INFLUENCE OF GUT MICROBIOTA IN DIABETES AND OBESITY: A REVIEW

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ABSTRACT Gut microbiota is essential for performing many important functions in the human body. Major functions include aiding the immune system against pathogenic bacteria, regulating metabolism, digestion, intestinal permeability and metabolite synthesis. Dysbiosis in the gut microbiome could have been observed in various diseases. Among the metabolic disorders, obesity and diabetes negatively impact health and overall Quality of Life globally. Recent microbiome studies have indicated a potential causal role of gut microbiota in metabolic disorders. Changes in the gut microbiome could reshape the intestinal barrier and modify the host's metabolic and signalling pathways. However, it remains unclear whether gut dysbiosis could be the leading cause of metabolic disorders such as diabetes and obesity. Studies conducted in humans have been inconclusive in establishing a relationship between particular taxonomic groups with metabolic disorders such as diabetes and obesity. This review is conducted to evaluate the contemporary evidence of the role of gut dysbiosis in diabetes and obesity.

KEYWORDS Dysbiosis, Diabetes, Obesity, Microbiome, Probiotics

Introduction

Gut microbiota constitutes a complex community of microorganisms in humans' and animals' digestive tracts. The symbiotic gut microbiota comprises about 1500 species distributed over 50 phyla [1]. Most microorganisms, including bacteria, viruses, and some eukaryotes, colonize the digestive tract immediately after birth [2]. Interindividual variations in the composition of gut microbiota (dysbiosis) and function are subjected to various factors, including host genetics, diet, age [3], mode of birth [4] and antibiotic exposure [5]. Changes in gut microbiome composition are observed in certain disease conditions. However, it remains unclear whether gut dysbiosis could be a leading cause of certain diseases. Obesity and diabetes remain two of the most prevalent non-communicable diseases globally. Increasing evidence suggests that perturbations in the gut microbiome led to metabolic and weight changes in the host. Animal [6,7] and human studies[8,9] have shown alterations in gut microbiota in the event of metabolic disorders. Therefore, this review article evaluates the contemporary evidence of the role of gut microbiome dysbiosis in metabolic disorders such as obesity and diabetes.

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2. Gut microbiome:

2.1 Gut microbiome in health:

The gut microbiome is essential for regulating and performing important bodily functions. They produce anti-microbial substances that enhance the host's immune system against invading pathogens [10]. Other essential roles of the gut microbiome include maintaining digestion and metabolism [11]. They control the proliferation and differentiation of epithelial cells [12], influence the gut-brain axis [13] and modify insulin secretion and resistance [14,15]. Synthesis of thiamine, biotin, riboflavin, cobalamin, nicotine, and vitamins B and K for the host is facilitated

by gut microbiota [16]. With diverse protective roles, the gut microbiota is vital in maintaining normal gut physiology and health. Although not an exhaustive list, Table 1 lists a few gut microbes and their benefits for the host.

2.2 Gut microbiome in disease:

Alternations in gut microbiota composition have been associated with host health disturbances. Some of the consequences include allergy [24], inflammatory bowel diseases (IBD), autoimmune diseases, cardiovascular disease, obesity and diabetes [25]: table 2 lists a few gut microbes and the disease conditions associated with their shift in volume.

3. Gut microbiota and metabolic disorders:

3.1 Diabetes and obesity:

According to the World Health Organisation (WHO), more than 1.9 billion adults are overweight, with over 650 million obese as of 2016 [33]. The increasing consumption of high-calorie foods and the switch from leisure-time physical activities to sedentary activities has ultimately resulted in a positive energy balance (where energy intake exceeds energy expenditure), and these have become the main risk factors for obesity and obesity-related diseases [34]. In positive energy balance, the adipose tissue exceeds its ability to store all the excess energy as triglycerides. This causes the lipids to spill out into circulation. This excess supply of lipids to non-adipose tissues causes the impaired capacity to increase fat oxidation. This results in ectopic fat storage. Excessive fat accumulation in adipocytes triggers an increase in the secretion of pro-inflammatory adipokines. This can lead to the development of insulin resistance, associated with Type 2 Diabetes Mellitus (T2DM) development and Non-Alcoholic Fatty Liver Disease (NAFLD) [35]. An increase in obesity also reflects the higher prevalence of T2DM and, thus, various diabetic complications. Dietary treatment and lifestyle changes are essential for the management of both diabetes and obesity; however ineffective in most cases. The use of different drugs to treat obesity that contribute to improving T2DM control and promoting weight loss has recently been approved [36]. Similarly, medications for the treatment of T2DM, such as Selective sodium-glucose cotransporter 2 inhibitors, have been shown to improve not only diabetes but also reduce obesity [37]. Hence, obesity and diabetes influence each other's development and progression.

