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The role of gut microbiota in the development and management of Type 2 diabetes: Insights into the gut-pancreas axis and its potential for therapeutic interventions

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Abstract

Background: T2D also known as Non-Insulin Dependent Diabetes mellitus (NIDDM) is a common endocrine disorder of insulin resistance and reduced glucose removal by pancreatic β-cells. Recent studies show that gut microbiota play a vital part in the pathogenesis of T2D. Gibson et al., pointed that dysbiosis, a disruption in the composition of the gut microbiota can affect insulin sensitivity glucose homeostasis and pancreatic function in several ways as through inflammation and the microbial metabolite signals.

Aim: This research will seek to determine the relationship between gut microbiota and T2D with keen interest on the gut-pancreas axis and the treatment possibilities under microbiota intervention.

Methods: A systematic analysis of published papers in Medline and Cochrane involving clinical trials and cross-sectional studies was carried out and 16S rRNA sequencing, metagenomic, and metabolic analysis including fasting blood glucose and insulin resistance assessment were also performed for the confirmation of the findings. Possible relationships of gut microbiota with T2D were explored and compared with the existing treatment modalities including probiotics, prebiotics, and metformin and others.

Results: This study revealed peculiar characteristics of the microbiota of the tested T2D patients as compared to the control group with revealed decreased levels of Akkermansia muciniphila and increased levels of Firmicutes. Some studies that were reviewed have shown that dysbiosis has an impact on the function of the pancreas, secretion of insulin as well as the metabolism of glucose. Specifically, diet change, probiotics, and metformin therapy were evidenced to restore and enhance the quality of mucosal microbiota and metabolic profiles.

Conclusion: It is suggested that gut microbiota alteration can be considered as an innovative therapeutic approach to T2D via modifying the gut–pancreas connection. Further studies are required to identify the targeted therapeutic interventions according to the patient microbiome and to evaluate its effects over a long time period.

Keywords: Type 2 Diabetes, gut microbiota, dysbiosis, gut-pancreas axis, insulin resistance, probiotics, prebiotics, metformin, therapeutic interventions.

Introduction

T2D is a long standing condition that can be described as a pathological state where insulin demand and supply is compromised due to reduced insulin sensitivity and decreased pancreatic β-cell activity leading to high blood glucose levels. Prevalence of T2D has risen to epidemic level across the globe with over 460 million population as per the updated IDF data. In fact, the WHO estimates that this number will reach 60 million by 2020 and go up to 700 million by 2045. T2D is now considered as one of the major diseases that results in increased morbidity and mortality, complications such as cardiovascular disease, neuropathy, nephropathy, retinopathy, and infections. These complications have a significant impact on the health care facilities meaning that the costs of treating and taking care of patients have been on the rise [1].

T2D is a polygenic or a polygenetic disease, which means that it results from the combination of genetic and non-genetic factors. Some of the factors common with the development of the disease include bmi, lack of regular physical exercise, unhealthy eating habits and taking inadequate physical activity. Nevertheless, many of these people do not get T2D, which has led to the assumption of other factors that caused the disease. Recently, the focus has been shifted to the way that gut microbiota affects metabolism, which could provide the additional angle for the understanding of the pathophysiology of T2D and its possible treatment. The pathogenesis of T2D is driven by two primary defects: : diabetes as characterized by insulin resistance and pancreatic β-cell dysfunction. Insulin resistance is a condition that results from a decreased ability of the target tissues; including the liver and skeletal muscles as well as adipose cells to respond to insulin bound for uptake and utilization of glucose. There is a rise of a hormone known as insulin in an initial stage of insulin resistance and this is known as hyperinsulinemia. However, after time passes, the β-cells of the pancreas get impaired and cannot release adequate insulin to regulate the blood glucose concentration and therefore lead to the manifestation of T2D [2].

Beside the issue with insulin sensitivity, impaired function of pancreatic β-cells also has a major role in the development of T2D. With sustained progression of the disease, changes in the dynamics of the β-cell mass and its function, defects in insulin secretion in response to glucose become obvious. This defect is further compounded by other factors such as glucotoxicity, lip toxicity, oxidative stress and low-grade inflammation. Individually, insulin resistance and β-cell dysfunction maintain hyperglycaemia and the progression of metabolic disorder, the two phenomena are interrelated and have a negative feedback relationship [3].

Treatment of T2D is complex and often consists of life-style changes pharmacological interventions and insulin therapy in higher stages of T2D. Life-style modifications such as diet modification, exercise and weight loss remain the main strategies of managing T2D. Thus, such foods as whole grains, fruits, vegetables, and lean protein products can positively contribute to the increase in the sensitivity of tissues to insulin and to the regulation of norms of blood glucose. Physical activity is known to improve insulin sensitivity and capacity of the muscle to take in glucose in the body hence supplement glycaemic regulation. Lifestyle changes are sometimes not very effective making pharmacotherapy to be the next option for managing the condition. These are metformin tablets in oral medications for decreasing blood glucose levels and increasing the sensitivity of muscles to insulin. If oral drugs are inadequate for glycaemic control, injectable drugs including the GLP-1 receptor agonist and Insulin may be prescribed to help control blood glucose levels better. Although these therapies are helpful in the management of T2D they mostly deal with the effects of the disease and not the causes. This has rendered the identification of other targets which can be exploited in order to treat IBD and has become apparent that the gut microbiota could be considered as having therapeutic potential [4].

