance these groups with a ratio such that the immune and metabolic homeostasis is maintained. Unfortunately, there is a significant disruption in this balance, particularly in patients with type 2 diabetes mellitus (T2DM). In this case, the studies have shown increased Firmicutes to Bacteroides ratio, and decreased the beneficial butyrate production bacteria such as *Faecalibacterium prausnitzii* that increase metabolic dysfunction. (10-11)

Key Roles of Gut Microbiota

Gut microbiota performs several vital functions like digestion and metabolism, Dietary fibers are fermented by the microbiota, into short chain fatty acids (SCFAs), such as acetate, propionate and butyrate. Another group of these SCFAs functions to regulate glucose and lipid metabolism, control appetite and serve as energy substrates to colonocytes. These processes are disrupted in T2DM from alters SCFA production, increasing hyperglycemia. (12) By regulating the immune response, the microbiota helps modulate immune homeostasis through a balance between proinflammatory and anti- inflammatory responses. Chronic low-grade inflammation in diabetic patients is exacerbated by dysbiosis of the microbiota, which promotes the inflammation contributing to insulin resistance. (13- 14) Gut Barrier Integrity, establishing an intact gut barrier is a key function of the microbiota, so that harmful substances like lipopolysaccharides (LPS) must not enter the bloodstream. Intestinal permeability, or 'leaky gut', is increased in diabetes which then perpetuates systemic inflammation and worsens metabolic derangements. (15)

3. Dysbiosis and Its Role in Diabetes

Dysbiosis, or an imbalance of microbes, is caused by a range of dietary and other lifestyle factors such as antibiotic and anti-inflammatory use. LPS release, metabolic endotoxemia, chronic inflammation and reduced SCFA production and worsen glucose intolerance and insulin resistance all are related to this imbalance. (16-17)

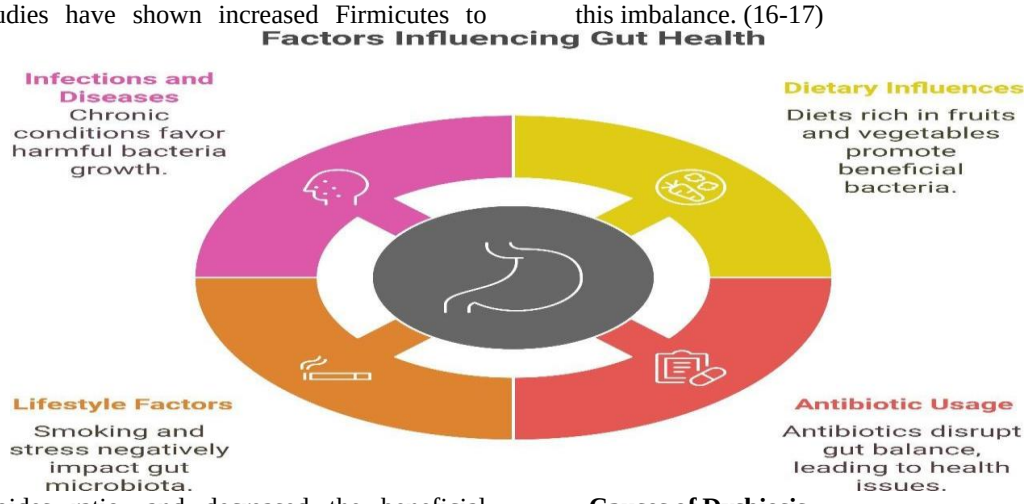

Fig.1 Factors Influencing Gut Health and the Onset of Dysbiosis.

Causes of Dysbiosis

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Dietary influences play a significant role in shaping gut microbiota, with diets high in refined sugars and fats promoting harmful bacterial growth and low fiber intake reducing beneficial microbial populations, while diets rich in fruits, vegetables, and fish oils are considered more favorable due to their anti-inflammatory properties. Antibiotic usage further disrupts gut microbiota by indiscriminately killing both beneficial and harmful bacteria, often resulting in an imbalance linked to conditions like inflammatory bowel disease (IBD) and obesity. Lifestyle factors such as smoking, alcohol consumption, and stress negatively affect the composition of gut microbiota, contributing to dysbiosis. Additionally, chronic infections and inflammatory conditions can alter the gut environment, encouraging the growth of pathogenic bacteria over beneficial ones.

Mechanisms Linking Dysbiosis to Diabetes

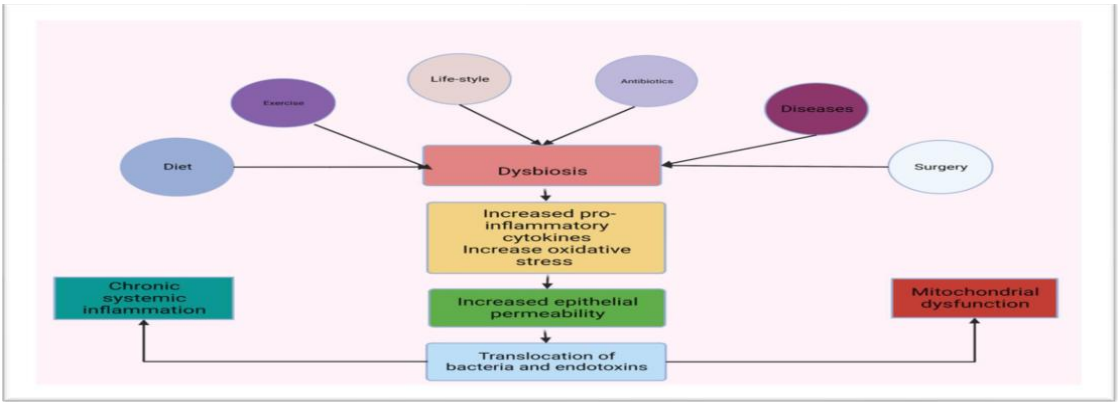

Fig 2. Schematic diagram shows predisposing factors for dysbiosis and a link between dysbiosis, chronic inflammation and mitochondrial dysfunction.

