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REVIEW ARTICLE

The Role of Gut Microbiota in the Development of Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus presents a significant global healthcare challenge with a steadily rising prevalence. Recent research has shed light on the correlation between gut bacteria and the improvement or progression of type 2 diabetes. This review article delves into an evaluation of current knowledge of how the gut microbiota affects type 2 diabetes, focusing on the impact of microbial imbalances on insulin resistance, inflammation, and metabolic dysfunction. By evaluating current knowledge in this field, the study highlights the potential of modifying the gut microbiota through food plan adjustments, probiotics, prebiotics, and fecal transplants as a promising strategy for managing type 2 diabetes. Additionally, it explores how specific microbial species and compounds influence glucose metabolism and insulin sensitivity, potentially providing targets for microbiota-focused interventions to ameliorate the burden of type 2 diabetes.

Introduction

Diabetes Mellitus is a multifaceted chronic condition without a definitive cure that impacts substantial populations globally. It is a chronic, progressive metabolic condition arising from the body's inability to effectively regulate blood glucose levels, resulting in hyperglcemia[1–3]. In 2019, type 2 diabetes had a staggering global prevalence, affecting approximately 463 million individuals. Studies indicate that this number will rise to 700 million people by 2045[10]. This exponential increase poses a significant challenge for healthcare policies, as diabetes profoundly influences individuals and healthcare system resources and expenditures, with an estimated $412.9 billion in financial costs in the U.S. for 2022[11].

The two main classes of diabetes mellitus are type 1 (T1D) and type 2 diabetes mellitus (T2D). T1D is an autoimmune state in which the body's immune system erroneously targets and eradicates insulin-producing cells in the pancreas[4-7]. Insulin, a pancreatic hormone, plays a crucial role in blood glucose regulation by facilitating glucose entry into cells for energy utilization. In cases where this process is impaired, glucose remains in the bloodstream, leading to hyperglycemia. Therefore, individuals with type 1 diabetes rely on insulin to manage their blood sugar levels. Conversely, in type 2 diabetes mellitus (T2D), there is dysfunction of pancreatic β-cells, and the body develops resistance to insulin's effects in peripheral tissues or fails to produce adequate insulin, leading to progressive metabolic disturbances such as impaired glucose metabolism and chronic low-grade inflammation[8,9]. The development of this condition is influenced by a combination of genetic and lifestyle elements such as unhealthy diet, overall physical fitness and activity levels, obesity[1,2,8,9] and environmental factors, including air pollutants and medications[12]. Both types of diabetes can result in prolonged hyperglycemia, resulting in irreversible and widespread damage to organs with severe complications like heart disease, kidney impairment, nerve damage, and vision issues if not appropriately controlled. Regular blood glucose monitoring, use of medications, and routine medical examinations are essential for managing diabetes mellitus and preventing complications. Lifestyle modifications, such as improved diet, smoking cessation, weight management, and increased physical activity, are crucial to effective diabetes management.

In addition to the factors mentioned above, there appears to be a novel association between T2D and disruptions in the gut microbiota. The gut microbiota (G.M.) constitutes a highly diverse ecosystem within an individual, shaped by environmental factors, genetics, diet, and antibiotic use. It comprises many microorganisms, including bacteria, archaea, fungi, protozoa, and viruses, that naturally inhabit the gastrointestinal tract[19]. These microorganisms interact with each other and with the host. A wealth of clinical studies has brought to light the profound impact of G.M. on glucose metabolism, suggesting that changes in the G.M. dynamics in diabetic populations and animal models play a pivotal function in the pathogenesis of T2D[13–18]. Moreover, a growing body of evidence has highlighted the central role of G.M. in a range of metabolic processes, from obesity and non-alcoholic fatty liver disease to chronic inflammation, insulin resistance, and diabetes mellitus[19]. These findings collectively underscore the significant role of G.M. in human health and metabolic well-being.

This review delivers a comprehensive account of the distinct gut bacteria implicated in glucose metabolism and the insulin pathway, elucidating their connection to T2D. The identified molecular mechanisms associated with T2D in relation to gut microbiota are explored. The subsequent section highlights potential therapeutic approaches, such as modifying the gut microbiota through food plan adjustments, probiotics, prebiotics, and fecal transplants, and ongoing advancements in this field, offering practical insights for managing T2D.