The human gut comprises of a large number of microorganisms known as the gut microbiota and these organisms are extremely important in metabolic regulation. Within the past few decades, gut microbiota has been identified to be an important factor of development of metabolic diseases such as obesity and T2D. The GM plays a crucial role in mediating different physiological functions such as metabolism, and SCFAs production which has proclivity to reduce inflammation and glucose level.

Some facts concerning the gut microbiota include the following: the group and variety of microorganisms can differ among people and depends on the diet, genetic predisposition, and other factors. In a healthy person, gut microbiota is what can be referred to as a symbiosis of microbial species that play a positive role in the promotion of health and metabolism. In normal circumstances, this balance is maintained, but in patient's with T2D, this balance is broken and the state is referred to as dysbiosis. Dysbiosis then characterizes a decrease in beneficial microbial species and emergence of pathogenic species which initiates low grade inflammation and negatively affects glucose tolerance [5].

It has been proved in literature that dysbiosis of gut microbiota play a crucial role in the pathogenesis of metabolic diseases, such as T2D by perturbing metabolic signals. For example, some of the microbial species are implicated in synthesis of SCFAs, which have been known to be involved in controlling glucose and lipid homeostasis. T2D patients' fecal samples show altered bacterial composition and specifically in the number and activity of SCFA-producing bacteria resulting in low levels of SCFAs and dysregulation of glucose levels. Furthermore, the gut microbiota plays a role in modulation of the gut secreted hormones such as GLP-1 that contributes to increased secretion of insulin besides promoting satiety. Dysbiosis can therefore alter the synthesis of these hormones augmenting insulin resistance is coupled with β-cell dysfunction.

More than that, gut microbiota may regulate the integrity of the barrier in the intestine. When the environment within the human gastrointestinal tract is abnormal as is the case with dysbiosis, the integrity of the lining of the gastrointestinal tract is lost and endotoxins such as lipopolysaccharides (LPS) can get into the blood stream. It was also found that LPS is inflammatory cytokine that can also stimulate insulin resistance and cause metabolic syndromes. The former, called the metabolic endotoxemia, has been assumed to contribute to the development of T2D and other metabolic diseases [6].

The gut-pancreas axis is the two-way interaction between the gut microbiota and the pancreas; this interaction helps in the control of blood glucose and insulin release. New data indicate that gut dysbiosis can alter the outcomes of pancreatic functions through changes in gut hormone secretion, production of metabolites and regulation of inflammations, among others.

Another way that the gut microbiota affects the pancreatic function is through generation of SCFAs, with special preference to butyrate, acetate and propionate. These SCFAs are known to stimulate release of GLP-1, a gut hormone having a positive impact on insulin secretion from pancreas and also on glucose tolerance. Also, SCFAs have been described to display anti-inflammatory properties and their action contribute to decline in pancreatic β-cells oxidative stress and inflammation, which are significant factors of T2D pathogenesis [7].

The last factor to be considered an essential component of the gut-pancreas axis is the ability of microbial metabolites to regulate immune processes. Dysbiosis also leads in increased levels of Pro-inflammatory cytokines that effect β-cell functionality with a subsequent deuteriation of insulin sensitive stage. Modulation in gut microbiota can help to decrease the process of inflammation and preventing the decline of insulin producing capacity of pancreas, thus regulating blood glucose in T2D population.

Given the growing evidence supporting the role of the gut microbiota in T2D, the objective of this article is twofold: The two related research questions for the systematic review are; (1) Are there any associations between gut microbiota and development of T2D? (2) Is there evidence pointing to the use of probiotics and prebiotics for the management of T2D? In explaining the descriptions involved in the gut-pancreas

relationship and modulating effects on glucose homeostasis, this study seeks to contribute to the development of new treatment approaches pertaining to the modulation of gut microbiota toward enhanced metabolic health.

Consequently, this article aims at focusing on the growing biomarker importance of the gut microbiota in T2D development and treatment. To this end, by remining on gut-pancreas axis, it seeks to deliver a holistic view of how gut microbiota impacts glucose homeostasis and whether modulating the microbiome can be used in the treatment of diabetes. Advances have shown that gut microbiota has potential to become a new target for optimizing the patients with T2D [8].

Materials and Methods

The understanding of gut microbiota in the development of T2D and the new approach of managing T2D has a strong background of multidisciplinary. However, to capture all the aspects that are vital in enabling a total understanding, the kind of study design that is used may differ considerably depending on what the study is all about. For example, such methods as systematic reviews, clinical trials on human participants, animal models belong to the most common ones in this field [9].

Thus, depending on the result of the present systematic review, differences in gut microbiota compositions between T2D patients and non-diabetics, and effects of certain strains on the disease, can be established. This involves seeking for literature studies, clinical trials, and meta-analysis on the noted characteristics of gut microbiota and T2D relationship. Therefore, the inclusion and exclusion criteria are set very strictly so that only the best-quality components are taken into consideration. The systematic review is used in portraying a synthesis of the existing body of knowledge in relation to the identified trends, emerging research gaps and directions for future research.

