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Review Article

Probiotics and Diabetes: A Review

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ABSTRACT

Diabetes is among the set of metabolic diseases in which there are high blood sugar levels over a long period of time. Diabetes mellitus is categorized into four general types: type 1, type 2, gestational diabetes, and "other specific types". According to the World Health Organization, the international occurrence of diabetes is about 10%, reaching up to 33% of the inhabitants in some areas. In recent years, there has been an increased attention to pro-and prebiotics among the public and in the medical community due to their probable role in improving health especially in prevention and treatment of diabetes. A probiotic is considered typically as a viable microbial dietary supplement that positively affects the host through its impacts in the intestinal tract. Therefore, we aimed to carry out a review article about the proposed roles and healthcare potentials of probiotics in controlling and management of diabetes as well as reaching a comprehensive conclusion in this field.

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Introduction

Diabetes is among the set of metabolic diseases in which there are high blood sugar levels throughout a prolonged period of time (1). Severe complications comprise diabetic ketoacidosis and non-ketotic hyperosmolar coma. Moreover, serious long-term complications include cardiovascular disease, stroke, foot ulcers and damage to the eyes (2). Diabetes mellitus is categorized into four general groups: type 1, type 2, gestational diabetes, and "other specific types" (3). Type 1 diabetes mellitus is considered by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas that causes insulin deficiency. This type can be categorized as immune-mediated or idiopathic (4, 5).

Type 2 diabetes is the most prevalent type and characterized by insulin resistance, which may be combined with moderately reduced insulin secretion (6). Gestational diabetes mellitus (GDM) is similar to type 2 diabetes in several aspects, including a combination of fairly inadequate insulin secretion and responsiveness. It happens in approximately 2–10% of all pregnancies and may improve or disappear after delivery (7, 8). Other specific types of diabetes contain prediabetes which shows a condition that happens when a person's blood glucose concentrations are upper than normal but not high enough for a diagnosis of type 2 DM (9) and latent autoimmune diabetes of adults (LADA) that is a state in which type 1 DM progresses in adults. Adults with LADA are commonly misdiagnosed in initial stages as having type 2 DM, according to age rather than etiology (10).

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. In addition, the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (11). Treatment approaches

for diabetes frequently include pharmacological treatment aimed at augmenting insulin secretion or increasing insulin sensitivity (12) and remarkably have been revealed to cause weight gain and other problems and possibly worsen the disease (13). Therefore, there has been an increased attention to pro-and prebiotics among the public and in the medical community due to their probable role in improving health particularly in prevention and treatment of diabetes in recent years (14).

A probiotic is described typically as a viable microbial dietary supplement that positively affects the host through its impacts in the intestinal tract. Probiotics are now extensively consumed in the form of fermented milk products such as yogurt or as freeze-dried culture. The main probiotic bacteria related to dairy products have been *Lactobacillus acidophilus, L. casei,* and Bifidobacteria (15, 16). It has been revealed that some of the health benefits of pre-and probiotics include immune enhancement (17, 18), hypocholesterolemic effects (19, 20), prevention and controlling diabetes (21) as well as obesity (22). According to the global rise in occurrence of diabetes and the reality that this disease is an international public health crisis in all nations, particularly developing countries, we aimed to carry out a review article about the proposed role and healthcare potentials of probiotics in controlling and management of diabetes as well as reaching a comprehensive conclusion in this field.

Probiotics and Diabetes Type 1

It is often indicated that type 1 diabetes results from a complex interaction between different degrees of genetic susceptibility and environmental aspects (23). Current observations in humans and animal models have drawn consideration to a probable participation of the gastrointestinal tract in the pathogenesis of autoimmune diabetes (24). It has been revealed that probiotics can adhere to mucosal surfaces and prevent the attachment of other pathogenic bacteria, to secrete factors that increase barrier integrity and control cells of the immune system (25). In addition, they can diverge tissue cytokine secretion from a pro-inflammatory to an anti-inflammatory profile (26-28).