Materials and Methods

SEARCH STRATEGY

The present comprehensive review involved the utilization of PubMed, SCOPUS, Web of Science,

and Google Scholar databases to pinpoint English-language studies that center on the pathogenesis, clinical presentation, guidelines, and prevention of postoperative infections. Additionally, websites of various organizations and various online search engines, including Google, were also actively searched for the unpublished grey literature on the subject under study. The references of each chosen article were thoroughly scrutinized and cross-referenced with other materials to ensure the reliability of relevant data.

Moreover, for this comprehensive review, the studies selected included epidemiological and health assessment studies, with data de-identified, alongside multi-center studies and peer-reviewed and published review articles. The identification of duplicate study sources was mostly through comparison of the selected literature to those from comparable publication years, even as literature sources with increasingly valid details were chosen and used. The literature search strategy entailed the use of various keywords that included gut microbiota, type 2 diabetes mellitus, host-microbiota interactions, dysbiosis, and gastrointestinal microbiome. As a result, the search strategy yielded 872 articles, with only 109 being included.

INCLUSION AND EXCLUSION CRITERIA

Following the removal of all duplicates, we selected the pertinent literature in three distinct stages. The initial stage entailed screening the literature's titles and abstracts, while the subsequent stage entailed excluding articles found to be irrelevant to this study. The final stage entailed carrying out a full-text exploration of the various selected literature to ascertain that only relevant studies were included. Thus, three independent reviewers were assigned to screen the articles, and potential disagreements and discrepancies during screening were mainly resolved through consensus and consultations.

For this comprehensive review, the inclusion criteria took in original studies, including crossover research design studies, prospective cohort studies, and randomized controlled trials, that satisfied the following set inclusion criteria: reputable journals' scientific publication of original research findings that are also peer-reviewed. Further, to be included, the studies had to be published in English, with publishing years ranging between 2010 and 2024. Furthermore, to be included, the study must focus on gut microbiota and its role in Type 2 Diabetes Mellitus development.

On the other hand, the exclusion criteria included editorials, sponsored clinical trials, and narrative reviews. Additionally, systematic reviews and meta-analyses that did not utilize standard tools in evaluating the function of gut microbiota in type 2 diabetes mellitus development were excluded from this study. Still, studies were excluded in instances where the assessment of gut microbiota's role in Type 2 Diabetes mellitus was conducted without any correlation to target populations. The exclusion criteria also included studies published in languages other than English, dissertations, and non-peer-reviewed journal-published studies. Articles authored by non-academics, opinion pieces, secondary studies, and other non-primary study research were excluded. Lastly, inaccessible articles whose methods and materials needed to be more adequately sound were excluded. Therefore, the evaluation and screening of the articles led to the exclusion of 763 articles.

For this comprehensive review, the following relevant data was extracted from the included studies: (i) The general attributes of the study, including the names of authors, year of study and publication, and the sampling method used; (ii) the study population attributes that included study sample size, age and gender of the study participants, and follow-up; (iii) interventions utilized and their durations, and (iv) and the key study findings.

QUALITY ASSESSMENT

The studies included in this review were appraised using AXIS, which refers to a critical appraisal tool with 20 items for cross-sectional studies [30]. Each included study was evaluated by three independent reviewers, and potential disagreements were

resolved using group discussions and consensus. Each study was scored 1 (yes) or 0 (no), as well as "don't know" for the inapplicable items, respectively. Generally, the included studies were of moderate to high quality, with only twenty-eight studies being moderate quality and the rest being high quality.

DATA EXTRACTION

The authors utilized a data extraction form to extract data from the included studies efficiently. Thus, data regarding the various attributes of the studies, such as the authors' names, year of publication, size of the samples used, research design, and findings, were collected from each study. The three reviewers independently extracted such data, and any potential disagreement was resolved through consensus and discussions among the reviewers.

OVERVIEW OF GUT MICROBIOTA AND RELATION TO TYPE 2 DIABETES

Numerous studies have indicated that the gut microbiota of individuals with T2D exhibits dysregulation. Evidence consistently suggests that species such as Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia, and Roseburia are negatively associated with T2D, indicating their potential role beyond serving as biomarkers for the condition. Conversely, Ruminococcus, Fusobacterium, and Blautia positively correlate with T2D[19,20]. These include Bacteroides caccae, Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum, Eggerthella lenta, and E. coli, which are enriched in T2D patients and are known opportunistic pathogens. On the other hand, butyrate-producing bacteria such as Clostridiales sp. SS3/4, E. rectale, Faecalibacterium prausnitzii, Roseburia intestinalis, and Roseburia inulinivorans have been observed in higher proportions in healthy control groups. Additionally, A. muciniphila and Desulfovibrio sp., which are mucin-degrading and sulfate-reducing species, are also associated with T2D. Interestingly, while some studies show that obese individuals with less severe metabolic syndrome have upregulated abundances of A. muciniphila, other studies suggest that this bacterium is enriched in T2D patients[19,20].