In clinical studies involving human subjects, participants are typically divided into two groups: one consisted of patients diagnosed with T2D and the other one was the group of people without diabetes. Accordingly, the study will seek to compare the sort of gut microbiota in the two groups of subjects. The clinical studies are often descriptive, or they can be experimental. In observational studies, the focus is on the variations in gut microbiota acting in people's usual environment, whereas in interventional studies, researchers attempt to modulate gut microbiota using probiotics, prebiotics, or other interventions and examine effects of these interventions on glucose metabolism and general health. The subjects are usually followed for some time and samples of his or her gut microbiota and metabolic profile are taken from time to time [10].

Rodent models are also employed in gut microbiota related studies to a great extent. Mice especially are most frequently used animals because in terms of metabolism and the composition of gut microbiome they are similar to humans. In such cases, conventional studies use germ-free mice (lacking gut microbiota), to analyse the effects of certain bacterial strains on glucose and insulin homeostasis. This makes for exceptional control and regulation of the experimental parameters on gut microbiota and its effects on metabolic fitness in a manner that cannot be easily replicated in human subjects due to bioscientific and ethical considerations.

This means that the type of study to be used in a particular investigation has to be determined by the objectives of this research. For example, the human clinical trial is necessary to establish the correlations between human gut microbiota profile and T2D, and although animal model is used for masting the cause-effect relationships. In any of the cases, ethical clearance is sought and the participants have to give their consent especially in the case of human participants [11].

Recruitment is another very important factor that has to be regarded when conducting a clinical study in order the result s to be generalized among all the participants. Usually, participants selected are male and

female adults who are 18 years and above. Individuals are classified into two groups: T2D patients (and in particular the first group of them, for whom clinical records are available) and healthy NT persons with no history of metabolic diseases.

The inclusion criteria for the T2D group are specific and usually demand the diagnosis of T2D according to the authentic criteria such as ADA in which patients should have fasting plasma glucose level ≥126mg/dl, HbA1c ≥ 6%. 5 percent or a documented history of diabetes that is well-established. Another example of potential participant classification is the duration of diabetes, BMI and other associated diseases, including hypertension or hyperlipidaemia. The criteria used to select the control group essentially involve a negative history of metabolic disorders, no signs of glucose intolerance and BMI within the normal range.

In the case of animal models sample selection also includes choosing certain mice strains that best match the human metabolic reactions. For instance, using mice model with obesity or diabetes like the ob/ob (Leptin-lacking) or db/db (leptin receptor knocking-out) are used for modelling an aberrant gut microbial communities associated with metabolic disorders. Clean or germ-free mice are also important to study the effects of the particular bacterial species and strains are which implanted into germ-free condition.

The proper description of gut microbiota composition is an essential part of the epidemiological investigations of the relationships between the microbiome and T2D. There are several techniques that are applied to analyse gut microbiota and the most commonly used are to determine the number of bacteria in the gut.

The most frequently applied method is the sequencing of 16S rRNA gene which is found in all the bacteria and is a housekeeping gene. This technique can help in the characterization of bacteria at the genus level provided that variable regions of the 16S rRNA gene are analysed. Stool samples are collected from the participants and then DNA is isolated, selected regions of the 16S rRNA gene are then amplified by PCR. They are then sequenced by high throughput sequencers like Illumina or Ion Torrent platforms among others. This data is then matched with other bacterial databases for purposes of identifying microbial taxa and determining their relative quantities [12].

The other common method is known as shotgun metagenomics which is more informative than the above-discussed 16S rRNA gene sequencing as it sequences all the DNA in the sample. This method enables determination of bacteria at the subspecies level and the understanding of the possible metabolic and enzymic profiles of the microbiota through the genes they harbor. This is especially essential when it comes to the gut microbial effects on certain responsible metabolic pathways and pathways include SCFAs, Bile acids, and Immunomodulation.

However, metabolic assessments are crucial for the research evaluating the GI microbiota and T2D since the alteration in the microbiota affect the host physiology. Various blood glucose and insulin sensitivity tests are done in the course of the study to evaluate the subjects' metabolic profile.

The fasting plasma glucose (FPG) test is performed to determine glucose levels which have been obtained after fasting for 8 hours and gives an estimation about the homeostasis of the blood glucose in the body. The oral glucose tolerance test (OGTT) another definitive test that evaluates the Glucose tolerance. In this test, a participant is given a glucose solution and blood glucose level is taken at 30-minute intervals for 2 hours. This test aids in defining people with insulin resistance and those with impaired glucose tolerance, which are characteristic of T2D.

Also, they included haemoglobin A1c test – which evaluates average blood sugar control over a period of 90 days. This test therefore gives an average blood glucose for the last two to three months unlike FPG or OGTT that give a nodal value of glycaemic control.

For assessing of the insulin sensitivity, the homeostasis model assessment of insulin resistance HOMA-IR is applied. This index is the estimate of the insulin resistance calculated by the results of fasting glucose

and insulin levels. It can be seen from the above result that HOMA-IR has a high value when insulin resistance is high [13].

Lots of data are produced from microbiota profiling, glucose level, and metabolic testing; hence, high analytical and statistical techniques apply. As a result, scientists process the sequencing data in silico by employing bioinformatics to make reciprocity of the gut microbiota taxonomic. These profiles are then compared between individual with T2D and healthy controls using multivariate statistical techniques.

