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Review Article

The Scope of Therapeutic Use of Probiotics in Management of *Diabetes Mellitus*

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Abstract

Diabetes mellitus is considered a global health problem which affects all sections of society, creating health and economy hardships. A large number of studies have identified risk factors that cause metabolic disorders such as genetic predisposition, unhealthy lifestyle, and altered gut microbiota. These factors are responsible for causing an increased adiposity, β-cell dysfunction, hyperglycemia, hypercholesterolemia, adiposity, dyslipidaemia, systemic inflammation, defective secretion of incretins and oxidative stress associated with type-2 diabetes (T2D). Probiotics particularly *lactobacilli* and *bifidobacteria* have recently emerged as the potential therapeutic agents with proven efficacy demonstrated in various *in vitro* and *in vivo* animal models adequately supported with their established multifunctional roles and mechanism of action for the prevention and disease treatment. The dietary management of DM by using probiotics is considered a novel strategy to slow development and progression of DM. Altering gut microbial composition holdsa significant potential for prevention and treatment of DM. This review will highlight the new developments in probiotic interventions and future prospects for exploring probiotic therapy in the prevention and management of DM.

Keywords: *Diabetes; Probiotics; Bifidobacteria; Microbiota*

Introduction

The World Health Organization (WHO) defines probiotics as living organisms which, when administered in adequate amounts, confer a health benefit on the host." Microorganisms include bacteria, viruses, and yeasts. The most common probiotics are certain types of bacteria [1].

Scientists estimate that about 500 different species of bacteria live in and on human body. In the typical human gut, there are about 100 trillion microorganisms belonging to these 500-odd species. The word "probiotic" means "for life and as we all rely on these organisms to maintain optimum health.

It was well established that probiotics can benefit human health in a number of ways:

a. Boosting the immune system especially in people with uncontrolled diabetes
b. Counteracting antibiotics effects.

The *Lactobacillus spp* converts lactose into lactic acid. This is why some people with lactose intolerance can eat yogurt or drink acidophilus milk without experiencing side effects and alleviate lactose intolerance.

Fighting irritable bowel syndrome: Probiotics may turn out to be helpful in the fight against obesity. Certain foods contain probiotics that either occur naturally in the food or are added during processing. Food sources of probiotics include the following:

a. Yogurt
b. Kefir (a cultured drink that is similar to yogurt)
c. Acidophilus milk
d. Buttermilk

e. Sour cream
f. Aged cheeses (Gouda, Swiss, etc.)
g. Cottage cheese that contains active cultures
h. Miso (a fermented soybean paste)
i. Tempeh (a fermented soybean product)
j. Sauerkraut

Cornell researchers have achieved this attainment in rats by engineering human *lactobacilli*, a common gut bacteria, to secrete a protein called Glucagon-like peptide 1 (GLP-1).

A 2003 study led by Atsushi Suzuki of the University of Tsukuba, Japan, first demonstrated that when exposed to the 37 amino acid, full-length form of GLP-1, intestinal epithelial cells that cover the guts are converted into insulin-producing cells. In a published study, the researchers engineered a strain of *lactobacillus*, a human probiotic, to secrete GLP-1, and then administered it orally to diabetic rats for 90 days. Rats with high blood glucose that received the engineered probiotic ended up with up to 30 percent lower blood glucose levels [2]. Probiotics may be involved in the maintenance of a healthier gut microbiota, and have also been identified as effective adjuvants in insulin resistance therapies [3]. The objective of this review is to clarify the currently described effects of probiotics in the prevention and management of DM.

Diabetic individuals have lower counts of *Bifidobacterium* and *Faecalibacterium prausnitzii*, both of them Gram positive with anti-inflammatory properties [4]. Despite the perturbations already observed in the intestinal microbiota of type 2 diabetic subjects, it is still necessary to elucidate whether the variations in the microbiota, intestinal barrier and metabolic endotoxemia are causes or consequences of diabetes.

Probiotics and Type 1 Diabetes Mellitus

Type 1 diabetes results from autoimmune destruction of pancreatic β-cells in genetically predisposed individuals [5]. B-cell destruction involves innate and adaptive immune responses, and when around 80% of the β-cells are affected, the first signs of diabetes become manifested [6]. The intestinal microbiota is capable of modulating the immune response and consequently autoimmunity; the influence of intestinal bacteria in the pathogenesis of T1D has been demonstrated [7].

Changes in intestinal microbiota may result in altered inflammatory responses, an important event in the pathogenesis of autoimmune diseases such as T1D [8]. Children with T1D showed higher counts of *Clostridium, Bacteroides* and *Veillonella*, followed by lower counts of *Bifidobacterium* and *Lactobacillus*, than healthy children [9]. A study found that healthy children have more diverse and stable intestinal microbiota as compared to children who developed T1D [10]. Gut microbiota has also been reported to play a pivotal role in pathogenesis of T2D, obesity and related inflammatory metabolic disorders. Accumulating evidence supports the new hypothesis that metabolic diseases like obesity and T2D develop because of low grade, systemic and chronic inflammation by disruption of the normal gut microflora induced by dietary intake of high fat and fructose diet.

Poorly balanced diets can shift the gut microbiome from healthy microflora towards unhealthy ones with the predominance of pathogenic microflora in chronic disease [11]. In addition, numerous metagenomic studies also investigated the gut microbial changes in obesity - the main precursor in the development of T2D in various animal and human studies [12].