In detail, Bifidobacterium, a group of microorganisms, may benefit from protecting against T2D. Most clinical investigations have consistently demonstrated a negative association between this group of microorganisms and T2D[21–25], with only one study reporting contradictory findings[26]. Additionally, specific subspecies of Bifidobacterium, such as B. dentium, B. pseudocatenulatum, B. bifidum, B. adolescentis, and B. longum, have been observed to be downregulated in diabetic patients treated with metformin or individuals who have undergone gastric surgery[27,28]. Animal studies have also yielded similar conclusions, as administering these microorganisms as probiotics to treat T2D has significantly improved glucose metabolism[29,30]. Moreover, the decline in Bifidobacterium levels has been associated with cognitive dysfunction in individuals with diabetes, a condition that encompasses a range of possible complications for T2D[31].

The efficacy of Lactobacillus in improving glucose metabolism in T2D patients has yielded inconsistent results in clinical trials. While some studies suggest a positive impact, others have reported no significant effect[20]. This variability may be attributed to Lactobacilli's species-specific or strain-specific nature, indicating that they may be more effective when combined in a probiotic mixture rather than administered individually.

For instance, Asemi et al.[32] demonstrated that a probiotic supplement containing Lactobacillus increased calcium and iron levels and reduced bilirubin in T2D patients who typically exhibit mineral changes. Similarly, Ejtahed et al.[33] reported that a probiotic yogurt dietary intervention containing Lactobacillus acidophilus and bifidobacterium lactis improved various metabolic parameters such as decreased fasting blood glucose and HBA1c, increased actions of glutathione peroxidase, increased erythrocyte superoxide dismutase and antioxidant status of 64 diabetic patients in a randomized, double-masked

controlled clinical trial. Similarly, studies such as the one conducted by Nerstedt et al.[34] found that Lactobacillus evoked a complex response in the gut of mice; this is highlighted by the differential regulation of numerous genes involved in essential physiological functions, including regulation of energy homeostasis, immune response, and host defense mechanisms.

In clinical scenarios, Bacteroides have demonstrated a favorable impact on glucose metabolism in individuals with T2D, as evidenced by various studies[22, 35, 36]. Animal studies have indicated that administering Bacteroides acidifaciens and uniformis can enhance glucose intolerance and insulin resistance in diabetic mice. Additionally, human studies have revealed that Bacteroides intestinalis, Bacteroides 20-3, and Bacteroides vulgatus were reduced in T2D patients. At the same time, Bacteroides stercoris were enriched post-sleeve gastrectomy (S.G.) operation in T2D patients experiencing diabetes remission. He et al.[37] also found that out of 23 Operational Taxonomic Units (OTUs) of Bacteroides identified in their study, 21 were negatively linked to T2D. Vrieze et al.[38] conducted fecal microbiota transplants from lean donors to insulin-resistant patients with metabolic syndrome, resulting in improved insulin sensitivity and increased levels of butyrate-producing bacteria, including Bacteroides. These investigations suggest that specific Bacteroides species could impact insulin sensitivity and glucose metabolism in humans and experimental models. However, it is crucial to emphasize that further research is necessary to understand the clinical implications of these findings fully.

Compelling evidence suggests that the bacterium Akkermansia muciniphila could hold significant promise in treating T2D. In individuals with refractory diabetes, Akkermansia muciniphila has been found to have a negative correlation with Hemoglobin A1c levels, indicating its potential beneficial impact on glucose homeostasis[39]. Furthermore, in patients with T2D, there is a significant increase in opportunistic pathogens, sulfate-reducing microbial functions, oxidative stress resistance, and a decrease in beneficial butyrate-producing bacteria, including A. muciniphila[40]. Studies on the influence of antidiabetic drugs on the microbiota have shown that biguanides like metformin can promote the growth of A. muciniphila, Escherichia, Bifidobacterium adolescentis, Lactobacillus, and Butyrivibrio, among others[41, 42]. Similarly, GLP-1 receptor agonists like liraglutide have been found to stimulate the proliferation of Bacteroides, A. muciniphila[43]. Additionally, SGLT2 inhibitors such as dapagliflozin have demonstrated the ability to increase the abundance of Akkermansia muciniphila and enterococcus in the gut microbiota[43].