Other statistical techniques that are usable are, for example, PCA which helps in simplifying the data by providing patterns of microbial communities. Linear discriminant analysis effect size (LEfSe) is the other method employed as a means of identifying bacterial taxa that are significantly different between groups. Cohort comparisons or simple regression analysis – for example, Pearson's or Spearman's correlation coefficient – is conducted to determine the relationship between particular microbe and metabolic variables including blood glucose level, insulin sensitivity, and HbA1c.

For interventional studies, ANOVA or a multivariate regression analysis is usual for determining the pro forma alteration in various components of gut microbiota and metabolic profiles by changes in diets, probiotics, or prebiotics. Self-control models also take into consideration possible medal distortions like age, BMI, medication use among others to make sure the resultant effects are as a result of the intervention. Therefore, the methods and materials used in the investigations of the gut microbiota and T2D are, by design, multidisciplinary, utilizing contemporary microbiota profiling methodologies, precise metabolic characterization, and reliable statistical methods. Such an approach enables a more extensive appreciation of the gut-pancreas interaction and offers a framework for designing antidiabetic therapies that consider the role of gut microbiota [14].

Results

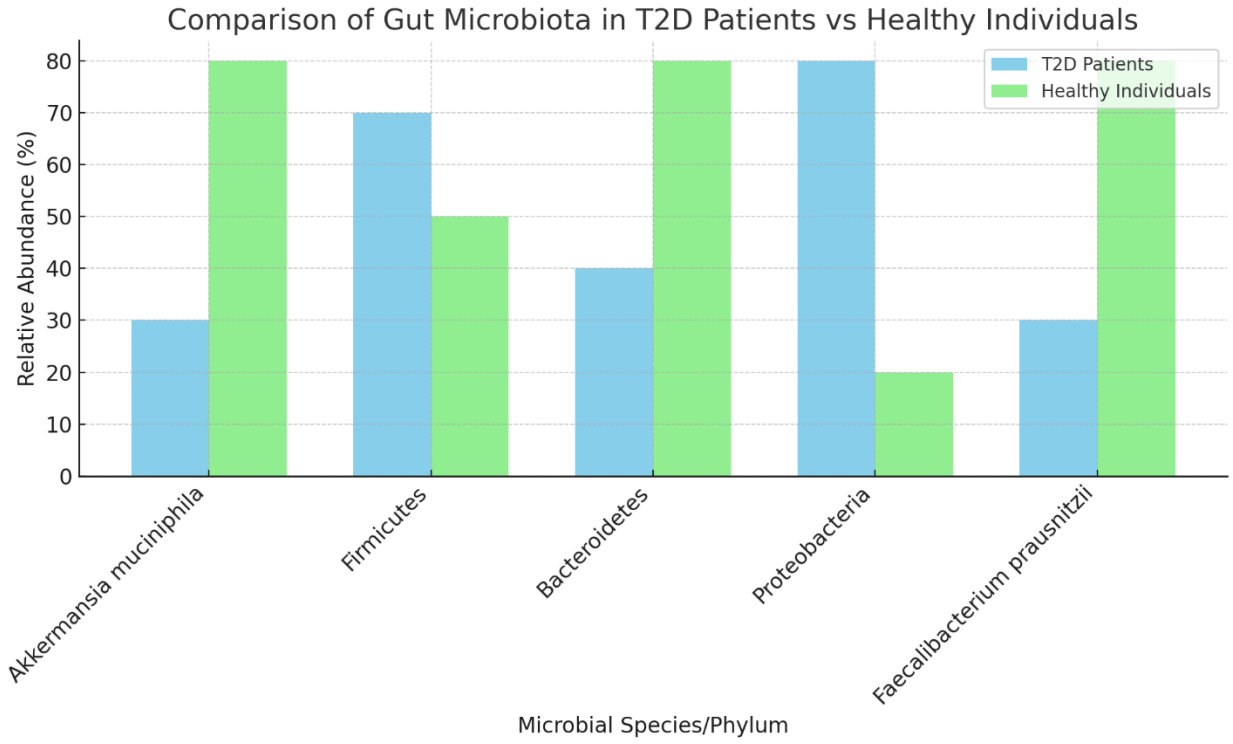
Research evidence shows that the population of gut microbiota in T2D patients is not similar to that of the healthy people. Microbial ecology or gut dysbiosis as it is also referred to is a prominent feature in T2D patients. The overall microbial load has decreased, and the population composition of T2D patients' gut microbiota turned out to be substantially different from that of the control group.

Some of the previous works have pointed to Akkermansia muciniphila, a bacterium that digests mucin, as a specific representative that is low in T2D patients. This bacterium has been linked with enhanced gut barrier integrity as well as anti-inflammatory properties. Low abundance of Akkermansia muciniphila in T2D patients include enhanced type of gut barrier permeability leading to metabolic endotoxemia that may cause enhanced insulin resistance. On the other hand, Firmicutes has emerged as higher in people with T2D due to the fact that it is a phylum that comprises several bacterial species which are involved in energy acquisition and fat accumulation. These changes point to a higher Firmicutes abundance at the expense of a decrease in Bacteroidetes; this results in an increased Firmicutes to Bacteroidetes ratio which is linked to obesity and metabolic disorder.