3.2 Autonomic neuropathy and gut:

Autonomic neuropathy is one of the major microvascular complications of diabetes. It causes changes in the neuronal structure and function [38]. 75% of diabetic patients suffer from gastrointestinal autonomic neuropathy (GAN) [39]. Gastrointestinal autonomic neuropathy affects the innervation of the autonomic nervous system of the gastrointestinal system in diabetes [40]. T2DM pathophysiology with GAN (T2DM_GAN) is multifactorial and complex. The major neurological system GAN affects are the enteric nervous system and vagal and splanchnic nerves [40]. Except for knowledge on clinical guidance on T2DM_GAN, knowledge gaps on underlying pathogenesis and mechanism remain. Significant changes in the composition of gut microbiota among T2DM patients are believed to contribute to the pathogenesis of T2DM [41]. A recent study noted exacerbation of dysbiosis in gut microbiota composition among adult T2DM patients. Further, the occurrence of T2DM was found to be associated with phyla Fusobacteria and class Gammaproteobacteria [42]. The above strengthens the speculation that gut dysbiosis is involved in metabolic disorders, especially diabetes.

3.3 Gut Microbiome and Diabetes:

With most of the gut microbiota being symbiotic with intestinal epithelial cells, it plays a predominant role in the metabolism of nutrients upon dietary intake, metabolism of drugs and xenobiotics, and structural and functional maintenance of the gut barrier, among others [43]. With research into the role of the gut in metabolic disorders increasing over the decade, various theories on the role of the gut microbiome in the pathophysiology of metabolic disorders have been developed.

3.3.1 Short-chain fatty acid theory:

Short-chain fatty acids (SCFAs) are organic carboxylic acids with 1-6 carbon atoms. SCFAs seem to have direct control over the islet-β cells, promote hepatic gluconeogenesis and enhance absorption, and transfer monosaccharide to hepatic portal vein circulation providing close to 30% of the energy essential for liver metabolism [44]. SCFAs in the human colon contribute to 90% - 95% of SCFAs in the human body [45]. Recent studies have suggested a close association between SCFAs and T2DM. Disturbances in the biosynthesis of short-chain fatty acids cause many pathological consequences for the host [46]. With the evidence of abnormal SCFAs-producing bacteria in people with diabetes, it is speculated that the abnormal generation of SCFAs contributes to the pathophysiology of T2DM.

3.3.2 Bile acid theory:

Bile acid, a metabolic product of liver cholesterol degradation, is essential to bile. The essential functions of bile acid include all functions, from absorption to the distribution of fat and fat-soluble vitamins. In addition to this, it acts as a signal molecule for regulating energy metabolism and suppresses excess intestinal bacterial proliferation. Further, it was found that intestinal flora was involved in vivo bile acid transformation along with its hepatic circulation for effective hydrolysis of foreign substances. Hence, in the event of disorder in the intestinal flora, it is believed to contribute to lesser production of secondary bile acids. This could cause disorders of glucose metabolism and the occurrence of T2DM [47].

3.3.3 Endotoxin theory:

Endotoxin, a lipopolysaccharide (LPS) component, constitutes Gram-negative bacteria's outermost cell wall layer. Factors giving rise to intestinal flora disorders, such as a high-fat diet, also cause a drop in the proportion of Bifidobacterium and Lactobacillus. This leads to the rise in Gram-negative bacteria, further leading to intestinal wall permeability and shifts in the intestinal flora. LPS forms a complex with CD14, a glucose phosphate isomerase-anchored protein recognized by toll-like receptor 4 (TLR-4), acting on skeletal muscle cells and adipocytes. This promotes inflammation, consequently, the development of insulin resistance through TLRs and Mitogen-Activated Protein Kinase) signalling pathways [47]. The longer duration of such inflammation-induced insulin resistance is believed to generate T2DM.

