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Relationship between Probiotics and Type 2 Diabetes Mellitus: A Review

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Abstract

Objective: Diabetes is a chronic medical condition that can be caused by either inherited or acquired insufficiency insulin secretion, or the body's inability to effectively utilize the insulin it produces. There are three primary classifications of diabetes: type 1, type 2, and gestational diabetes. Type 2 diabetes mellitus (T2DM) is characterized by elevated levels of fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c), indicating a disturbance in glucose metabolism. The term "probiotics" refers to living microorganisms that provide beneficial effects on the host's health. The effects of probiotics on T2DM in humans have shown conflicting results. Some studies have demonstrated that probiotic treatment substantially reduces HbA1c, FBG, or insulin resistance (IR) in patients with T2DM. However, other studies have found no significant difference between probiotic-treated patients and those receiving a placebo.. The use of probiotics was found to enhance glucose metabolism and HbA1c levels in individuals with T2DM. These findings are in line with previous reviews conducted on this topic.

Keywords: Diabetes, Probiotics, Insulin

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Introduction

Diabetes is a chronic condition that can be either inherited or acquired. It occurs when the pancreas fails to produce enough insulin or when the body becomes resistant to the insulin it produces (1). Living with diabetes requires ongoing adjustments to one's lifestyle (2,3). Failure to control diabetes can lead to severe complications such as nephropathy, retinopathy and cardiovascular failure (4). Among all forms of diabetes, type 2 diabetes mellitus (T2DM) is the most prevalent and a significant public health concern (5). The global prevalence of diabetes has exceeded 420 million individuals, suggesting a potential upward trend (1). By 2045, it is anticipated that over 630 million individuals worldwide will be afflicted with T2DM (6). This highlights as a global issue that significantly impacts public healthcare spending. The estimated global cost of diabetes is projected to reach $827 billion (7).

In Iran, diabetes affects approximately 4.5% to 6% of the population, with the province of Yazd reporting a frequency of 14.2% in individuals over 30 yearsold (8). Additionally, there are other types of diabetes, such as latent autoimmune diabetes in adults (LADA) (10). T1DM remains a mystery, andbased on current understanding, it cannot be prevented (1).

Patients with T2DM may also experience various symptoms related to gastrointestinal dysfunction, such as delayed gastric emptying, diabetic gastroparesis, constipation, diarrhea, obesity, and other related conditions (12-14). As a result, the involvement of gastrointestinal dysfunction is considered a stage in the development of T2DM (15). T2DM is a prevalent and significant chronic disease. This mini-review demonstrates that the composition of the gastrointestinal microbiota is essential for comprehending the pathophysiology of T2DM. The ingestion of probiotics presents a potentially advantageous approach that yields favorable outcomes in the modulation of the gut microbiota compared to alternative methods of managing T2DM. The investigation of probiotics for diabetes prevention, progression, and symptom amelioration is highlighted by the fact that multiple probiotic strains, especially those belonging to the Lactobacillus and Bifidobacterium spp., have shown the ability to enhance T2DM-related indicators. With advancements in molecular biology and the "omic" age, it is hoped that a better understanding of the mechanisms involving T2DM and gut microbiota will emerge, allowing for a more precise comprehension of the relationship between microbiota composition and diabetes. Lastly, the intestinal microbiota can play a crucial role in the management of this chronic disease (16).

The process by which T2DM develops is intricate but generally understood. T2DM is categorized as a chronic inflammatory illness (13). Insulin resistance (IR) resulting from inflammation is a particular trait of the majority of T2DM patients. A growing body of research suggests that variables associated with gut microbiota may also contribute to the development of T2DM (17). In addition to considering the gastrointestinal symptoms of T2DM, it is suspected that the gut microbiota plays a role in the pathogenesis of T2DM (18). The prevalence of T2DM increases with age; however, due to rising obesity, inactivity, and poor diet, this condition is also being observed in children, adolescents, and young adults (19). The significant risk factors for T2DM are hereditary factors, excessive calorie intake, and lack of exercise, which have been extensively discussed (20). Obesity is a significant risk factor for developing T2DM. The epidemic of obesity is influenced by multiple causal variables, including overall energy expenditure, level of exercise, food consumption, genetics, socioeconomic position, educational attainment, and intestinal microbiota, which have been associated with obesity (21). The recent literature review on obesity and microbiota suggests that the ratio