Furthermore, it has been observed that T2D patients have high count of Proteobacteria phylum that has many pathogenic organisms. These bacteria are linked to inflammation, and the generation of LPS, which cause systemic inflammation and supplemental insulin resistance and organic β-cell dysfunction. I would also like to note that oxidative stress reduces the normalized number of Bacteroidetes and Firmicutes, short-chain fatty acid-producing bacteria that are necessary for gut health, including Faecalibacterium prausnitzii and Roseburia, intestinal bacteria in T2DM patients [15].

Microbial Species/Phylum		**Healthy Individuals**

	T2D Patients	
Akkermansia muciniphila	Reduced	Abundant
Firmicutes	Increased	Balanced
Bacteroidetes	Reduced	Normal
Proteobacteria	Increased	Minimal
Faecalibacterium prausnitzii	Reduced	Abundant



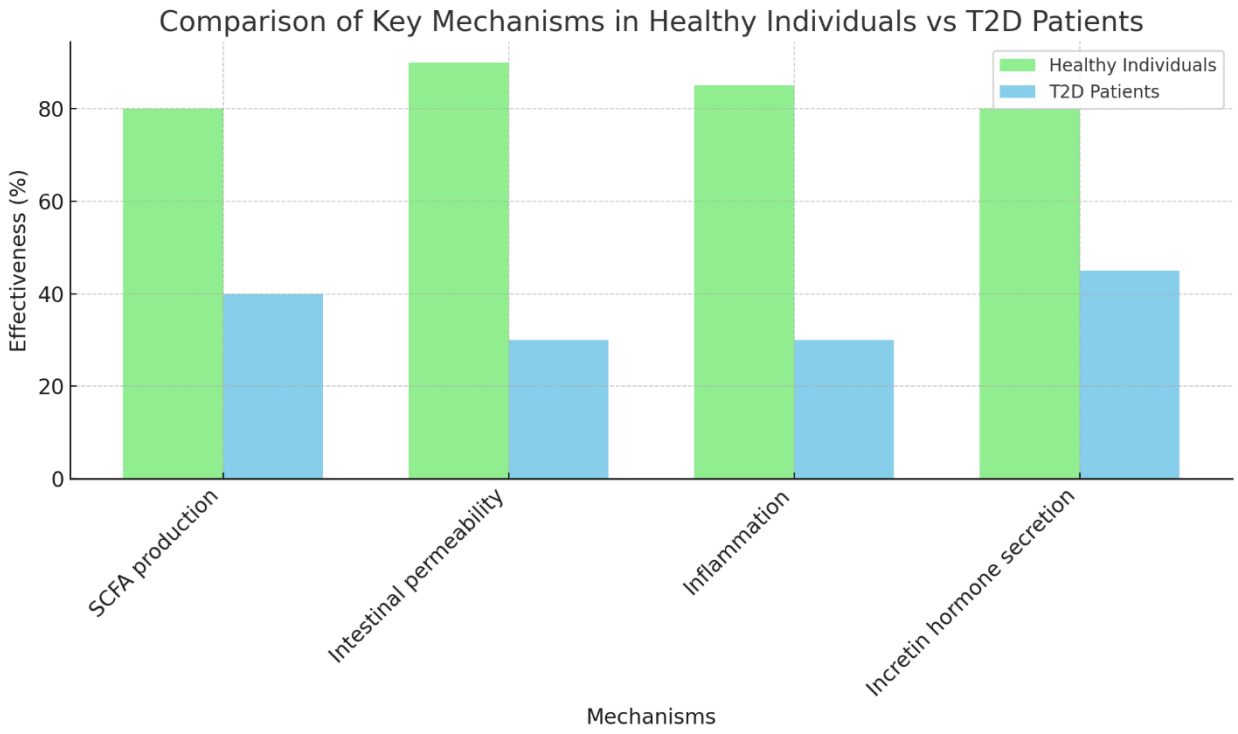
The gut-pancreas axis is one of the ways that gut microbiota impact the metabolic health in as a regard to its relationship with the pancreatic activities and insulin secretion. Such disruption of communication by dysbiosis of the gut microbiota in T2D results in poor regulation of glucose.

Acetate butyrate and propionate are some of the short-chain fatty acids produced by the bacteria in the gut and they are very essential in regulating the glucose level in the body. SCFAs are obtained through the fermentation of some dietary fibres with anti-inflammatory properties that improve insulin sensitivity and stimulate pancreatic β-cells. However, in T2D, SCFA-producing bacteria like Faecalibacterium prausnitzii and Roseburia are decreased that lead to decrease level of SCFA which affect the insulin secretion and causes glucose intolerance.

Furthermore, it causes alteration of gut permeability such that toxic substances from the bacteria including lipopolysaccharides(LPS) are absorbed into circulation. This, known as metabolic endotoxemia, increases systemic inflammation and has a negative effect on Pancreatic β-cell and Insulin secretion. C chronically stimulated inflammation mediated by LPS is also capable of end injuring pancreatic cells and hence worsening T2D as a result of insulin deficiency [16].

The gut microbiota is also known to modulate the release of incretin hormones which include the glucagon-like peptide-1 (GLP-1) that aids in the stimulation of insulin release and glucose homeostasis. Imbalance in the gut bacteria affects incretins secretion and increases problems in regulating blood glucose level.