MOLECULAR MECHANISMS

Due to the vast array of impacts that gut microbiota has on various metabolic processes, including glucose and lipids metabolism, inflammation, and intestinal membrane permeability, numerous molecular mechanisms have been developed to establish the connection between gut microbiota effects and T2D.

GLUCOSE METABOLISM DYSFUNCTION

It has been suggested that dysfunctions in metabolic organs such as the adipose tissue, gut, liver, pancreas, kidney, or muscles may arise from disruptions in glucose homeostasis and insulin resistance within these tissues, which are associated with gut dysbiosis[44]. An imbalance in the gut flora could result in inadequate glucose metabolism. Research has demonstrated that using B. Lactis as a probiotic increased the production of glycogen molecules and reduced gene expression related to hepatic gluconeogenesis[44, 45]. These improvements were accompanied by an enhanced availability of the glucose transporter-4 and an upregulation of the insulin-induced glycemic pathway. The glucose transporter 4 (GLUT-4) is a chaperone protein for the functional transport of glucose through muscle and adipose tissue[46, 47]. It plays an essential role in blood glucose regulation by facilitating glucose uptake into cells in response

to insulin. When insulin is delivered into the bloodstream in response to high blood glucose levels, GLUT-4 is translocated to the cell membrane, which can transport glucose into the cell, lowering the blood glucose level. The presence of Lactobacillus species has been found to correlate positively with an upregulation of GLUT-4[44, 45]. This upregulation, in turn, leads to a reduction in the activity of flavin monooxygenase 3 (Fmo3), an enzyme involved in glucose metabolism[48, 49]. Fmo3 is positively associated with the development of hyperglycemia and hyperlipidemia disorders[50].

The metabolic activity of Lactobacillus species has been found to have significant beneficial effects on the insulin glycemic pathway. This can be attributed to the upregulation of kinase enzymes such as phosphatidylinositol-3-kinase (PI3K), AMP-activated protein kinase (AMPK), RAC-beta serine/threonine-protein kinase (Akt2), and insulin receptor substrate 2 (IRS2), as well as hepatic glucogenesis[51–53]. These processes collectively enhance insulin sensitivity in metabolic organs, the primary dysfunction underlying T2D.

Additionally, the G.M., particularly Lactobacillus and Bifidobacterium, play a crucial role in the proper glucose metabolism. They actively contribute by impeding the breakdown of complex sugars by suppressing glucosidase enzymes[54, 55]. This mechanism effectively prevents the occurrence of postprandial hyperglycemia. Furthermore, the metabolic actions of the G.M. include the secretion of glucagon-like peptide-1 (GLP-1), a peptide hormone synthesized in entero-endocrine l-cells in response to food consumption[56–58]. GLP-1 is critical in regulating blood glucose levels by promoting pancreatic insulin release with glucagon inhibition, another hormone that elevates glycemic levels. These findings highlight the fascinating and complex interactions between gut microbiota and glucose metabolism.

INTESTINAL MEMBRANE PERMEABILITY

The intestinal membrane functions as a physical barrier, effectively compartmentalizing the inner contents of the intestine from the bloodstream. Any abnormalities in the internal structure of this membrane, which is maintained by tight junction proteins like Tjp-1 and occludin, can result in the transportation of harmful metabolic proteins into the bloodstream, a condition known as endotoxemia[59,60]. Research has reported that individuals with T2D are more susceptible to the disruption of the intestinal membrane with increased intestinal permeability and the subsequent risk of endotoxemia [61, 63, 64]. Interestingly, certain species of bacteria, such as Bacteroides and Akkermansia muciniphila, have been observed to enhance the expression of genes responsible for producing structural proteins in the intestinal membrane[63, 64]. Other bacteria, such as Faecalibacterium, and butyrate-producing bacteria, such as Roseburia, can potentially reduce gut permeability[20]. This, in turn, reduces the likelihood of endotoxemia.

It is fascinating how specific gut microbiota, such as Akkermansia muciniphila, Lactobacillus, and Bacteroides species, can directly influence our metabolic health. They stimulate the synthesis of diacylglycerol lipases in adipose tissues, leading to a higher rate of fatty acid oxidation [66, 67]. The activation of the TGR5-PPAR-α pathway, a crucial metabolic pathway involved in various physiological processes, including energy metabolism, glucose homeostasis, and inflammation, has been associated with the specific butyrate production by these gut microbiota[60-65, 68–70]. This butyrate, in turn, promotes the metabolic pathway and enhances fatty acid oxidation.