The connection between dysbiosis and diabetes involves several interrelated mechanisms, Chronic Low-Grade Inflammation, increased intestinal permeability is a result of dysbiosis that leads to the serosal entry of invasive bacterial endotoxins, such as lipopolysaccharides into the bloodstream. Triggering this translocation leads to systemic inflammation, a well- established contributor to insulin resistance and the subsequent development of type 2 diabetes. (18) Alterations in short-chain fatty acid (SCFA) production occur, as beneficial gut bacteria ferment dietary fibers to produce SCFAs like butyrate, propionate, and acetate, which are critical for glucose metabolism and appetite regulation.

Alterations in SCFA production leads to dysbiosis and are associated with glucose homeostasis and diseases such as diabetes. (19) Changes in Gut Permeability (Leaky Gut) but a healthy gut lining acts as a barrier to stop those harmful substances from translocating. Dysbiosis can disrupt this barrier, leading to the development of a 'leaky gut' that allows inflammatory agents to enter the bloodstream, contributing to metabolic endotoxemia and insulin resistance. (20)

Evidence from Clinical and Preclinical Studies

The connection between gut health and diabetes is gaining increasing attention, with research uncovering how gut microbiota may influence the onset and progression of the disease. Both clinical and experimental studies highlight the profound impact of gut microbial changes on metabolic health, glucose regulation, and insulin sensitivity.

Clinical Studies

Reduced Gut Microbial Diversity in Diabetes

People with diabetes, especially Type 2 Diabetes Mellitus (T2DM), show significant differences in their gut microbiota compared to those without the condition. For example, a meta-analysis in *Nature Reviews Endocrinology* revealed that diabetic patients often have a lower diversity of gut microbes, marked by an imbalance in the Firmicutes-to-Bacteroidetes ratio and an increase in opportunistic pathogens. (21). Similarly, research published in *Cell Metabolism* found that pro-inflammatory species like *Ruminococcus gnavus* are more abundant, while beneficial bacteria such as *Akkermansia muciniphila*, known for its gut barrier- strengthening and anti-inflammatory effects, are reduced in diabetic individuals. (22)

Microbial Metabolites and Insulin Resistance

The gut microbiota produces metabolites essential for metabolic health, such as short-chain fatty acids

(SCFAs). However, in diabetes, dysbiosis alters SCFA levels, which can worsen glucose metabolism. Studies report reduced butyrate levels an SCFA known to enhance insulin sensitivity in diabetic patients. (23) Additionally, gut dysbiosis affects bile acid metabolism, contributing to impaired glucose regulation and insulin resistance. (24)

Gut inflammation and Metabolic Endotoxemia

Gut microbiota also influences systemic inflammation, a key feature of diabetes. For instance, higher levels of lipopolysaccharides (LPS) in the blood caused by increased gut permeability are common in T2DM patients, leading to a condition called metabolic endotoxemia, which is strongly linked to insulin resistance. (25) Encouragingly, clinical interventions with probiotics and prebiotics have shown reductions in inflammatory markers like C-reactive protein (CRP), demonstrating how gut health can be leveraged to manage systemic inflammation. (26)

This emerging understanding of the gut-diabetes axis highlights the potential for microbiota-targeted therapies in managing and preventing diabetes.

Preclinical Studies

The alteration of gut microbiota was studied through a landmark experiment published in science, where gut microbiota from obese and diabetic humans was transplanted into specially bred gnotobiotic mice to investigate its causal role in diabetes. A landmark study published in science transplanted gut microbiota from obese and diabetic humans into germ-free mice. The recipient mice became diabetic and obese, and this provided evidence of the manner that the transplanted microbiota affects metabolism. The same experiments with microbiota from diabetic animals resulted in increasing gut permeability and systemic inflammation in experiment mice were observed. A landmark study published in science transplanted gut microbiota from obese and diabetic humans into germ-free mice. The recipient mice developed glucose intolerance and increased adiposity, indicating the metabolic influence of the transplanted microbiota. Similar experiments with microbiota from diabetic animals showed enhanced gut permeability and systemic inflammation in recipient mice (27-28).

Lessons from Mechanistic Studies in Animals

Preclinical studies have elucidated the mechanisms by which dysbiosis contributes to diabetes. Chronic Inflammation: The mice provided with high fat diet had an altered gut microbiota which results in high LPS, inflammation and insulin resistance. Gut dysbiosis which is caused by antibiotics was shown to reverse these effects in a study conducted (29). SCFA Deficiency Clinical studies have shown that butyrate supplementation normalizes insulin sensitivity in animals because of improved mitochondrial biogenesis and lowered oxidative stress in skeletal muscles (30). Leaky Gut Syndrome In diabetic animal models' disruption of tight junction proteins in the intestinal lining due to dysbiosis resulted in increased gut permeability and systemic inflammation Glucose homeostasis was also affected (31).

Cross Country Studies and New Developments

Recent multi-omics studies combining metagenomics and metabolomics have provided a comprehensive understanding of the gut-diabetes axis. Personalized Microbiome Profiles, an article in The Lancet Diabetes & Endocrinology found that population means differences in gut microbiota and specific population descriptive characteristics can be explained by differences in diet and genetics, suggesting that [personalized interventions] are feasible (32). Signatures as Biomarkers, brand new about the gut microbiome, some of them have been patented as potential predictors of diabetes. For instance, a reduced number of Bifidobacterium and Lactobacillus species were related to prediabetes (33).