of Firmicutes to Bacteroidetes change with obesity. Therefore, a more comprehensive examination of the intestinal microbiome, encompassing bacterial families, genera, and species, is necessary to gain a deeper understanding of the connection between gut microbiota and obesity (22). The term "probiotics" is commonly defined as "beneficial microorganisms that are alive and can be given to a host to improve their health." It derives from the Greek words "Pro," meaning "promotion," and "Biotic," meaning "life" (23). In many various cultures and ethnicities, from the eastern to the western, fermented foods such as yogurt, kefir, kimchi, sauerkraut, tempeh, miso, and kombucha are a regular part of the meal (24-26). The term "probiotic" was coined by Ferdinand Vergin in a 1954 article titled "Anti-und Probiotika." The study investigated different types of microorganisms to compile a list of beneficial bacteria and to determine the negative impact of antibacterial agents and antibiotics on the gut microbiota (27). A few years later, Lilly and Stillwell defined probiotics as beneficial microbes that stimulate the growth of other microorganisms through the production of growth-promoting substances (28). Over time, with further research and clinical trials conducted in human and animal models, the definition of "probiotics" has evolved. According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), probiotics are living microbe strains that enhance the host's health when administered in sufficient quantities (29). This definition is also endorsed by the International Scientific Association for Probiotics and Prebiotics (ISAPP) (30,31).

Probiotic benefits

The consumption of probiotics is an efficient and appealing method for modifying the microbial composition of the digestive tract, as well as for maintaining and improving human health (32). Probiotics work through key mechanisms such as enhancing the integrity of the epithelial barrier, enhanced adherence to intestinal cells, and pathogen suppression through filling adhesion sites, generating antibacterial compounds, and influencing immune function (33). These processes contribute to the regulation of gut bacteria and inhibition of pathogen growth (34).

In recent years, the use of beneficial bacteria found in probiotics has shown effectiveness in the field of aquaculture (35 Lactic acid bacteria (LAB) and Bacillus spp. are among the most commonly used probiotic microorganisms in aquaculture (36-40)Probiotics have several beneficial impacts on health all over the limbs, including the suppression of the growth of pathogenic bacteria, production of short-chain fatty acids (SCFAs), modulation of gastrointestinal tract pH balance, and activation of the body's defense mechanisms. However, it is important to note that some of these effects may depend on the specific probiotic strain, underscoring the importance of strain identification in investigating their applicability in disease management (41). Studies on animals have indicated that probiotics may positively affect glucose metabolism and increase insulin sensitivity (42,43). However, there are conflicting reports about the impact of probiotics on T2DM. While some trials have shown significant reductions in HbA1c, fasting blood glucose (FBG), or insulin resistance (IR) in individuals with type 2 diabetes who received probiotic treatment (44,45), other research did not find a significant difference compared to those who received a placebo (46,47).

Researchers look at the impact of probiotics on three T2DM markers to fully assess the role of probiotics in T2DM patients and create the theoretical framework for probiotics to be widely used in clinical settings to treat T2DM-homeostasis model appraisal of IR (HOMA-IR), HbA1c, and FBG (48). Glycemic control comes with the genera Lactobacillus, Bifidobacterium, and Streptococcus. (46,49,50).Individuals with T2DM may experience dysbiosis (imbalance of microorganisms) in the gastrointestinal tract

and low-grade systemic inflammation. This dysbiosis and inflammation are associated with a higher ratio of Firmicutes to Bacteroidetes, the two main species in the GI tract, and a lower ratio of lactic acid-producing species such as Lactobacillus, Bifidobacterium, and Streptococcus (51). These organisms can produce SCFAs like acetate which can subsequently, via the use of cross-feeding mechanisms, be transformed into other SCFAs such as butyrate (50,52,53). SCFAs, such as butyrate and propionate, are able to increase glucagon-like peptide (GLP)-1, which is an incretin hormone that regulates postprandial insulin production by increasing the amount of insulin released in response to the consumption of glucose (54-56). Intestinal gluconeogenesis and glucose absorption through the portal vein are both controlled by SCFAs (55,57,58).