INFLAMMATION REGULATION

T2D is a state of low-grade inflammation characterized by an imbalance in inflammation regulation, whereby pro-inflammatory metabolic proteins, such as specific cytokines interferon γ (IFN-γ) and interleukin (IL)-2 or chemokines, are increased[71, 72]. These cytokines are crucial in stimulating macrophages and inducing adipose tissue inflammation, obesity, and glucose intolerance. Moreover, Interferon γ has been found

to lead to a time-dependent decrease in insulin-stimulated glucose uptake, hinting at a possible link to insulin resistance[71]. Certain gut microorganisms and their byproducts, such as lipopolysaccharides(a component of the outer membrane of gram-negative bacteria), can also contribute to low-grade inflammation and endotoxemia[60]. On the other hand, IL-4, IL-5, IL-10, and IL-13 possess anti-inflammatory properties and participate in antibody production, eosinophil activation, and inhibition of macrophage functions, adding another layer of complexity to the gut microbiota's role in metabolic disorders[71].

Interestingly, certain types of gut bacteria, namely Akkermansia muciniphila, Roseburia intestinalis, Bacteroides fragilis, and Lactobacillus subspecies, have been found to stimulate the production of anti-inflammatory cytokines like IL-10 or IL-22, thereby improving insulin sensitivity and glucose metabolism[20, 49, 51, 73]. Some studies discovered that monocolonization of mice with Bacteroides fragilis reduced colonic inflammation and damage, which could be advantageous in preserving intestinal homeostasis, promoting host immunologic development, and preventing infectious colitis[73]. Conversely, these same bacterial species have also reduced the levels of pro-inflammatory cytokines. One possible mechanism for this downregulation is the production of butyrate by the gut microbiota. Studies have demonstrated that butyrate can inhibit the pro-inflammatory activity of nuclear factor-kappa B proteins[68, 74, 75].

I. Therapeutic strategies for Type 2 diabetes targeting the gut microbiot

At present, most clinical interventions aimed at preventing or managing individuals with T2D primarily involve the use of antidiabetic drugs. These medications target glucose metabolism and insulin at a systemic level, producing advantageous and adverse outcomes. Due to the intricate nature of glucose metabolism and the numerous interactions involved, implementing these strategies can be challenging. Moreover, antidiabetic drugs have the potential to influence the composition of the gut microbiota, resulting in conflicting impacts on glucose control and insulin sensitivity. In light of these considerations, novel strategies concentrating on the gut microbiota show potential for the future.

FECAL MICROBIOTA TRANSPLANTATION (FMT)

Fecal Microbiota Transplantation (FMT) involves transferring a stool sample from a screened donor with a healthy gut microbiome to a recipient with a disease characterized by an abnormal microbiota of the GIT to restore a balanced and thriving gut ecosystem[76,77]. The transfer is made by administering fresh stool diluted with saline solution in a liquid form or a frozen or freeze-dried product via gastroscopy, colonoscopy, nasogastric tube, retention enema, or capsules[81]. FMT has been approved in the USA (2013) and Canada (2015) for treating recurrent and refractory Clostridioides difficile infection (CDI) outside clinical trials[76,81]. Multiple studies demonstrate success rates in CDI cases with two or more recurrences ranging from 44% to 96% (due to variability in study design). This surpasses the success rate of vancomycin pulse and taper treatment, which typically hovers around 60%[81]. Feng et al. Also highlighted in their meta-analysis that FMT could lead to clinical remission in patients with ulcerative colitis. Additionally, they found that oral FMT demonstrated superior efficacy compared to other delivery[77]. Similarly, Ren R. et al. observed significant improvement and long-term remission in thirty-one patients with active ulcerative colitis following low-intensity single donor FMT[84].