4. Impact of Gut Microbiota on Diabetes Therapies

Enhancing Oral Hypoglycemic Agents, interventions aimed at modulating the gut microbiota have potential to improve the efficacy of oral hypoglycemic agents (OHAs), such as metformin, SGLT2 inhibitors, GLP1 receptor agonists, and nonpharmacological interventions such as diet and exercise, which constitute the backbone for treating diabetes. It also upregulates Akkermansia muciniphila, a beneficial microbe linked to improvement in insulin sensitivity, as well as modulating metformin's pharmacokinetics: increasing absorption and the availability of metabolites, like SCFAs. Gut microbiota promotes SCFA production and decreases glucose absorption to enhance therapeutic effects for SGLT-2 inhibitors. GLP-1 receptor agonists that benefit from gut microbes such as

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Bifidobacterium, that stimulate GLP-1 secretion, are likewise improved.

Table No.1 Role of Gut Microbiota in Modulating Diabetes Therapies: Key Interactions and Effects.

Overview	The gut microbiota significantly influences diabetes pathogenesis and the effectiveness of therapies, including OHAs, insulin resistance modulation, and non- pharmacological interventions like diet and exercise.
Therapeutic Area	**Key Points**
Enhancing Oral Hypoglycemic Agents (OHAs)	Gut microbiota interacts with OHAs, impacting absorption, efficacy, and overall therapeutic response.
Effects on Metformin Absorption and Efficacy	
1. Altered Metabolism in the Gut	1) Gut microbiota modulates metformin pharmacokinetics, particularly its absorption. 2) Certain bacteria enhance metformin's efficacy by promoting metabolites like SCFAs, which influence glucose metabolism (34). 3) Gut microbiota affects transporters responsible for metformin absorption (35).
2. Changes in Gut Microbial Composition	1) Metformin induces shifts in gut microbiota composition, enhancing its effectiveness. 2) Increases beneficial microbes like *Akkermansia muciniphila* linked to improved metabolic outcomes (36).
Role in SGLT-2 Inhibitors and GLP-1 Receptor Agonists	
1. SGLT-2 Inhibitors	1) Gut microbiota influences the pharmacodynamics of SGLT-2 inhibitors, affecting glucose metabolism. 1) Alters gut microbiota, increasing SCFA production and reducing glucose absorption, enhancing therapeutic effects (37).
2. GLP-1 Receptor Agonists	1) Gut microbiota impacts GLP-1 secretion. 2) Certain microbes, like *Bifidobacterium* species, stimulate GLP-1 release, enhancing drug efficacy (38).

Diabetes therapies efficacy is greatly influenced by the gut microbiota. In this example, metformin has been shown to change the gut microbiota composition, raising the level of Akkermansia muciniphila, which promotes insulin sensitivity, and reduces inflammation.(39- 40)

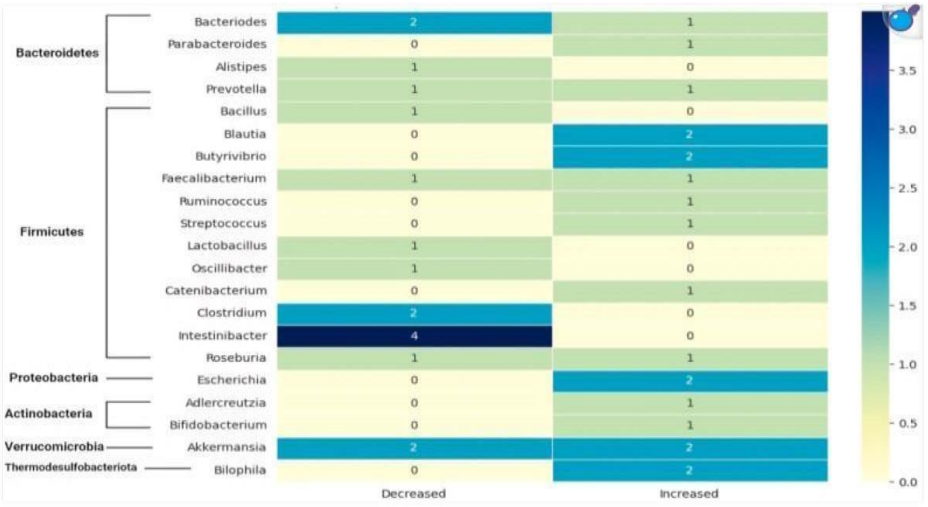

Fig.3 Impact of Metformin on Specific Microbial Taxa in the Human Gut Microbiota.

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Modulation of Insulin Resistance

Changes in the gut microbiota have a major effect on insulin resistance, a central feature of type 2 diabetes (T2D), through modulation of processes like the production of short chain fatty acids (SCFAs) and bile acid signalling. Microbial metabolites of dietary fiber fermentation, SCFAs include acetate, propionate and butyrate. In addition, they activate G-protein coupled receptors (e.g., GPR41 and GPR43,) improve gut barrier integrity, decrease inflammation and control adiposity (41). SCFA infusions have been shown in clinical studies to improve insulin sensitivity and reduce plasma glucose levels (42), and microbial diversity influences SCFA production and function of insulin resistance
(43). Like gut microbiota, bile acids, modulated by gut microbiota, also affect metabolic processes, converting primary bile acids to secondary bile acids that act to bind to receptors like FXR and TGR5 to regulate glucose metabolism (44). Impaired glucose control has been associated with altered bile acid metabolism in diabetic patients, which may in turn demonstrate therapeutic potential of modulating gut microbiota to improve insulin resistance (45).