Calcinaro *et al.* carried out a study in order to investigate the effect of oral probiotics administration in prevention of spontaneous autoimmune diabetes in the non-obese diabetic mouse (28). Finally, they reported that orally administered probiotic compound containing Bifidobacteria

(*B. longum, B. infantis and B. breve*), Lactobacilli (*L. acidophilus, L. casei, L. delbrueckii subsp. L. bulgaricus and L. plantarum*) and *Streptococcus salivarius subsp. thermophilus* preventing autoimmune diabetes and causing immunomodulation by a decline in insulitis severity. Furthermore, some of the investigations approved that feeding probiotic bacterial strains, frequently lactic acid bacteria, to non-obese diabetic mice or bio breeding diabetes prone (BB-DP) rats can postpone or prevent diabetes (28-30).

Interestingly, Roesch et al. performed a culture independent analysis of gut bacteria in BB-DP and bio breeding diabetes-resistant (BB-DR) rats (31). Their results revealed that stool from BB-DR rats encompassed much higher populations of probiotic-like bacteria, including Lactobacillus and Bifidobacterium that show probiotic activity, however BB-DP rats had higher numbers of Bacteroides, Eubacterium and Ruminococcus that none is recognized for probiotic activity. These observations are in consistent with previous works (28, 29, 32, 33).

Based on primary remarkable results in animal models that mentioned before, consumption of probiotics to delay or prevent type 1 diabetes in humans has become an area of interest. Studies in healthy humans have proven that exposure to *L. plantarum* and *L. genera* may postpone or inhibit autoimmune diabetes (34, 35). Moreover, PRODIA study in Finland was conducted in order to determine whether the consumption of probiotics during the first 6 months of life reduces the appearance of type 1 diabetes mellitus (T1DM)-associated autoantibodies in children with genetic risk for T1DM. Their attention-grabbing results showed the ability of probiotics to reduce diabetes autoantibodies in this group (36). In conclusion, despite numerous studies presenting health benefits of probiotics and the interest in their application in prevention and controlling autoimmune diabetes, more comprehensive studies with newly developed techniques are required to elucidate probiotics' possible role.

Probiotics and Prediabetes

Prediabetes is a highrisk condition for type 2 diabetes mellitus (37, 38). The increasing incidence of diabetes emphasizes on the necessity of focusing on several approaches in order to prevent and manage prediabetes (37, 39, 40). Probiotics as a group of functional foods might have antidiabetic effects (37, 41, 42). Mahboobi et al. conducted a randomized clinical trial in order to assess the effects of probiotic supplementation on markers of blood lipids, and blood pressure in patients with prediabetes (37). This study involved 60 prediabetic patients, aged 25-65 years old that were randomly assigned to the dietary

intervention for 8 weeks. Subjects with fasting plasma glucose concentrations of 100-125 mg/dl, 2 h glucose tolerance test levels of 140-200 mg/dL or both, for <2 months, were considered as qualified persons (43). Their studies showed that probiotics did not have important effects on lipid markers although they had positive impacts on systolic blood pressure.

In addition, Mazloom et al. indicated a similar result that probiotic capsules containing lactic acid bacteria did not have any satisfactory effects on fasting blood glucose levels, insulin resistance and blood lipids after 6 weeks of intervention in diabetic patients (44). Lewis and Burmeister also reached a similar conclusion (45). However, other studies indicated beneficial effects of probiotic consumption in managing and prevention of diabetes (29, 46-48). Furthermore, Kellow et al. in another investigation evaluated the effect of dietary prebiotic supplementation on insulin resistance and inflammatory biomarkers in adults with pre-diabetes (41). They revealed that dietary prebiotic supplementation reduced oxidative stress, inflammation, insulin resistance and hyperglycemia. In conclusion, it can be inferred that although some studies approved the usefulness of implementing pro-and prebiotics in the management and prevention of diabetes, however some studies stated non-significant effects of this dietary supplementation on improvement of health condition in prediabetic patients.