In recent times, scientific investigations have delved into the potential of FMT as a therapeutic approach for managing T2D. Several research studies have documented the positive effects of FMT, demonstrating its ability to enhance insulin sensitivity and reduce blood glucose levels in patients diagnosed with T2D. The precise mechanism through which FMT enhances T2D remains incompletely comprehended; however, it is believed to be associated with the reinstatement

of a healthy gut microbiome, as it plays a pivotal role in glucose metabolism[76, 77]. FMT has demonstrated the ability to facilitate the transformation of the gut microbiome in T2D patients to resemble that of an average population, which could contribute to the amelioration of insulin resistance and regulation of blood glucose levels[78, 80, 83]. Notable findings emerged from a ninety-day controlled open-label trial conducted by Su et al.[86], which examined the effects of a specialized diet comprising prebiotics, probiotics, whole grains, and FMT in individuals with T2D. The study revealed a reduction in blood glucose levels, blood pressure, blood lipid levels, and BMI and an increase in beneficial bacteria in the gut. Bifidobacterium and Prevotella are among the bacteria utilized for FMT in T2D treatment [84, 85]. These bacteria have been observed to increase in abundance in T2D patients who have undergone FMT. Furthermore, a decline in Sulfate-reducing bacteria (SRB), Bilophila, and Desulfovibrio has been noted in T2D patients following FMT[86, 87].

A 24-week study using sixty-one patients with T2D and obesity, utilizing a double-blind, randomized controlled design, demonstrated that FMT with lifestyle interventions resulted in notable changes in the recipient's microbiota, such as an increase in Bifidobacterium and Lactobacillus compared to FMT alone, improvement in lipid profile, and liver stiffness[78]. In a recent investigation conducted by Ding et al.[79], seventeen patients who underwent FMT experienced reconstitution of the gut microbiome, resulting in significant reductions in HBA1c, uric acid, and blood glucose levels, as well as an increase in c-peptide levels. Of note is the variation in response to FMT among patients, with the responders exhibiting higher levels of the family *Rikenellaceae* and the genus *Anaerotruncus* (family *Ruminococcaceae*) in their pretreated fecal sample compared to the non-responders. Wu et al.[80] conducted a similar study and investigated the restoration of intestinal microecology in thirty-one patients with T2D through FMT. The findings revealed that FMT alone and FMT combined with metformin significantly improved insulin resistance, HBA1c, BMI, fasting plasma glucose, and post-prandial blood glucose levels by modulating gut microbiota diversity and specific species within four weeks of intervention. Another investigation by Tanase et al.[82] also highlighted the role of gut dysbiosis in developing diabetic micro and macrovascular complications.

Selecting donors for FMT in treating type 2 diabetes involves a systematic screening procedure[88, 89]. This procedure primarily focuses on identifying infectious disease-related pathogens and fecal-associated pathogens, conducting glucose tolerance tests, and measuring islet function. This selection process aims to identify donors who possess a diverse and abundant microbiota that can effectively enhance the transplantation process. Donors who exhibit relatively abundant dysregulated strains in patients are given preferential consideration. The notion of "super fecal donors" has been proposed, which refers to donors with vibrant microbiota diversity that can significantly improve the outcomes of transplantation[90]. Furthermore, depending on the donor and recipient's microbiota status, early intervention with antibiotics or dietary modifications may be employed to enhance clinical outcomes.

Despite the potential benefits of fecal microbiota transplantation in enhancing glucose metabolism and insulin sensitivity among individuals with type 2 diabetes, it is vital to acknowledge the existing drawbacks and constraints associated with this treatment approach[76, 77]. Safety concerns regarding FMT exist, including the potential transmission of infectious diseases or adverse effects such as bacteremia, diarrhea, or abdominal discomfort, as well as procedural risks[76, 77]. The lack of standardization in FMT protocols, encompassing donor selection, preparation, and administration methods, could impact the effectiveness and safety of the treatment. Additionally, the understanding of the long-term safety and effectiveness of FMT in managing type 2 diabetes remains limited, necessitating further investigation to assess its prolonged influence on patient health[76, 77]. The

effectiveness of FMT can vary significantly from person to person due to factors such as genetics, lifestyle, and the initial composition of microbiota, all of which can impact the treatment results. The utilization of FMT also raises ethical considerations about donor confidentiality, informed consent acquisition, and potential psychological repercussions on individuals[76, 77].

Moreover, FMT's accessibility is limited, with less than 3% of potential donors successfully passing the screening process at a significant U.S. stool bank, and its high cost may restrict its widespread adoption in clinical practice[81]. Furthermore, the complete understanding of the intricate relationship between the gut microbiota, metabolic control, and immune response in type 2 diabetes remains elusive, necessitating urgent and thorough investigation to unravel the underlying mechanisms of FMT. According to surveys and research, additional barriers largely stem from issues related to evidence, public perception, manufacturing practices, patients' health status and discomfort, financial constraints, infrastructure limitations, treatment modalities, and legal or social considerations.