Gut Microbiota and Non-Pharmacological Interventions

A recent review noted the importance of gut microbiota in improving the effect of non-pharmacological interventions (diet, exercise) in diabetes management. Diets high in fiber promote growth of SCFA producing gut microbes, which promote glucose metabolism and insulin sensitivity and reduce inflammation (46-47). Exercise expands the scope of the microbial community to include beneficial bacteria and strengthens insulin sensitivity and reduces the risk of T2D (48). Dietary fibers and prebiotics are inulin and FOS, and they help to promote the growth of beneficial gut bacteria and improve metabolic health and Glycemic control in diabetic patients (49-50).

Table:2 Role of Gut Microbiota in Non-Pharmacological Interventions for Diabetes Management

Intervention	**Gut Microbiota Influence**	**Impact on Diabetes**
High-Fiber Diet	Promotes growth of SCFA-producing gut microbes.	Improves glucose metabolism insulin sensitivity, and reduces inflammation.
Exercise	Increases microbial diversity and supports beneficial bacteria.	Enhances insulin sensitivity and lowers T2D risk.
Dietary Fibers	Encourages beneficial Bacteria growth through SCFA production.	Improves blood glucose control and reduces insulin resistance.
Prebiotics (e.g., inulin, FOS)	Stimulates beneficial gut bacteria growth.	Enhances metabolic health and glycemic control.

5. Therapeutic modulation of gut microbiota

Microbiota targeted interventions including probiotics, prebiotics and fecal microbiota transplantation (FMT) are becoming diabetes management approaches. Lactobacillus and Bifidobacterium probiotics balance your microbes, while inulin prebiotics grows them. There is potential for FMT in very severe cases, however: there are ethical and practical problems with it. (51-52)
These three approaches can all exert unique mechanisms of action to govern gut health, metabolism, and glucose regulation. In this section, we give a complete overview of these therapies with their potential, clinical evidence, and challenges. Probiotics Live microorganisms which, when administered in sufficient numbers, confer a health benefit on the host (53). The most frequently used type of beneficial bacteria in probiotic formulations are Lactobacillus and Bifidobacterium that help maintain gut health, influence metabolism processes that may impact diabetes.

Table No.3 Therapeutic Strategies for Managing Diabetes: Probiotics, Prebiotics, and Fecal Microbiota Transplantation.

Therapy	**Substance/ Procedure**	**Mechanism**	**Effects on Gut Microbiota**	**Effects on Glucose Metabolism**

Probiotics	Lactobacillus	Enhances gut barrier integrity	Increases beneficia bacteria	Improves insulin sensitivity, reduces inflammatio n
	Bifidobacterium	Modulates gu microbiota, produces SCFAs	Promotes SCFA production, regulates gut microbiota	Improves glycemic control, reduces systemic inflammatio n
Prebiotics	Inulin	Fermented by gu bacteria into SCFAs	Increases *Bifidobacteriu m* and other beneficia bacteria	Improves insulin sensitivity, reduces blood sugar levels
	Fructo- oligosaccharides (FOS)	Stimulates growth of *Lactobacillus* and *Bifidobacterium*	Improves gut barrier function and immune response	Improves glucose metabolism, reduces insulin resistance
Fecal Microbiota Transplantatio n (FMT)	Fecal material from healthy donors	Restores healthy gut microbiota	Restores balance o gut microbiota particularly in obese and insulin- resistan individuals	Improves insulin sensitivity and glucose control.

Types of Beneficial Bacteria like Lactobacillus, Lactic acid bacteria (54) are lactobacilli to help maintain acidic environment in the gut unfavourable to pathogenic bacteria. We have previously shown that species like Lactobacillus rhamnosus and Lactobacillus acidophilus stimulate the fermentation of dietary fibers and production of short chain fatty acids (SCFAs) which are crucial for gut health and metabolic regulation (55). Bifidobacterium, This genus of bacteria is ubiquitous in the human gut, especially early in life, and is necessary for carbohydrate fermentation, as well as immune modulation and suppression of harmful bacteria. Probiotics are used specifically with certain strains of Bifidobacterium bifidum and Bifidobacterium lactis to correct gut microbiota balance and overall metabolic health (56).

Diabetes management via gut microbiota modulation through probiotics, prebiotics and fecal microbiota transplantation (FMT) constitutes a promising line of therapeutical endeavours. A study (57) revealed that the use of probiotic supplementation of Lactobacillus and Bifidobacterium species has benefited glycemic control assists in the improvement of insulin sensitivity. Other study alongside it by Zhao et al. (58) noticed that there have been boost in glycemic control and insulin sensitivity with a probiotic supplementation with Lactobacillus and Bifidobacterium strains. Slavin

(59) and De Vadder (60) do back up those findings on how prebiotics such as inulin and fructo oligosaccharides affects SCFA production, improves glucose metabolism, and placet inflammation. However, FMT from lean donors improve insulin sensitivity and diabetes control in T2D patients, but donor selection, long term safety, and standardization challenges remain. Donor selection and screening are critical in fecal microbiota transplantation (FMT), as the safety of recipients hinges on the microbiota composition and the absence of pathogens. Ethical concerns also emerge regarding the long- term effects of microbiota transplantation, particularly if it involves undetectable pathogens or disease transmission.

The long-term safety of FMT remains under investigation, with researchers expressing concerns about unintended side effects, such as changes in microbial diversity or increased susceptibility to infections. Additionally, the lack of standardization in FMT procedures poses significant challenges. Variations in donor microbiota composition, preparation methods, and delivery techniques can influence the efficacy of the procedure, while environmental factors, diet, and genetics further complicate its application as a

standardized therapy for diabetes. (61- 62) Metabolic health is incredibly reliant on the gut microbiota and has major implications for managing diabetes. Induction of diabetes progression by dysbiosis and modulation of microbiota as a way to improve therapeutic efficacy are promising. Microbiota targeted approaches are needed for further research to integrate them into personalized diabetes care.