Probiotics and Diabetes Type 2

Diabetes mellitus type 2 (previously noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic illness that constitutes approximately 90% of cases of diabetes (49).

The human gastrointestinal tract encompasses in average 10^{14} Colony-Forming-Unit (CFU)/mL and 500 to 1000 species and live in symbiosis with their host (40, 50). Bacteroidetes and Firmicutes are prevailing in the normal mouse and human intestines (50, 51). The population of these bacteria is adjusted by diets for example high fat (52) and is also vital in development of obesity, diabetes type 2 and dyslipidemia (33, 53-55).

It has been suggested that changed intestinal microbiota increases intestinal permeability and mucosal immune response, participating to the development of diabetes (40, 56). Alteration of intestinal microbiota by probiotics may be involved in the maintenance of a healthier gut microbiota, and have also been recognized as influential adjuvants in insulin resistance treatments (40, 46, 57-60). In this part, we review some of the studies in order to assess therapeutics aspects of using probiotics in the prevention and management of type 2 diabetes mellitus.

Mazloomi and his colleagues conducted an investigation in order to assess the effects of omega-3 fatty acid-fortified soymilk fermented with *B. lactis,* on the body weight, blood glucose and lipid profile of diabetic rats (61). Their findings suggested that fermented soy milk fortified with omega-3 fatty acids may be useful in preventing or delaying the development of type-2 diabetes. Another animal study, researchers observed that a fermented milk product containing probiotic bacteria meaningfully postponed the onset of glucose intolerance, hyperglycemia, and hyperinsulinaemia in diabetic rats caused by high fructose concentration (29, 62).

Yun et al. carried out an animal study in order to assess the effect of *L. gasseri* BNR17 insulated from human breast milk on blood glucose and body weight in type 2 diabetic animals (63). The sample groups consumed BNR17 (10^7, 10^8, 10^9 and 10^{10} CFU) or rosiglitazone (8 mg/ kg) orally twice a day for 12 weeks. Their results showed that *L. gasseri* BNR17 had a suppressing consequence on blood glucose levels and improved diabetic symptoms in db/db mice. They finally concluded that blood glucose-lowering lactic acid bacteria are anticipated to be beneficial as a therapeutic for treating type 2 diabetes in humans. Other investigations also approved the effects of probiotics in management of type 2 diabetes (29, 64-66). However, Al-Salami et al. stated that probiotic treatment had no significant effect on blood glucose concentration in healthy rats, but decrease blood glucose in diabetic rats due to an increased gliclazide (sulfonylurea) bioavailability (67). It should be noted that there are mixed and contradictory results in animal model and more comprehensive studies in this field are required.

According to favorable results in animal models that stated before, the implementing of probiotics to delay or stop type 2 diabetes in humans has become a field of attention. A human study revealed that patients with T2DM who consumed 300 g/d of probiotic yogurt containing *L. acidophilus* La5 and *B. lactis* Bb12 for 6 weeks had a noteworthy decrease in fasting glycemia and hemoglobin A1c (59, 62). In addition, Amar et al. concluded that a probiotic treatment with *B. lactis* 420 reversed high-fat diet (HFD) induced bacterial adherence, translocation, mesenteric adipose tissue (MAT) inflammation and insulin resistance (68).

Furthermore, another investigation reported that there was a meaningful increase in HDL (high-density lipoprotein) cholesterol and a substantial decrease in fasting glycemia in elderly T2DM patients who consumed a regular dose of 200

mL of a symbiotic drink including 10^8 CFU/mL *L. acidophilus*, 10^8 CFU/mL *B. bifidum* and 2 g oligofructose over 30 days (46). Using probiotics has been recognized beneficial not only in improving fasting glycemia and insulin resistance, but also in making lipid profile better as well as improving cardiovascular diseases risk factors. Ejtahed et al. concluded that probiotic yogurt improved total cholesterol and LDL-C (low density lipoprotein) concentrations in type 2 diabetic people and may participate in improvement of cardiovascular disease risk factors (58).