Mechanism	**Healthy Individuals**	**T2D Patients**
SCFA production	Adequate levels promote insulin sensitivity	Reduced SCFA levels impair insulin secretion
Intestinal permeability	Intact, low LPS in circulation	Increased permeability, high LPS levels
Inflammation	Low inflammation, functional β-cells	Chronic inflammation, β-cell dysfunction
Incretin hormone (GLP-1) secretion	Adequate levels enhance insulin secretion	Reduced incretin levels impair glucose control



Available literature supports the concept that pharmaceutical or other interventions that alter gut microbiosis has beneficial effects on glucose homeostasis and insulin signalling in T2D patients. Interactions with diet, pre- and probiotics, as well as nutrients like metformin, are receiving increasing attention as a way of altering gut microbiota and thus the course of T2D.

Dietary Interventions: Fibre content in the diet was found to have a direct impact on the shifting of gut microbiota toward the increased production of SCFAs. A high fiber diet strengthens the so called friendly bacteria including Akkermansia muciniphila and Bifidobacteria in the gut and help enhance the gut barrier as well as a decrease inflammation. Research has shown that, diets that are rich in fiber can improve the insulin sensitivity and make the fasting blood glucose levels of T2D patients to reduce. The fermentation of dietary fiber results into production of SCFA which enable control of glucose and inflammation [17].

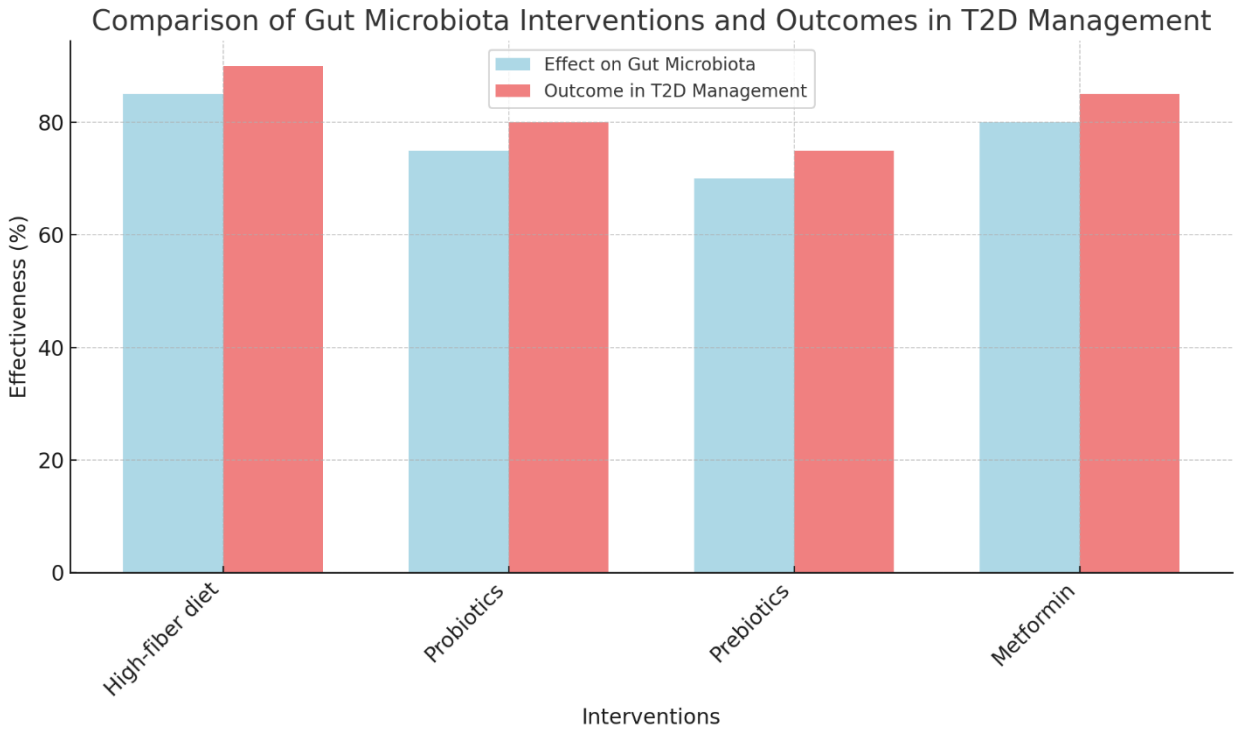
Probiotics and Prebiotics: Probiotics are live beneficial bacteria while prebiotics are compounds with capacities to stimulate growth of beneficial bacteria have also been seen to be effective in managing gut microbiota in T2D patients. Lactobacillus, Bifidobacterium has been researched used to treat symptoms of SIBO and help regain bacterial balance and decreasing inflammation. These probiotics can enhance insulin openness, decrease the permeability of gut, and limit the degree of LPS in the blood termed as metabolic endotoxin.

Prebiotics include the molecules that are not broken by our digestive system and include inulin and fructooli gosaccharides (FOS) and act as feed for useful gut bacteria. This action helps in the promotion of growth of SCFA producing bacteria with positive impact on gut and glucose intolerance. Several studies done on clinical trials have indicated that prebiotics has the potential of lowering fasting blood glucose, lowering HbA1c and improving the metabolic control among the T2D patients.