Table 1 Gut microbiome organism and its associated benefits

Reference	Micro-organism	Function
Metabolic functions		
Cantarel, et al., 2012 [17]	*Bacteroides thetaiotaomicron*	Carbohydrate metabolism
Magiwa et al., 2012 [18]	*Oxalobacter formigens*	Suppression of Oxalate synthesis
Dietary polyphenol activation		
Miladinovic et al., 2014 [19]	*Lactobacillus plantarum, L. casei, L. acidophilus, Bifidobacterium longum*	Conversion of dietary anthocyanidins into the active form
Immunomodulatory functions		
Gao et al., 2015 [20]	*L. reuteri ATCC PTA6495*	Reduction in IL-1b, IL-6 Activation histamine H2-receptor
Dogi et al., 2016 [21]	*L. rhamnosus* RC007	Elevation of IL-10/TNF-αratio
Mi et al., 2017 [22]	*BB. Infantis*	Elevation of IL-2, IL-12, and IFN-γ
Huang et al., 2019 [23]	*L. plantarum* C88	Reduction in IL-1b, IL-6, IL-8, TNF-α

IL – Interleukin; IFN-γ – Interferon-gamma, TNF-α – Tumour Necrosis Factor-alpha

Table 2 Gut microbiome organism and the associated diseases

Reference	Micro-organism	Disease involved
Zybailov et al., 2019 [26]	*The abundance of Ruminococcus bromii*	Chronic Kidney disease
Zhu et al., 2013 [27]	Increase in Bacteroides spp. and decrease in firmicutes spp.	NAFLD
Loomba et al., 2017 [28]	Abundance of Escherichia coli, and Bacteroides vulgatus	Advanced fibrosis in stage, NAFLD 3-4
Roiger et al., 2017 [29]	Increase in firmicutes spp. and decrease in Bacteroides spp.	Rheumatoid arthritis
Jeffery et al., 2011 [30]	Increase in *Clostridium spp., Ruminococcus spp.* and a decrease in *Ruminococcus albus, Bacteroides fragilis, B. vulgates* and *R. callidus*	Inflammatory Bowel Disease
O'Connor et al.,2018 [31]	Reduction in *Staphylococcus aureus, Faecalibacterium prausnitzii* and *Clostridium spp.*, and higher abundance of *Bifidobacterium adolescentis*	Allergic reactions
Pistallato et al., 2016 [32]	Increase in *Bacteroidetes* and *Firmicutes*. Reduction in *Akkermansia* and *Allobaculum* genera.	Alzheimer's disease

NAFLD – Non-Alcoholic Fatty Liver Disease; spp. - species

4. Changes in the Gut Microbiome in Obesity:

Dysbiosis in the gut associated with obesity is evident as early as childhood. A study conducted to determine if early gut microbiota composition could provide insight into weight gain in early childhood showed an increase in Staphylococcus aureus among children becoming overweight and an increase in Bifidobacterium among children maintaining their weight [48]. A higher Firmicutes-to-Bacteroidetes ratio was also correlated to obesity among children [49,50]. Research has indicated gut dysbiosis in obesity among adolescents as well. In a study conducted on obese adolescents, an abundance of Bacteroides fragilis, Lactobacillus spp. and a significant reduction in Bifidobacterium longum, Clostridium coccoides and Bifidobacterium adolescentis was noted. A positive correlation was observed between weight loss, Bacteroides fragilis, and Clostridium leptum. A negative correlation was observed between Clostridium coccoides, Escherichia coli, Lactobacillus and Bifidobacterium [51]. Such aberrations in gut microbiota composition in childhood could provide prognostic, preventive and therapeutic value for weight management in adulthood. In a study conducted on obese Japanese adult patients, obese individuals had a higher Firmicutes to Bacteroidetes ratio. Furthermore, a positive correlation was observed between the following microbes Blautia hydrogenotorophica, Eubacterium ventriosum, Coprococcus catus, Ruminococcus obeum, Ruminococcus bromii, and obesity was observed [52].