6. Challenges and Future Perspectives

Variability in Gut Microbiota Composition (Inter-individual Differences (Age, Geography, Diet)

Gut microbiota composition is a complex phenomenon, and variability therein is guided by inter-individual variation such as age, geography, and diet. This variability is important to understand for the application of microbiota, based therapies for diabetes management. There is a great deal of change in the gut microbiota through an individual's life, beginning with a high Bifidobacterium and Lactobacillus dominance in infancy, which is essential for immune development and milk digestion. As age progresses, the diversity of the microbiome increases yet declines in older adults, associated with a decrease in beneficial bacterial Firmicutes, and an increase in pathogenic Proteobacteria. As shown by Claesson et al. (63) aged shift is associated with different health conditions, including diabetes, associated with reduced microbiome diversity in older people. Such shifts could affect disease progression and responses to treatment, Franzosa et al. (64) added. Additional variability is caused by geographic location since environmental factors as well as lifestyle practices vary among regions. For example, we see rural populations with plant based, high fiber diets (or a 'western diet') that have higher microbiome diversity and better metabolic health compared to urban populations and shift to focus on the processed foods. A study shows (65-66), for example, show poorer metabolic health in populations of Western provenance with low microbiome diversity, and better health in rural African populations with more diverse microbiomes. These findings emphasize the importance of tailoring microbiota-based interventions at geographic scale.

Diet, by far the greatest influencing factor, has a huge impact on gut microbiota. A plant based diet contains a high amount of fiber, and this promotes a rich microbiome with lots of beneficial bacteria such as Bifidobacterium and Firmicutes, which control blood sugar and inflammation. Larsen et al. (67) have noted, conversely, that a high fat, sugar, and processed food Western diet decreases microbial diversity and encourages growth of pathogenic bacteria. There is promise in the improvement of the gut's health and insulin sensitivity from dietary modifications that emphasize fiber intake in the diabetic patients (68). Despite this, however, setbacks to microbiota based therapies from the notoriously high variable gut microbiota composition exist. We conclude that this variability requires personalized medicine approaches based on individual differences in microbiome composition, age, geography and diet. Based on these factors, tailored strategies have the potential to optimize therapeutic outcomes, and to develop diabetes management on a case by case basis.

Table No.4 Factors Influencing Gut Microbiota Composition

Factor	Impact on Gut Microbiota Composition	Implications for Diabetes
Age	Decrease in diversity with age, shift towards more pathogenic bacteria.	Older individuals with diabetes may show less microbial diversity, affecting insulin sensitivity.
Geography	Variations in microbiota based on environmental factors and lifestyle (urban vs rural).	Regional differences in diet and lifestyle contribute to diverse microbiomes and diabetes prevalence.
Diet	High-fat, processed foods reduce diversity; high-fiber promotes beneficial bacteria.	Diet-induced shifts in microbiota can influence glucose metabolism and insulin resistance.

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The composition of gut microbiota varies with these factors, which implicate microbiota based therapies with significant variability. With these differences helping to shape the nuances of oncology, we can't provide a one size fits all approach to medicine and need to be aware of how personalized medicine can create personalized treatment strategies for each individual to optimize therapy.

Implications for Personalized Medicine

Gut microbiota composition is highly variable, implications for personalized medicine, which seeks to tailor medical treatment to a patient's genetic, environmental and microbiological profiles, are significant. In the field of diabetes, this orientation focuses on the design of microbiome based interventions aimed at individual's unique composition of microbiota. For example, probiotics that might help in some people control of glucose could not work in other people because the gut flora were different (69). Microbiome analysis advances, such as metagenomics and microbiome sequencing, ensure clinicians know exactly which bacterial strains should be targeted for maximum treatment through the identification of those differences in each patient. Additionally, dietary recommendations with potential to improve diabetes management through microbiota modulation are personalized. Diet has a major impact on gut microbiota, so dietary interventions geared to a patient's microbial profile are likely to improve the effectiveness of these therapies. As an example, patients with lower microbial diversity may be better served with fiber rich diets, which promote growth of beneficial bacteria. Patients with out of balance bacterial populations may gain from targeted prebiotic or probiotic therapies. Individualized interventions are such that interventions are not only effective but more complementary to the patient's microbial environment, offering a more specific and comprehensive approach to diabetes care. These microbiome-based insights can be integrated into personalized medicine to adjust the variability in gut microbiota composition and thereby improving patient outcomes for diabetes.

Long-term Safety of Microbiota-Based Therapies

Despite the promising role they play in managing diabetes, microbiota-based therapies, such as probiotics, prebiotics, and fecal microbiota transplantation (FMT), are all concerned with the long term safety of these therapies. There have been short term benefits of probiotics and prebiotics: improving glucose metabolism and insulin sensitivity. Nevertheless, continued use is worrisome. For example, some probiotic strains may become pathogenic or promote an overgrowth of specific microbial populations, so that gut homeostasis may drift away in time (70). As with prebiotics, such as inulin, although prebiotics certainly promote beneficial bacteria, prebiotics like inulin can also cause gastrointestinal discomfort, bloating or gas in some people and is thus a barrier to their widespread and long term application. Another microbiota based intervention that may hold some safety potential is FMT which restores a healthy microbiome; its long term safety is not known. When fecal samples are not adequately screened for pathogens, adverse events, including infections have been reported. In addition, adding a new microbiome to a recipient's gut may replace the native microbiota, resulting in either dysbiosis or other problems (71). FMT looks promising in clinical trials for its metabolic effects in diabetes, but to see is where it can take us long term needs more work.