Other studies also concluded the effects of pro- and prebiotics in improvement of lipid profile including decrease in LDL and TG and increase HDL level; consequently decrease cardiovascular diseases risk factors in diabetic patients (69-73). In conclusion, although many studies approved the beneficial effects of using pro- and prebiotics in prevention and treatment of diabetes type 2, however, more comprehensive and original investigations will be needed in order to reach a reasonable and practical conclusion in this field.

Probiotics and Gestational Diabetes Mellitus (GDM)

The prevalence of GDM was first diagnosed during pregnancy, is on the rise in concordance with the increase in overweight and obesity in the obstetric population (74, 75). GDM is considered by maternal insulin resistance and inflammation (76-79). Nowadays, clinical experiments of exercise and dietary interventions to inhibit the onset of gestational diabetes have had varied results and have proven disappointingly tough (79). Probiotics are progressively under study for probable metabolic benefits, with some current attention in the role of probiotics in the prevention of GDM (74, 79, 80). In this part, we review the results of some of the studies about the using probiotics in prevention of GDM in order to reach a reasonable conclusion in this field.

Nitert et al. conducted an RCT study in order to assess the effects of implementing probiotics in the prevention of gestational diabetes in overweight and obese women (74). They concluded that probiotics offer a therapeutic choice for the prevention of GDM that is simple, cheap and easy to include into standard clinical care. They also stated that probiotic supplementation in pregnancy is considered safe according to the safety data available (74, 81, 82). In pregnancy, Bacteroidetes and Staphylococcus species are augmented in overweight compared with normal weight women (79, 83).

A recent study examined the variations of gut microbiome during pregnancy in a group of 91 women, 16 of whom took probiotics (*B. lactis and L. rhamnosus*) during their pregnancy and 13 of whom were overweight or obese (79, 83-85). They indicated that there was a noticeable alteration in maternal gut microbiome from the first to third trimester. Furthermore, it was reported that when the third trimester microbiome transferred to germ-free mice caused adiposity and insulin resistance (79, 84). Interestingly, they concluded that probiotics intake or antibiotic use during pregnancy (N=7) did not meaningfully influence the overall gut microbiome (79, 84).

The Finish study involved 256 normal weight pregnant women investigated the effects of probiotics/diet intervention during early pregnancy until 1-year postpartum on some parameters (86). The probiotics intervention consisted of *L. rhamnosus GG* and *B. lactis* BB12 and dietary counselling concentrated on increasing the percentage of polyunsaturated fatty acids in the fat component of the diet. Their results showed a reduced possibility of elevated maternal glucose concentration, decreased incidence of GDM (79, 87) and reduced frequency of maternal waist circumference (88) as well as meaningful decrease of maternal fasting glucose concentrations in the third trimester in the diet/probiotic group.

They suggested that the observed effect of probiotics on glucose metabolism and gestational diabetes mellitus is most possibly attributable to their immunoregulatory properties. Adjustment of inflammatory pathways by probiotics may be of specific importance due to the substantial involvement that inflammation plays in insulin resistance (86, 89, 90). In conclusion, implementing probiotic as a cost-effective, simple and safe therapeutic option is suggested by most of the studies, however more investigations from all around the world are needed in order to approve using pro-and prebiotics in prevention of gestational diabetes (26/4.)

Conclusion

Consuming pro-and prebiotics as dietary supplementation has become popular among the public and in the medical community because of their potential role in promoting health especially in prevention and treatment of diabetes. It can be inferred that there are varied and different opinions regarding implementing probiotics and dietary intervention along with pharmaceutical ways, however, we strongly suggest that more comprehensive investigations and reviews should be carried out in order to approve probiotics' role in diabetes management, principally in nutritional fields.

Conflict of Interest

None declared.

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