In a study to determine the gut dysbiosis in weight gain, an increase in Lactobacillus reuteri and Lactobacillus E. coli were noted among obese individuals, Lactobacillus paracasei & Lactobacillus plantarum were associated with individuals with normal weight. The study also found an association between the population of B. animalis with individuals who were normal weight, while L. reuteri was associated with obesity [53]. In a study on differences in the intestinal microbiota of overweight women with or without metabolic disorders, an increase in the amount of Eubacterium rectale-Clostridium coccoides that belong to Firmicutes was noted among overweight women with metabolic disorders. A Spike in the population of E. rectale and C. coccoides was positively correlated with obesity-related parameters such as BMI, body weight, serum triglycerides and visceral fat area [54]

Treatment-induced gut microbiome changes also provide circumstantial evidence for the involvement of gut dysbiosis in obesity. A decrease in Firmicutes and an increase in Bacteroidetes was observed after Rouxen-Y gastric bypass [55]. One of the surgical interventions for obesity is Laparoscopic sleeve gastrectomy (LSG). A study in patients who underwent LSG and followed a very low-calorie diet indicated a shift from obesity-associated gut microbiome to lean gut microbiome phenotype, further strengthening the possible involvement of microbial components in obesity [56]. In addition, firmicutes-to-Bacteroidetes ratio alterations have been observed following diet therapy. The pieces of evidence above point to a possible involvement of microbial components in obesity.

5. Changes in Gut microbiome condition in patients with type-1 diabetes:

Studies on the role of the microbiota in human Type 1 Diabetes Mellitus (T1DM) patients have been conducted at various stages of the metabolic disorder, from patients with a genetic predisposition to developing T1DM to those clinically diagnosed with T1DM[57-59]. Large-scale studies on the preclinical stage of T1DM (indicated by the appearance of at least one T1DM-specific autoantibody) can provide insight into the contribution of the gut microbiome in T1DM. Studies conducted in children provide evidence for gut microbiome changes preceding the clinical development of T1DM [57-61]. Although the exact mechanisms of gut microbiome change contributing to T1DM pathogenesis are unknown, alterations in the intestinal mucosal permeability seem to be hypothesized to contribute to T1DM [62,63] majorly. A reduction in the gut microbiome has been observed among children with T1DM.

Additionally, microbial diversity reduction has been observed in the presence of at least two positive auto-antibodies specific to T1DM and initially after seroconversion but before T1DM onset among children [57]. As for microbiota composition, alterations in the Bacteriodetes to Firmicutes ratio have been observed, with an abundance of gram-negative Bacteroides and thinning gram-positive firmicutes population [64]. Finally, metagenomic studies recently correlated the alternations in gut microbiome with seroconversion risks in T1DM.

Previously, Bacteroides were identified to be associated with increased intestinal permeability and inflammation of the gastrointestinal system. Among children genetically predisposed to T1DM, Bacteroides dorei peaked at 7.6 months, preceding the first appearance of anti-islet autoantibodies. This suggests the prognostic value of gut microbiome dysbiosis in detecting T1DM development in children with genetic predisposition [65]. Among children at risk of developing T1DM, an increase in intestinal permeability was noted, which was also correlated with microbiota alterations [66,67]. Firmicutes phylum has been identified to produce protective SCFAs, suggesting that firmicutes reduction could be deleterious as it leads to diminishing butyrate production. The TEDDY study to associate gut microbial dysbiosis with T1DM indicated no taxonomic differences in the gut microbiome were noted among children who seroconverted or had clinical T1DM [68]. Although the TEDDY study indicated no taxonomic differences, the metagenomic analysis indicated a significant decrease in active genes involved in SCFA production [68].