Table No.5 Key Microbiota-Based Therapies and Their Long-Term Safety Concerns.

Therapy	Short-Term Benefits	Long-Term Safety Concerns
Probiotics	Improve gut health, increase SCFA production.	Potential for pathogen overgrowth or infections; risk of altering gut homeostasis.
Prebiotics	Promote growth of beneficial bacteria.	Gastrointestinal discomfort (bloating, gas), imbalance in gut microbiota with prolonged use.
FMT	Restore healthy microbiome, improve glycemic control.	Risk of pathogen transmission, long-term gut dysbiosis, ethical issues with donor screening.

(This table lists major microbiota-based therapies (e.g., probiotics, prebiotics, FMT) along with their known long-term safety concerns, providing a clear summary of current knowledge.)

It is crucial to subject these therapies to rigorous clinical trials and post market surveillance for safe and effective use in chronic disorders such as diabetes. As reliable long term treatments, microbiota based interventions will be advancing through the identification of potential risks and

unintended consequences.

Advances in Microbiome Research

Much of this research on gut microbiota and diabetes has arisen in the past 5 years, covering an explosion in the data available. Out of these advancements, metagenomics and microbiome sequencing take the throne as transformative technologies. Metagenomics can be used to investigate genetic material from whole microbial communities, without culturing single species, to provide a look at the breadth and function of gut microbial diversity. This approach has revealed previously uncharacterized microbial species and their possible contribution to the pathogenesis of diabetes (72). Indeed detailed cataloging of the microbiota in diabetic patients has been made possible by the advent of high-throughput microbiome sequencing methods, such as 16S ribosomal RNA sequencing. Our research demonstrates that diabetics are frequently nutrient deprived of BIFs and enriched for Pathogens, thereby implicating microbiota imbalances with the disease (73). For example, such insights are creating personalized microbiome-based therapies that predict diabetes risk and therapeutic response by discovering biomarkers.

But metagenomics also has the potential to discover microbial genes encoding key metabolites such as short chain fatty acids (SCFAs), which are key mediators of glucose metabolism. Due to their influence on insulin sensitivity and metabolic health, these metabolites are attractive therapeutic targets. It maps microbial pathways for the production of SCFAs, to develop targeted therapies that can modulate specific microbial functions that aid in the management of diabetes (74). Furthermore, metagenomic dataset integration with clinical research provides a means to assess and design tailored interventions to restore diabetic patients' gut microbiota balance. These advances together not only further our understanding of the role gut microbiota play in diabetes, but also form a solid basis from which new, microbiota driven treatment methods can be developed.

Integration with AI for Therapy Optimization

Artificial intelligence (AI) integration within the microbiome research space offers unparallel opportunities to fine tune diabetes therapies. Vast amounts of microbiome data can be processed using AI algorithms and complex patterns and correlations can be uncovered that a traditional method cannot. As an example, AI can predict how an individual's microbiome will react to certain dietary interventions or microbiota based therapies and adjust real time protocol courses in order to improve outcomes (75). AI on the other hand uses microbiome data combined with patient specific factors such as genetics, lifestyle and medical history to create highly personalized treatment plans. This helps identify what interventions should be made to each patient uniquely and with the least side effects. In addition, drug discovery for microbiome based diabetes therapies depends on AI. Using machine learning algorithms to analyse microbiome datasets, they work to identify new therapeutic targets and novel microbial strains that can repair a diabetic patients' gut microbiome. It could further hasten the creation of more sophisticated probiotics, prebiotics, and other modulators of the microbiome professessed for development of improved metabolic health. The advance of AI integration offers potential for revolutionizing microbiota based treatments from more efficient, precise, and accessible aspects to furthering the field of diabetes management. (76)

7. Implications and Prospects

Summary of Key Findings

Recent studies point to getting the gut microbiota right as fundamental to diabetes onset, progression, and management. Insulin resistance, metabolic inflammation and dysregulated glucose metabolism, hallmark features of type 2 diabetes, are closely linked to composition and diversity of gut microbiota. For instance, (77) provide robust evidence of links between dysbiosis and diabetes, showing via meta-analyses that having one does increase the risk of getting the other. (78) have provided a deeper understanding of exactly what specific changes in gut microbiota composition there are in diabetic individuals: a dramatic increase in pro inflammatory species, and a decrease in anti-inflammatory bacteria. Dramatic shifts that initiate these microbial events lead to disfunction in glucose homeostasis, such as SCFA production and bile acid metabolism. (79) complemented these findings by characterizing the role of microbial metabolites, proceeding to describe how butyrate may serve to regulate insulin sensitivity and further join dysbiosis and insulin resistance. Gut microbiota has, however, proved to be an important factor affecting the efficacy of metformin in treatment. In a clinical trial, (80) showed that types of gut microbiota are correlated

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to improved clinical outcomes in diabetes Type 2 patients taking metformin. The study identified bacterial strains that boost bioavailability and glucose regulating effects of metformin, and contributes deeper molecular insights into these interactions.

Microbiome therapies that capitalize on innovations also have promise as diabetes management. As an example, Velloso randomized controlled trial in 2023 found improvement in insulin sensitivity and inflammatory biomarkers in Type 2 diabetic supplemented with probiotics containing Lactobacillus and Bifidobacterium strains. (81) Like prebiotics, inulin and fructo-oligosaccharides (FOS) have also shown the capacity to increase beneficial bacterial growth and reduce systemic inflammation in diabetic individuals (82). A cutting edge direction in diabetes therapy is based on tailored probiotic formulations of individual microbiota compositions. Fecal Microbiota Transplantation (FMT) is another emerging intervention. (83) showed that FMT from lean, healthy donors to obese, insulin resistant patients improved insulin sensitivity reducing glucose levels, suggesting FMT may be a therapy of diabetes. Despite the extensive clinical development of this exciting cancer therapy, safety, ethics and durability of efficacy are significant barriers to its widespread clinical application.