PREBIOTIC AND PROBIOTIC SUPPLEMENTATION

Prebiotic and probiotic supplementation have demonstrated potential in the management of T2D. *Probiotics* are live microbes that exert health benefits when administered appropriately. A *prebiotic* is a food substance that stimulates the activity or growth of some probiotic bacteria in the colon, particularly lactobacilli and bifidobacteria[94]. Specific strains of probiotics, such as Bifidobacterium animalis subsp. lactis 420, Lactobacillus acidophilus, and Lactobacillus casei have been found to enhance glucose control, decrease inflammation, and provide protection against oxidative stress in patients with T2D[91, 92].

A study by Stenman L.*K. et al.*[91] examined the impact of probiotic supplementation with Bifidobacterium animalis ssp. lactis 420 on reduction of high-fat weight gain, glucose tolerance, inflammation, and gut microbiota in obesity and diabetic animal models. The study's findings revealed that probiotic supplementation significantly reduced body mass, glucose intolerance, liver inflammation, and lipopolysaccharide levels in the plasma compared to the placebo group. Research conducted by Uusitupa et al.[92] discovered that Bifidobacterium animalis subsp. lactic 420 has the potential to rebalance the gut microbiome composition by increasing the prevalence of microbes such as Akkermansia muciniphila and reverse inflammatory response in patients with T2D. In a systematic review and meta-analysis by *Yao et al.*[93], the effects of probiotic supplementation on insulin sensitivity and glycemic control in T2D patients were evaluated. This review encompassed 12 randomized controlled trials involving a total of 684 participants. The findings revealed that probiotics significantly lowered fasting insulin, plasma glucose, and HbA1c levels compared to control groups. Furthermore, probiotic supplementation was linked to improvements in insulin sensitivity among individuals with T2D. Another randomized controlled trial by *Mahboobi et al.*[94] examined the effects of prebiotic and synbiotic supplementation on lipid control, glycemic control, and gut microbiome composition in individuals with T2D. *Synbiotics* are synergistic compounds that combine probiotics and prebiotics, promoting the host's metabolic health by stimulating selective growth and activating beneficial microorganisms[94]. The results indicated that prebiotic supplementation led to a significant reduction in HbA1c levels, fasting plasma glucose, lipids, and an improvement in insulin sensitivity compared to the placebo. Additionally, prebiotic supplementation was associated with alterations in the composition of gut microbes, including an increase in beneficial bacteria such as Bifidobacterium.

A study by *Toejing et al.*[95] examined the impact of probiotic supplementation on blood glucose control, inflammation, and gut microbiota in individuals diagnosed with T2D. The study involved a total of 50 participants who were assigned randomly to two groups: one group received *L. paracasei* HII01 (50 × 109 CFU/day),

while the other group received a placebo. The supplementation or placebo was administered for 12 weeks. The study's findings revealed that the probiotic supplementation significantly reduced fasting blood glucose and inflammation markers IL 6, hsCRP, LPS, and TNF-α compared to the placebo group. Furthermore, the probiotic supplementation induced changes in gut microbiota composition, characterized by increased beneficial bacteria and decreased pathogenic bacteria[95]. Moreover, Yadav et al.[96] revealed that a dietary intervention involving probiotic dahi improved glucose intolerance, hyperglycemia, hyperinsulinemia, dyslipidemia, and oxidative stress in a rat model with diabetes induced by high fructose consumption. Another study, which was randomized and placebo-controlled, conducted by Asemi et al.[32], demonstrated that an oral supplement containing multiple probiotics significantly decreased bilirubin levels, increased iron and calcium, and enhanced the oxidative status in T2D patients. Prebiotics, like polydextrose, have also been examined in conjunction with probiotics and antidiabetic medications. An investigation in diabetic mice demonstrated that the use of sitagliptin along with pre-and probiotics effectively decreased various T2D indicators like glycemic control and insulin tolerance[20, 97]. Comparable outcomes were noted in Zucker diabetic rats and streptozotocin-induced diabetic mice when prebiotics were paired with antidiabetic medications such as metformin and sitagliptin[20, 98].

The findings of these studies indicate that incorporating prebiotic and probiotic supplements could enhance glycemic control, reduce oxidative stress, and alleviate inflammation in individuals with T2D. Nevertheless, further investigation is necessary to ascertain the distinct attributes of gut microbiota responsible for varying reactions to antidiabetic medications and pinpoint the specific co-pre- and probiotics essential for optimizing medication response. Clinicians are advised to consider these discoveries when formulating treatment strategies for patients diagnosed with T2D.