Although the Bacteroids population increased, reductions in Prevotella species were observed in T1DM. Prevotella species have been associated with protective functions in the gut, and this adds to evidence that dysbiosis leading to an increase in harmful gut microbiota could lead to T1DM development. Metaproteomic analysis in new-onset T1DM patients has revealed depletion in specific microbial taxa involved in protein productions for functions such as microvilli adhesion and maintenance of mucosal barrier [60]. Recently, a study has shown the involvement of the Human Leukocyte Antigen (HLA) in modifying the composition of the human gut microbiome, suggesting that T1DM susceptibility influences the shape of the microbiome [59]. A Plethora of studies has provided evidence for microbiome changes among people with T1DM susceptibility.

While there is enough evidence to associate T1DM with gut microbial alterations, it is very challenging to establish a causal relationship between T1DM in humans and gut microbiome alterations. The major challenge is the complexity posed by microbiota and immune system cross-talk. The gut microbiota interacts with the immune system and is important in triggering seroconversion in T1DM patients [63,68,69]. Confounding factors include diet, geographical locations and lifestyle, which can also contribute to gut microbiome dysbiosis [70,71]. While

evidence suggests associations between gut microbiota in the development of human T1DM, no placebo-controlled trials indicate stable long-term changes in gut microbiome with T1DM. Only an association between dysbiosis and T1DM is suggested, with human studies showing inconsistencies. Multi-omic approaches conducted in larger cohorts of patients and intervention studies can provide more insight into associating gut dysbiosis and T1DM and pave the way for the effective treatment of T1DM.

6. Changes in Gut microbiome condition in patients with type-2 diabetes:

The association between T2DM and gut microbiome has been studied. A study conducted to determine if the gut microbiome alterations were consequences of a particular glycaemic status revealed that the intestinal flora composition was altered among patients with impaired glucose tolerance, untreated diabetes and glucose tolerance groups. No correlation between impaired fasting blood glucose group patients and gut dysbiosis was observed [72]. Butyrate, metabolites of intestinal bacteria, can affect insulin sensitivity. A decrease in butyrate has been attributed to diabetes [73]. Improving the gut microbial synthetic ability of butyrate or natural increases in butyrate-producing bacteria could effectively treat or prevent diabetes. A large cohort human study with 952 volunteers analysed the human genome and intestinal metagenome, indicating the improvement in insulin response post-meal was mediated by an increase in butyrate driven by host genetics. Increased risk of T2DM was attributed to the increased population of Eubacterium and Roseburia intestinalis and abnormal propionate production. This concurs that gut microbiome alterations could be pre-diabetic [73]. Lactobacillus species was positively associated with fasting blood sugar (FBG) and high glycosylated haemoglobin (HbA1c) levels. The population of Clostridium species was negatively correlated with FBG, HbA1c, insulin and plasma triglyceride and positively correlated with adiponectin and High-Density Lipoprotein (HDL). Clostridium and Akkermansia muciniphila were also significantly decreased among T2DM patients, while Ruminococcus, Dorea, Sutterella, and Streptococcus were significantly increased [74].

Animal studies have indicated significant improvement in insulin resistance in sterile mice with lower insulin resistance following healthy gut microbiota transplantation [7,75]. Functional analysis indicates increased glucose membrane transport, heterogeneous biomass degradation, methane metabolism, sulphate reduction and branched-chain amino acid transport, while functional genes involving flagella assembly, butyrate biosynthesis, bacterial chemotaxis, and vitamin metabolism were decreased. Additionally, seven anti-oxidative enzymes related to stress were found to be upregulated in T2DM [76].

Furthermore, there was up-regulation in gut barrier function, signalling pathways involved in energy absorption and metabolism, fatty-acid synthesis, cysteine, methionine and glyceride metabolism [74]. This indicates the importance of gut microbiota in energy metabolism. Due to such complex associations between intestinal flora and T2DM, future prospective cohort studies in different regions are warranted for understanding the relationship between the gut microbiome and T2DM.