Gut Microbiota and Diabetes Management Clinical Relevance

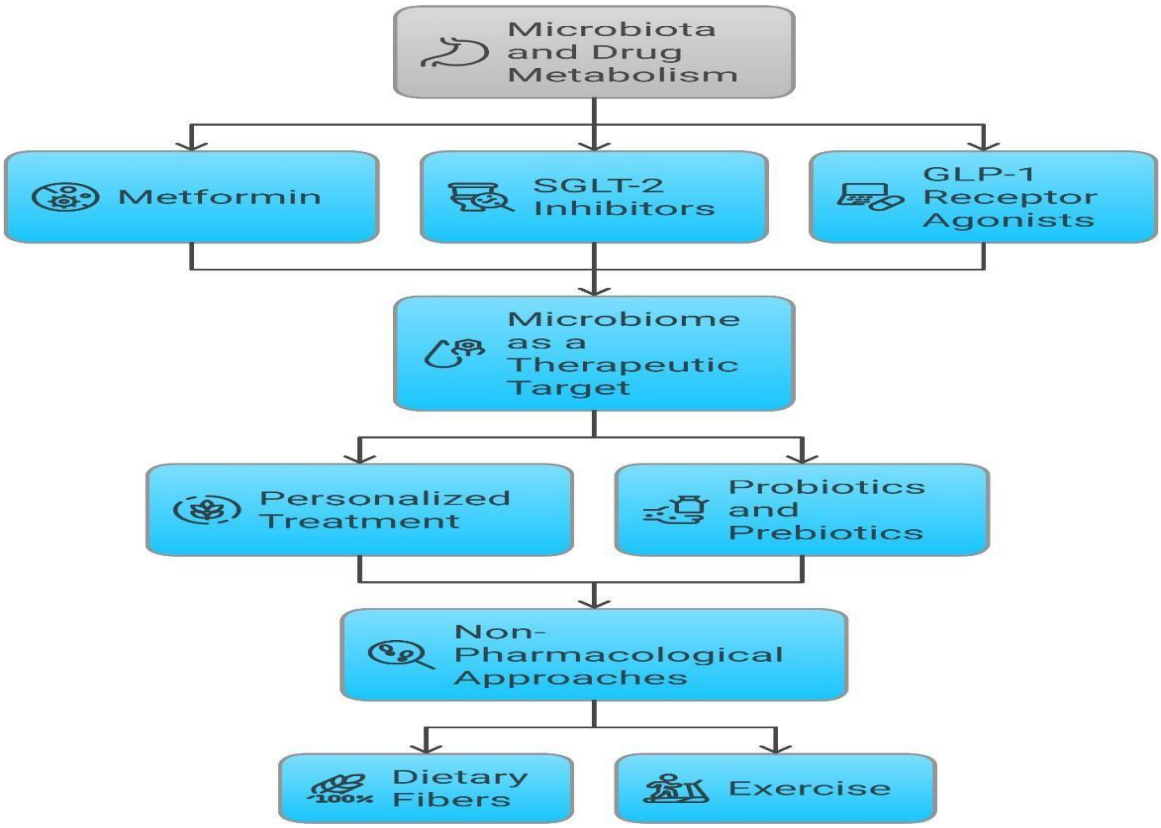

Fig.4 The flowchart illustrates the role of gut microbiota in drug metabolism, affecting diabetes treatments like metformin, SGLT-2 inhibitors, and GLP-1 receptor agonists. It highlights the microbiome as a therapeutic target, leading to personalized treatment, probiotics, and non- pharmacological approaches such as dietary fibers and exercise.

Gut microbiota in diabetes is a topic of great clinical relevance and has led to microbiome based therapies becoming an important adjunct to standard diabetes therapy. The current advances in next generation sequencing (NGS) now enables the profiling of individual gut microbiota and clinicians can use these findings to tailor personalized interventions. Thus, treatment strategies utilizing probiotics, prebiotics and dietary modification are tailored to the microbial signatures associated with insulin resistance and dysregulated glucose metabolism (84). Lactobacillus and Bifidobacterium species have proven specific efficacy in improving insulin sensitivity. Supplementation with Lactobacillus

strains showed that improving glycemic control also reduced inflammatory markers in ways that directly address both the metabolic and inflammatory side of diabetes, as revealed by Velloso (85). Why is this important as chronic low grade inflammation is an underlying factor in insulin resistance. In fact, other food components (prebiotics, inulin, fructo-oligosaccharides [FOS], and resistant starch) have been shown to be useful in diabetic care. These are dietary fiber and they are substrates for the beneficial gut bacteria to produce microbiota diversity and activity. Research indicates that dietary prebiotic treatments restored insulin sensitivity and restocked the gut microbial diversity of Type 2 diabetes patients, complementary to pharmaceutical therapies. (86-87)

Another innovative approach taking off is Fecal Microbiota Transplantation (FMT). According to a recent 2022 systematic review analyzed data from several FMT trials and found that, FMT from lean healthy donors increases insulin sensitivity and glucose metabolism in Type 2 diabetic patients. But some safety and infection risk mitigation concerns and an imperative for routine use have been raised, leading to the need for further research. This implies that combining microbiome modulation through probiotics, prebiotics, and FMT with traditional therapies, as well as changes of lifetime routine including an increase on dietary fiber and physical activity, could have an additive beneficial effect on the outcomes of diabetes management.

Table No.6 Key Areas for Further Research.