T2DM and Probiotics

T2DM is also defined by the possibility of an increased presence of pathogenic bacteria in the gastrointestinal tract, including Enterobacteriaceae. Inflammation and dysbiosis increase the risk of developing leaky gut syndrome, leading to impaired intestinal barrier function. Another concern is the elevated levels of lipopolysaccharide (LPS), which contribute to metabolic endotoxemia (51). The levels of LPS have a strong correlation with the integrity of the intestines. As a result, it is common knowledge that the intestinal barrier inhibits the circulation of LPS from the intestinal lumen into the rest of the body when the body is in a state of equilibrium (59). Tight junction proteins and adhesion of intestinal epithelial cells regulate intestinal permeability, forming a barrier that prevents the entry of pathogens, toxins, and products from the gut lumen into the circulation (60). It is possible that the release of LPS into the circulation as a result of a breakdown in the intestinal barrier would cause inflammation, leading to the development of a variety of disorders, including obesity (61), atherosclerosis (62), and diabetes (63). Lowering LPS levels in the blood has been proposed as a potential treatment approach for T2DM (64).

Species of Lactobacillus, Bifidobacterium, and Streptococcus are responsible for regulating glycemic control through satiety signaling, maintaining gut integrity, and protecting pancreatic cells from free radical damage (41,55,57,65-67). It is known that the gut microbiota, in its eubiotic state, contributes to improved insulin sensitivity by inhibiting the expression of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF]-, interleukin [IL]-6, and IL1) that are linked to insulin resistance and the destruction of pancreatic beta cells via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-B) (68-75). Therefore, dysbiosis observed in individuals with T2DM may negatively affect glycemic control, insulin production, and insulin activity (54-56).

Probiotic consumption has the potential to benefit various metabolic disorders associated with T2DM, including modifications to insulin exocytosis pathways, inflammation, and oxidative stress (51,76-78). Individuals with T2DM may benefit from probiotics, specifically the bacteria from the Lactobacillus, Bifidobacterium, and Streptococcus to restore a healthy microbial balance in the gut, thereby improving glucose metabolism and glycemic outcomes (51). In light of this, the primary purpose of this research is to assess the quality of randomized controlled trials (RCTs) that have investigated the effects of probiotic supplementation on glycemic outcomes in adults with T2DM, particularly fasting plasma glucose (FPG), fasting plasma insulin (FPI), A1c, and homeostatic model assessment of insulin resistance (HOMA-IR) (79).

Results of probiotics using for T2DM treatment

This review included a total of nine RCTs (44,46,76,80-85). Among these, four were placebo-controlled, double-blind experiments (80-83), and five were randomized, controlled,

parallel intervention trials with double blinding (44,46,76,84,85). The studies were conducted in various locations, including Iran, Brazil, Sweden, Malaysia, and Ukraine, with five of the investigations taking place in Iran (44,46,76,80-85). Four of the nine studies revealed that the average length of time between a patient's diagnosis of T2DM and subsequent treatment was roughly seven years (76,80,83,84). Five of the nine studies excluded patients who controlled their T2DM with insulin (44,76,80,81).