7. Probiotics in Diabetes and Obesity:

Probiotics are nutrient foods that contain microbiota, which can lead to changes in gut microbiota composition upon consumption. Over the years, literature has indicated safe use and probiotic tolerance among healthy individuals. However, the research on the safety and efficacy of probiotics in disease management across various population groups is yet to be established. Therefore, the United States Food and Drug Administration (FDA) and National Institutes of Health (NIH), through the Agency for Health Care Quality and Research, commissioned an evidence-based review of probiotic safety [77].

7.1 Probiotics in Obesity:

In recent years, research has indicated probiotics' effectiveness in treating obesity. Supplementation of L. gasseri has been shown to reduce obesity-related problems among people who are overweight or obese. Consumption of yoghurt containing L. gasseri BNR17 at high (1010 CFU/g/day) or lower (109 CFU/g/day) over 12 weeks has shown improvements in visceral body fat and waist circumference (wc) compared to the placebo group [78]. Body weight and hip circumference changes have also been noted [79]. The supplementation of L. curvatus 8HY7601 and L. plantarum KY1032 for 12 weeks significantly decreased subcutaneous fat and body weight [80]. Supplementation of Lactobacillus amylovorus (LA) and Lactobacillus fermentum (LF) have reduced adiposity among healthy overweight participants. Supplementation with yoghurt microencapsulated with LA (1.39 x 109 CFU) or LF (1.08 x 109 CFU) or placebo yoghurt for 6 weeks has indicated a reduction in body fat mass, with LA treatment indicating the highest efficacy [81]. Another study with L. plantarum-enriched yoghurt (1.5 x 1011 CFU/50g/day) supplementation for 3 weeks has also shown a reduction in body weight [82].

Consumption of yoghurt containing 108 CFU/g/day of L. gasseri SBT2055 over 12 weeks has indicated a significant reduction in body weight, body fat mass and hip circumference (hc) and wc. However, after 4 weeks of stopping the intervention, the effect was reduced, indicating the need for continuous supplementation, even at lower dosages (106 CFU/g/day), to have a continued effect [83]. In addition, supplementation of capsules of B. brevi B-3 (2 × 1010 CFU) regularly for 12 weeks reduces fat mass [84,85].

Supplementation of Lactobacillus rhamnosus CGMCC1.3724 (3.24 x 108 CFU/day) has reduced body weight in both men and women [86]. B. pseudocatenulatum CECT 7765 (109-10 CFU/day) reduces body weight among obese children with insulin resistance [87]. L. rhamnosus Strain GG (12 billion CFU/day) has improved parameters involving obesity-related liver complications.

Among children, supplementation with L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. longum and L. bulgaricus (Each 2 × 108 CFU/ per day) for 8 weeks has been shown to reduce weight and BMI and wc among children [88].

A probiotic mixture containing the following organisms, B. animalis subsp. lactis SGB06, B. bifidum SGB02, S. thermophiles, S. thermophilus SGSt01, L. plantarum SGL07, L. delbrueckii spp. bulgaricus DSM 20081, L. reuteri SGL01, L. acidophilus SGL11, and Lactococcus lactis subsp. lactis SGLc01 for three weeks significantly reduced subcutaneous fat and body weight [89].

Probiotics as an add-on therapy have been speculated to improve the effectiveness of current treatments for obesity. Gastric bariatric surgery is one of the treatments available for treating obesity. Supplementation with L. casei (3.5 × 109 CFU), L. rhamnosus (7.5 × 108 CFU), L. bulgaricus (108 CFU), L. acidophilus (109 CFU), B. breve (1010 CFU), B. longum (3.5 × 109

CFU), S. thermophilus (108 CFU) for 16 weeks (from 4 weeks before surgery to 12 weeks after surgery) in patients after gastric bariatric surgery compared to placebo significantly improved anthropometric parameters [90].

7.2 Probiotics in T2DM:

Studies have evidenced probiotics' efficacy in treating and maintaining T2DM. In a study conducted in Denmark, ingesting L. helveticus fermented milk for 12 weeks reduced Fasting Blood Glucose among T2DM patients [91]. Supplementation with L. casei has also been effective in improving T2DM parameters. In an Iranian study with 40 patients, the intervention group significantly reduced insulin concentrations, insulin resistance and fasting blood glucose. A slight reduction in glycated haemoglobin level was noticed in patients supplemented with L. casei [92]. Probiotic treatments have shown effects on the improvement in T2DM parameters. In a Brazilian study, probiotic L. reuteri DSM 17938 (1010 CFU/day) and placebo were supplemented to T2DM patients for 12 weeks. Probiotic supplementation improved the insulin sensitivity index among a subset of patients who had highly diverse gut microbiota [93].