Metformin: The effect of medications used in T2D management on gut microbiota has been documented with metformin as the most pathogenic medication used in the management of T2D. Metformin enhances Akkermansia muciniphila several folds recognized for improved insulin sensitivity and low inflammation.

It also has an impact on the shift of gut microbial composition by enhancing the level of bacteria that promote SCFAs in an effort to controlling glucose levels. Surprisingly, all the above-rationalized therapeutic consequences of metformin depend on their influences on the microbiota rather than a direct effect on glucose homeostasis.

Intervention	Effect on Gut Microbiota	Outcome in T2D Management
High-fiber diet	Increases SCFA-producing bacteria	Improves insulin sensitivity, reduces inflammation
Probiotics (Lactobacillus, Bifidobacterium)	Restores microbial balance, reduces LPS levels	Enhances insulin sensitivity, reduces gut permeability
Prebiotics (inulin, FOS)	Promotes growth of beneficial bacteria	Lowers fasting glucose, improves metabolic health
Metformin	Increases Akkermansia muciniphila, alters microbiota composition	Improves glycemic control, reduces inflammation



Discussion

The Modulating Effect of Gut Microbiota in the Development of T2D

Alterations of gut microbiota are involved in the development of T2D, as gut microbiota affects metabolic networks that regulate insulin response, blood sugar levels and pancreatic activity. Since changes of the composition of gut microbiota in subjects with T2D is called dysbiosis, these essential pathways get interrupted leading to advancement of the disease. The following mechanisms have been postulated through which the changes in the microbiota impact directly on insulin sensitivity and blood glucose homeostasis.

Making that, one of the mechanisms is related to interaction between gut microbiota and inflammation, which plays a role in insulin resistance. Normally, the gut barrier is tightly regulated so as to allow only substances beneficial to the body to pass through while excluding other damaging microbial parts like lipopolysaccharides (LPS). Nonetheless, in T2D, dysbiosis affects the barrier function of the intestinal tract, making it permeable otherwise termed as 'leaky gut' where LPS, a molecule on the outer membrane of the gram-negative bacteria including Proteobacteria gets absorbed into the bloodstream. After pro-inflammatory cytokines burst LPS circulates in the bloodstream and activate other immune cells, namely monocyte/macrophage, to release pro-inflammatory cytokines such as TNF-α and IL-6. Inflammation on the other hand causes disruption of insulin signalling pathways because insulin receptors can no longer properly bind to insulin in tissues including the liver, muscle, and adipose tissue, thus, the development of insulin resistance occurs [18].

Besides inflammation, gut microbiota also modulate I diabetes through the metabolic product like SCFAs. SCFAs are three-carbon molecules that are butyrate, propionate, and acetate generated from the fermentation of dietary fibres via certain bacterial species in the gut. The above stated metabolites offer various functions in the body including glucose homeostasis, enhanced sensitivity to insulin and maintenance of the integrity of the intestinal barrier. For instance, butyrate, which is a SCFA, has been established to possess beneficial effects on insulin signalling since its promotes mitochondrial biogenesis in skeletal muscle and hepatic cells. Also, SCFAs activate the production of GLP-1 which is an incretin hormone that mediates insulin secretion from pancreatic β-cells when there is food consumption. However, negative imbalance in the T2D patients is characterized by low level of SCFAs resulting from reduction of bacteria like Faecalibacterium prausnitzii and Roseburia [19].

Also, the gut microbiota have been reported to affect bile acid metabolism and is of importance in regulating blood glucose levels. It contains certain bacterial species for the modification of primary bile acid to secondary bile acid including the Firmicutes phylum. These secondary bile acids stimulate some receptors included in the farnesoid X receptor (FXR) and TGR5 receptor both of which are vital in regulating glucose homeostasis and insulin resistance. The dysbiosis in T2D may have an impact on the composition of the bile acid, and this affects these metabolic pathways [20].

Gut microbiota and Pancreatic β-cell function also holds a central place in the causal pathways that characterise T2D. Dysbiosis and the in turn negative effect on beneficial metabolites such as SCFAs and bile acids would also affect the β-cell operation and lead to decreased insulin synthesis thereby increasing hyperglycaemia. However, sustained inflammation due to dysbiosis may also cause apoptosis of the β-cells and thus reduce the capability of the cells to secrete insulin to control T2D.

Gut microbiota and its possible influence: a review on therapeutic benefits of targeting bacteria.

Considering that gut microbiota contribute to the development of T2D, rebalancing the gut microbiome has become therapeutic approach that may be efficient in improving metabolic profile and managing T2D. The most researched schools of thought concern the processes of redeposit of essential beneficial microbial colonies with the help of probiotics and prebiotic components [21].

Probiotic refers to the living microorganisms which are effective when taken as supplements or found in foods which have been fermented. To date, many pieces of research have proved that probiotics such as Lactobacillus and Bifidobacterium can affect glucose metabolism and decrease insulin resistance by modulating the gut microbiota. For example, these bacteria Favor the synthesis of SCFAs that have been shown to improve insulin signalling and to decrease inflammation. They have also been shown to have the ability to reduce the permeability of the intestinal barriers thus minimizing the ability of LPS and other noxious substances to translocate into the bloodstream. It also reduces metabolic endotoxemia, thus lowering inflammation that is attributed to T2D and resulting in better glycaemic control.