Research Area	Key Focus
Long-term Safety and Efficacy	Large-scale clinical trials to validate findings of smaller studies on FMT and probiotics.
Personalized Medicine	Understanding individual microbiome diversity to develop tailored treatments.
AI and Machine Learning	Using AI toanalyze microbiome data and predict treatment outcomes.
Global Variations	Addressing regional differences in microbiota composition and their implications for therapies.
Ethical and Regulatory Issues	Developing guidelines and quality control standards for microbiome-based treatments.

Gaps in current gut microbiota-based therapies for diabetes management need to be comprehensively researched regarding long term safety and efficacy. Validation of findings from smaller studies on fecal microbiota transplantation (FMT) and probiotics requires large scale clinical trials to test their safety, and thus warrant their integration into clinical practice. Another critical area is in personalized medicine where, given the health variations of gut microbiota relating to genetics, diet, and lifestyle, we need to target our approach. Knowledge of microbial biomarkers of insulin resistance and glucose intolerance will help in the design of more effective therapies (88). Artificial intelligence and machine learning are also ramping up microbiome research by looking at vast full data sets, and finding beneficial bacterial strains and predicting therapeutic outcomes. Additional global variations in gut microbiota composition influenced by geographical and cultural factors underpinning the pressing need for more collaborative research to develop universally applicable treatments (89). Second, ethical and regulatory challenges to the use of microbiome-based therapies must be addressed by standardized guidelines and robust frameworks developed by agencies such as the FDA and EMA to secure safety, quality, and ethical use. The solutions to tackle these research priorities are the path to safer, more effective, and globally relevant microbiome interventions in diabetes management.

8. Summary

The gut microbiota is now considered as an important player in metabolism and has been well established in the development and treatment of diabetes. It regulates glucose homeostasis, insulin signaling, integrity of the gastrointestinal barrier and inflammation, which puts it at the center of both types of diabetes. The state of imbalance of the gastrointestinal microbiota refers to dysbiosis and its effect was linked to systemic inflammation, insulin resistance and metabolic endotoxemia which contributes to the advancement of diabetes. The beneficiaries are different microbe species

including *Akkermansia muciniphila* in association with better metabolic health and *Bifidobacterium longum* implicated in the onset of diseases. Probiotics, prebiotics and FMT have been seen to improve metabolic outcomes and boost the effectiveness of conventional pharmacological treatments such as metformin, in glycemic control to treat diabetes. Gut microbiota also affects the pharmacokinetics of OHA, enhancing drug uptake and action of oral hypoglycaemic agents. Moreover, this review shows that fiber intake, exercise, and other adjunct therapies can improve MPAs and positively mediate glucose homeostasis as well as dampen inflammation. However there are some issues which are still under development Some of them include the following Disregard for citizens' interests by revealing any information Possible excessive demand for information Detailed recommendations and a clear understanding of the possible difficulties and drawbacks of the given approach will help to prevent those problems from arising in practice. However, individual differences in microbial population, which differ by age, geography, and diet, hampers the direct targetability of microbiota-based applications. A few more riders of concern include long-term risks of FMT and other extended probiotic usage. Metagenomics, microbiome sequencing, and artificial intelligence are also pointing to specific actionable strategies based on the consumers' unique microbiota. In conclusion, understanding and modulating the gut microbiota for diabetes type has large potential but requires more solid work to cross the current hurdles and achieve maximal therapeutic effects. Precise and particular, interventions for modulating microbiota represent a hope of significant improvement in the diabetes treatment in the nearest future.

9. Future scope

New developments in microbiome research including metagenomics and next generation sequencing have provided new approaches to type 2 diabetes mellitus personalized medicine. It will be helpful to define how these tools can determine special microbial markers associated to diabetes so as to apply interventions like prebiotics and probiotics. Newer data suggest enhanced insulin sensitivity, and general metabolic profile, due to *Akkermansia muciniphila* and *Bifidobacterium longum* of probiotics. Further, fecal microbiota transplantation (FMT) is also under introducing to treat dysbiosis and improved glycemic control however, FMT has safety and side effects in the long run and risks of biological piracy. AI will transform microbiome study by predicting MI responses to treatments and revealing new microbial-based therapeutic targets. The next steps should logically be massive clinical trials in order to check the effectiveness and safety of these interventions. Interventions that target the microbiota along with existing therapeutic strategies enable scientists to establish an individual approach to diabetes with a consideration of international differences in the microbiota and dietary preferences.

10. Conclusion

The bidirectional relationship between gut microbiota and diabetes is a novel area of discussion in metabolic diseases. This review will summarise how microbial content and functions contribute to diabetes pathogenesis, immune activation, and impaired insulin signaling and glucose homeostasis. The current endotoxin concept also supports an association between gut dysbiosis, or a lack of useful microbiota and the overgrowth of pathogenic types, and insulin resistance and inflammation, which defines type 2 diabetes. Pharmacologic and dietary modulations of the gut microbiota constitute promising approaches that show potential for augmenting metformin therapy and other conventional anti diabetic agents including probiotics/prebiotics and FMT. Diet intervention and exercise, however, indicate the importance of the gut microbiota in maintaining metabolic health. But these are areas that still present some challenges as we shall see even with these improvements. Day-to-day intersubject variations in microbiota, coupled with the relative paucity of knowledge regarding the chronic safety and effectiveness of clinical microbiota manipulations, partially obscures clinical potentialities for microbiota-based interventions. Care for future diabetic patients requires developing specific approaches starting from the concept of microbiome and using AI to create patients' individual treatment plans. Meeting these barriers and integrating gut microbiota alteration with conventional treatments provide the foundation for further exploration and successful application of the strategy in diabetes cure for patients.

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