Lack of consistent evidence, limited regulation, potential side effects, cost considerations, dependency concerns, and the lack of personalization are some challenges associated with using prebiotic and probiotic supplementation in managing T2D. More scientific evidence is needed to validate the efficacy of such supplementation consistently. However, specific research studies suggest possible advantages, while contrasting findings indicate limited impact on glycemic control and other diabetes-related parameters[99-102]. The supplement industry needs to have stringent regulations imposed on pharmaceuticals, resulting in possible inconsistencies in the quality and efficacy of prebiotic and probiotic products, posing challenges for healthcare professionals and individuals seeking safe and efficient products. Although generally considered safe, prebiotic and probiotic supplements have the potential to induce digestive complications like bloating, gas, and diarrhea in specific individuals, which may not be advantageous for those with diabetes who are already prone to gastrointestinal symptoms. Additionally, the cost of these supplements, mainly when consumed daily over long durations, can pose a challenge for those with restricted financial means[101]. Some individuals may develop a dependency on prebiotic and probiotic supplements as their primary approach to managing diabetes, potentially disregarding other crucial components of their treatment plan, including medication, diet, and exercise. Furthermore, prebiotic and probiotic supplements may not be universally appropriate due to the unique nature of each person's gut microbiome, which can result in varying responses to supplementation. With tailored advice from a healthcare professional, individuals may achieve the intended benefits of prebiotic and probiotic supplementation in managing their diabetes[99-102].

PERSONALIZED NUTRITION PLANS

Research is currently being conducted on customized dietary plans as a possible therapeutic approach for type 2 diabetes, in conjunction with

medications that target the microbiome. By modifying the structure and operation of the gut microbiome, dietary plans aimed at the microbiome have demonstrated potential in controlling T2D. These plans typically consist of a fiber-rich diet, including fruits, vegetables, whole grains, legumes, and supplements such as probiotics and prebiotics to promote the proliferation of beneficial gut bacteria. Several clinical investigations have yielded significant findings on the effectiveness of microbiome-focused dietary plans in treating T2D. For instance, Mao et al.[103] conducted a meta-analysis and systematic control study, revealing that soluble fiber products and fiber from natural foods substantially improved glycemic control and insulin sensitivity among individuals with T2D. Similarly, Xu et al.[104] found that a high-fiber diet reduced FBG, HBA1c, and total cholesterol and increased short-chain fatty acid-producing bacteria. Their study also highlighted the superiority of a tailored dietary regimen regarding G.M. variation, glucose metabolism, and inflammation reduction in T2D patients compared to a standard dietary approach.

Furthermore, a comprehensive systematic review and meta-analysis by Ajala et al.[105] evaluated the impact of microbiome-targeted diets, including low-carb, low-fat, and Mediterranean diets, on glycemic control in T2D. This study's findings are particularly noteworthy, indicating that microbiome-targeted diets could significantly enhance glycemic control and metabolic parameters in individuals with T2D.

II. Conclusion and perspectives

The correlation between gut microbiota and T2D is complex and constantly changing, with important implications for understanding the disease's pathophysiology and treatment. Various research studies have demonstrated that changes in the structure and operation of gut microbiota can impact the onset and progression of T2D, with imbalances often linked to metabolic issues and insulin resistance. While the exact mechanisms by which gut microbiota influence the development of type 2 diabetes are not yet fully understood, it is clear that the microbiome plays a pivotal role in regulating host metabolism, immune response, and inflammation. Excitingly, interventions that target gut microbiota, such as dietary adjustments, probiotics, and fecal microbiota transplantation, hold promise as potential therapeutic options for managing T2D. While significant progress has been made in understanding the interaction between gut microbiota and T2D, there is still much to learn. It is crucial to continue investigating the precise mechanisms and identify new therapeutic targets and strategies for manipulating the microbiome to improve metabolic health. By gaining a deeper perception of this intricate relationship, we can develop more effective and personalized interventions for individuals with T2D.

In potential therapeutic advancements, computational methods in genomic and proteomic analyses of individual T2D patients show promise in tailoring therapy to the individual level[106-109]. By thoroughly understanding the distinct gut microbiota of each patient, predictive tests could be carried out on bacterial cultures that replicate this microbiota, thereby minimizing side effects and optimizing treatment based on individual traits. With the ongoing progress of multi-omics and their smooth integration into diagnostic procedures, such advancements have the potential to positively influence and enrich the quality of life for individuals living with T2D.

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