Studies have indicated that the efficacy of multi-strain probiotic interventions is higher than single-strain probiotic interventions for improving glycaemic parameters in T2DM patients. This has been attributed to the impact of multi-strain probiotics on the gut compared to single-strain probiotics. For example, in a study conducted in pre-diabetic individuals to determine the effectiveness of probiotic and symbiotic supplementation (probiotic + Prebiotic), symbiotic supplementation containing 6g/day of L. acidophilus, Bifidobacterium bifidum or Bifidobacterium longum indicated significant differences in diabetic parameters such as Fasting plasma glucose and insulin levels alongside HbA1c and homoeostasis model assessment for insulin resistance (HOMA-IR) [94].

Supplementation of Lactobacillus acidophilus (2×109 CFU/g/day), Bifidobacterium bifidum (2×109 CFU/g/day), L. reuteri (2×109 CFU/g/day), and L. fermentum (2×109 CFU/g/day) has indicated reductions in insulin levels and improvements in HOMA-IR [95]. In a study conducted to determine the efficacy of Ecologic barrier®, a mixture of Bifdobacterium bifdum W23, B. lactis W52, Lactobacillus acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W19 and L. lactis W58 (2.5 × 109 CFU/g/day each) in treatment of T2DM, subjects who consumed Ecologic barrier for 12 weeks indicated a significant reduction in abdominal adiposity and HOMA-IR, indicating anti-diabetic and anti-obesity properties [96]. A Malaysian study was conducted to estimate the effectiveness of a multi-strain probiotic supplement, Hexbio® containing probiotic strains L. acidophilus, L. casei, L. lactis, Bifidobacterium infantis, Bifidobacterium bifidum, and Bifidobacterium longum (1010 CFU/day each) against diabetes. Patients who consumed the probiotic supplement reached lower fasting insulin levels at the end of treatment. Slight reductions in HbA1c levels were also noted [97]. Another multi-strain probiotic, Symbiter ®, made with concentrated biomass belonging to 14 probiotic strains belonging to bacterial genera such as Bifidobacterium, Lactobacillus, Lactococcus, and Propionibacterium was tested for effectiveness against T2DM. Patients supplemented with "Symbiter" had significant reductions of HOMA-IR. Further, in a subset of patients who responded well to the probiotic treatment, significant reductions in HbA1c levels were observed [98]. Metformin is one of the most prominent medications used to treat T2DM. However, metformin treatment is associated with gastrointestinal complications. Probiotics have also been used for managing the gastrointestinal symptoms of metformin treatment. Treatment with the Bifidobacterium bifidum G9-1 strain reduced gastrointestinal complications from metformin treatment [99]. A double-blind study was conducted to determine the synergistic effects of metformin and probiotics. Supplementation of multi-strain probiotic (L. plantarum, B. breve, B. animalis sbsp. Lactis, L. bulgaricus, L. gasseri, B. bifidum, S. boulardii and S. thermophilus) for 12 weeks in a subset of T2DM patients on metformin indicated a significant improvement in various T2DM parameters such as HbA1c, fasting plasma glucose, insulin resistance, and plasma butyrate concentrations [100].

With the above evidence, treatment with either probiotic alone or in combination with current treatment methods could prove effective in managing T2DM, with various strains showing effectiveness against different T2DM parameters.

8. Summary:

Gut microbiome alterations are found in diabetes and obesity. However, taken together, studies have shown inconsistent alterations. This could be due to the complex association between intestinal flora, their functions in the gut and metabolic disorders. However, future prospective cohort studies with multi-omics approaches are warranted to explore the relation between gut microbiome and metabolic disorders deeply.

Conflict of Interest

The authors declare no conflict or competing interests.

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