Prebiotics, in contrast, are nondigestible food substances that selectively encourage the growth of 'friendly' gut bacteria to thrive. Inulin and fructooligosaccharides (FOS) are some of the most prevalent prebiotics which are catabolized by the gut bacteria into SCFAs. It had been found that prebiotic supplementation yields an incremental reduction in fasting blood glucose, as well as an enhanced level of SCFA-producing bacteria and increased insulin sensitivity in T2D patients. The inclusion of prebiotics assists to alter the microbial physiology for the better with the intention of maintaining glucose homeostasis besides other aspects of health [22].

Research has also shown that diets that targeted on fibre have a positive effect on the gut microbiota in addition to probiotics and prebiotics. Akkermansia muciniphila and Bacteroides from the fiber were identified to enhance the desirable aspect of the T2D through favourable consumption of fruits healthy vegetable and whole grain foods. Fiber fermentation results to the formation of SCFAs which as said here has various positive impacts on glucose homeostasis and insulin action.

In addition, there is increasing concern with strategies that employ specific genomes for the adaptation of microbiota found in human gut. Due to this, targeted and individualized therapies, which would address the specific composition of an individual's gut microbiota, therefore, have the potential of being more beneficial regarding the result that is to be achieved. For instance, a person with low levels of SCFAs producing bacterium may need to take particular prebiotic for increasing such bacterium levels. Likewise, people in possession of Proteobacteria have high levels of inflammation-associated bacteria and could benefit from proper probiotics that will help decrease the gut permeability and inflammation. The introduction of microbiome analysis in the clinic might result in the creation of metabolic health care regimens that rely on the individual's microbiome [23].

However, there are some issues that need to be resolved while translating the modulation of gut microbiota in the treatment of T2D. Some of the major limitations are the high heterogeneity between the studies conducted, inter-study variability in the methodology applied for sample collection as well as for analysis of the microbiome. Such disparities also hinder the generation of a clear understanding of the effectiveness of the different bacterial strains in the management of T2D or the specific intervention strategies that may be the most effective.

One of the problems is that gut microbiota is a very diverse and composite population of microorganisms. Sphincter-associated microbiota is composed of phage, bacteriophage, fungus, virus, bacterium, parasite, fungus spores and rod-shaped bacteria forming trillions of colonies that are dynamic and contextual. It may not be easy to pinpoint lipidenriched species or metabolites that are mostly involved in change of metabolism due to the fact that many complex factors such as what a person consumes, what the person takes or is genetically programmed to produce will dictate the composition of the bacterial community. Furthermore, the chronic impact of the probiotic and prebiotic in maintaining the gut and controlling T2D continues to be unknown, mainly because majority of the investigation has tended to short-term results.

In addition, the application of microbiota-targeted therapies is also not safe and effective enough. Overall, despite the global availability of the probiotics and prebiotics it is worthy to know that the impact will be contingent upon the individual's microbial flora and overall health. Also, risks that are associated with the

compound that may have side effects such as bloating or stomach discomfort should be considered especially in sensitive user groups.

Further studies are still required to better solve these issues and deepen our knowledge on the consequences of microbiota-targeted approaches in the long term. With regard to the existing and emerging interventions such as probiotics, prebiotics and others, large clinical trials with rigorous clinical design should be conducted to establish the effectiveness of these adjunct interventions in enhancing metabolic control among T2D patients. In addition, the incorporation of multiple 'omics' studies that include metagenomics, metabolomics, and transcriptomics in microbiome studies will help elucidate the functional capabilities of gut microbes and also shed light on how these microbes may modulate the host.

That is why the possibility to create individualized treatments according to the characteristics of the gut microbiota also has potential in the field of microbiome. Such approaches could provide better ways of treating T2D and other metabolic diseases thus providing better ways of increasing health in patient's diagnosed with such diseases [24].

Concisely, gut microbiota is significantly involved in the pathogenesis of T2D via regulation of insulin sensitivity, glucose homeostasis, and pancreatic function through inflammatory process, SCFAs and gut barrier function. Evidently, probiotics, prebiotics and changes in diet which affect the gut microbiome has a potential in enhancing glycaemic control and insulin sensitization in patients with T2D. Nevertheless, still, the issues connected with standardization, discussed complexity, and long-term impacts should be solved to adapt microbiome study outcomes to efficient clinical practices. New and more effective treatments could be derived from current ways of tailoring treatments according to the gut microbiota; therefore, more efforts should be invested in this promising line of research in the future [25].

Conclusion

Overall, gut microbiota has a significant impact on the pathogenesis and treatment of T2D as reflected by the control of insulin resistance, glucose homeostasis and pancreatic functions. Dysbiosis means that the microbial structure is changed and causes inflammation, counteraction of glucose metabolism, and insulin intolerance. The action that can be utilized in the present intent includes the use of the therapy like probiotics, prebiotics, changes in diets, and medications like metformin. Therefore, the current findings point up that the influence on gut microbiota in patients with T2D could dramatically improve the future treatment of this disease, focusing on the gut-pancreas axis. The combination of microbiota-based therapies with traditional approaches to T2D therapy can easily enhance the efficacy of the treatments and make them even more personalized. But more research is needed to know more about the benefits and precaution measures as well as to perfect these approaches and apply in clinics.

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