At the beginning of each of the nine trials, participants reported using oral hypoglycemic medicine and insulin, with no significant differences between the groups. The length of the intervention, probiotic dosage, the kind of medium used for probiotic administration, and the strain of bacterial probiotics varied across the studies (44,46,76,80-85). The intervention duration ranged from 6 to 12 weeks, and the colony-forming unit (CFU) dosages of the probiotics varied from seven million to over 100 billion per day (44,46,76,80-85). Products containing dairy were used as the vehicle for the administration of the probiotics (44,76,80,82,85) and capsules made from alternatives to dairy (81), powdered form (44,46,85), or supplements in liquid form (84). Bacterial species belonging to the genus L (acidophilus, bulgaricus, casei, and rhamnosus) were represented most frequently among the probiotic strains (44,46,76,80-85), B (bifidum, breve, longum, and infantis) (4,5,7-9,11,12,44,76, 80-82,85) and S thermophiles (76,80-82). Probiotics derived from dairy products were used in media for four different investigations, including goat's milk, kefir, and yogurt. In order to produce multi-strain probiotics, the dairy medium used by all four research teams was supplemented (76,80,82,83). Tonucci et al. utilized goat's milk with S thermophilus TA40, L acidophilus La5, and B lactis BB12 in it (76). Ostadrahimi et al. employed kefir with S thermophilus, L casei, L acidophilus, and B lactis (83). Yogurt that included L bulgaricus, S thermophilus, B lactis Bb12, and L acidophilus La5 was utilized in the experiment that Ejtahed et al. conducted (80). Last but not least, Mohamadshahi et al. utilized a yogurt that contains L bulgaricus, S thermophilus, B lactis Bb12 (DSM 10140), and L acidophilus La5 (82). The remaining five studies all utilized non-dairy probiotic supplements that were capsuled, powdered, or delivered in liquid form (44,46,81,83,84). Asemi et al. gave the participants a capsule that included multiple strains of bacteria, including L acidophilus, L casei, L rhamnosus, L bulgaricus, B breve, B longum, and S thermophiles (81). A multi-strain sachet powder that contained L acidophilus, L casei, L lactis, B bifidum, B longum, and B infantis was given to the participants in the study by Firouzi et al. (44). Kobyliak et al. used a sachet powder that contained multiple strains of bacteria, including Lactobacillus strains, Lactococcus strains, Bifidobacterium strains, Propionibacterium strains, and Acetobacter strains (85). Mobini et al. inquired the effects of two distinct single-strain probiotic dosages of L. reuteri DSM 17938, both of which were delivered in the form of a stick-pack powder (46). Feizollahzadeh et al offered L Plantarum A7 via soy milk (84). In eight of the nine investigations, the effects of FPG on blood sugar were assessed (44,76,80-85) and/or A1c (46,76,80-83). Five evaluated FPI (44,76,80,81,85), and four evaluated HOMA-IR (57,62,66,67). All four glycaemic outcomes were investigated in four of the nine trials (44,76,81,85). The probiotic interventions most frequently consisted of two or more of the bacterial strains L acidophilus, S thermophilus, L bulgaricus, and B lactis and were given for 6 to 12 weeks at doses ranging from seven million to over 100 billion CFU per day (44,46,76,80-85). Multi-strain, dairy-based probiotic interventions, particularly yogurt, and kefir, consistently led to statistically significant changes in glycemic parameters (76,79,85).

Conclusions

Based on this mini-review and quality assessment of nine RCTs, probiotic supplements show promise in improving glucose metabolismand have positive effects on glycaemic outcomes, in particular for the purpose of improving A1c in individuals with T2DM. This study seeks to do something new and exciting: emphasize the clinical relevance of a more targeted probiotic routine for the purpose of better glycemic results, including A1c, FPG, FPI, and HOMA-IR, among individuals with T2DM. Multi-strain probiotics containing Lactobacillus acidophilus, Streptococcus thermophilus, Lactobacillus bulgaricus, and Bifidobacterium lactis administered once daily for 6 to 12 weeks, at doses ranging from 7 million to 100 billion CFU, appear to have the most significant impact on these glycemic parameters. Minor gastrointestinal disturbances are the most commonly reported side effect, although each person is different and probiotic administration should be approached with caution in immunocompromised patients. Based on the available evidence, it is suggested that individuals with T2DM, may benefit from incorporating probiotics as an adjunctive treatment option However, this recommendation should be made on an individual basis, considering the specific needs and circumstances of each patient, and through collaborative discussion among all members of the healthcare team. Probiotic supplementation presents an appealing and emerging alternative for the management of T2DM, although further research is needed to fully understand its overall impact on glycemic control.

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Conflict of Interest

No conflict of interest.

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