Interestingly, the recent studies have revealed the compositional changes in the group of *bifidobacteria* and *lactobacilli* during the onset of insulin resistance in HFD mice. The gut microbial profile of these studies recorded reductions in *Bifidobacterium spp*. and *Lactobacillus spp*. with increased plasma LPS that caused metabolic endotoxemia via NF-kB activation on the molecular onset of insulin resistance [13]. Other gut flora-associated metabolites such as hippuric acid, methylxanthine, methyluria acid and 3-hydroxyhippuric acid were reduced considerably in individuals with impaired glucose tolerance. These metabonomic studies further supported the role of gut microflora in pathogenesis of diabetic and pre-diabetic states. Gut microbiota- associated metabolite biomarkers were decreased

in urine samples of individuals with impaired glucose tolerance indicating important role of gut microbiota in energy metabolism and immune function of host [14].

In another study that included 40 diabetic and 60 healthy ones, diabetic individuals could be differentiated from healthy individuals on the basis of presence of secondary metabolites of bile acids - the products of gut microflora in diabetic individuals. Cholate was more frequently detected in control or healthy individuals, where as its secondary product, deoxycholate, was found to be more prominent in diabetic group. The outcome of the study clearly indicated alterations in bile acid pool and their biosynthetic pathway in diabetic patients and ascribed the same to the role of altered gut microflora as a result of higher rate of conversion of primary bile acids to secondary bile acids [15].

Probiotics effect on type 2 Diabetes Mellitus and obesity

The data that emerged from various studies by different investigators have provided sufficient evidence that modulating the gut microbiota through dietary interventions may contribute in the prevention and control of inflammatory metabolic disorders including T2D and obesity. In one of the studies carried out by Ma., *et al*. [16], the human colonic adenocarcinoma T84 and HT29 were challenged with live and killed Lactobacillus reuteri cells, and the expression of NGF and anti-inflammatory molecules were analyzed. The live probiotic bacterial cells were able to upregulate the expression of NGF, inhibited the cellular accumulation and secretion of IL-8 induced by TNF-a. However, expression of IL-10 remained unaffected in both T84 and HT29 cells. In another study, He La cell line was explored as a model to investigate the activation of NF-k B signaling in the progression of inflammation [17].

Different animal models have been extensively explored to study the multiple mechanisms of probiotics in the management of diabetes. Initially, anti-diabetic effects of oral administration or diet supplementation of heat-killed *Lactobacillus casei* were studied in three different mice models such as (1) T2D mice model using KK-Ay mice, (2) type 1 diabetes mellitus model, i.e., NOD, and (3) Alloxan-induced diabetes in mice. In all these studies, the oral administration (0.05%) or diet supplementation (0.1%) of heat-killed cell of *L. casei* reduced the plasma glucose level and occurrence of diabetes [18]. In another study, using neonatal STZ-induced diabetic (n-STZ) rats, feeding of diet containing *Lactobacillus rhamnosus* GG for a period of 9 weeks (from the age of 9 weeks to 18 weeks) lowered the blood haemoglobin level and improved glucose tolerance in comparison to control group fed with common diet. In the *L. rhamnosus* GG treatment group, the serum insulin level at 30 min after glucose loading was significantly higher than in the control group ($p < 0.05$) [19]. Although the efficacy of probiotics as such or other formulations in food formats against diabetes has been extensively studied and demonstrated in appropriate human. This is precisely because very few attempts have been made in this regard to explore efficacy of probiotic therapy in diabetes on the affected human subjects. There are only a handful of published reports available in this context.

Probiotics and lipid profile

As oxidative stress, hypercholesterolemia and altered lipid profile play a major role in the pathogenesis and progression of diabetes, randomized, double-blind, placebo controlled clinical trials were conducted in separate studies to assess the effects of probiotic on blood glucose, antioxidant status and lipid profile in T2D [20]. In these studies, patients with T2D were assigned into two groups. The patients in the probiotic intervention group consumed 300 g/d of probiotic yoghurt containing 106 cfu/ml *L. acidophilus* La5 and 106 cfu/ml B. lactis Bb12 and those in the control group consumed 300 g/d of conventional yoghurt for 6 weeks. The probiotic intervention groups in these studies showed significant decrease in fasting blood glucose and HbA1c ($p < 0.05$) and increased the erythrocyte superoxide dismutase and glutathioneperoxidase activities, and total antioxidant status ($p < 0.05$) compared with control group. The probiotic yoghurt consumption also decreased the total cholesterol by 4.54%, LDL-C by 7.45% in intervention group. The total cholesterol: high-density lipoprotein (HDL)-C ratio and LDL-C: HDL-C ratio as atherogenic indices were significantly decreased in the probiotic group compared with the control group [21]. From the previous two studies, it is quite evident that consumption of probiotic yoghurt significantly improved the antioxidant status and lipid profile in the intervention group and presented multigenic approach for the management of T2D. Recently, a randomized, double-blind, placebo-controlled study was conducted on 20 volunteers (ten for placebo group and ten for symbiotic group), aged 50-60 years, over a total test period of 30 days to study the effect of a symbiotic drink (a preparation with a combination of both probiotics and prebiotics) on glycemia and cholesterol levels in elderly people with T2D mellitus. The results of

the symbiotic group that consumed 108 cfu/ml of *L. acidophilus*,108 cfu/mL *Bifidobacterium bifidum* and 2 g oligofructose showed a significant increase ($p < 0.05$) in HDL cholesterol, non-significant reduction ($p > 0.05$) in total cholesterol and triglycerides and a significant reduction ($p < 0.05$) in fasting glycemia. However, no significant changes were recorded in the placebo group [22]. Notwithstanding the positive efficacy of probiotics on diabetic patients as obtained from the aforesaid studies, conflicting results were also recorded in one clinical trial while assessing the effects of probiotic on attenuating systemic inflammation and improving insulin sensitivity. In this randomized, double-blinded clinical trial, the commercial probiotic *L. acidophilus* NCFM was used as intervention together with placebo in a group of 45 men for a period of 4 weeks. In this case, even after 4 weeks of intervention, no changes in the expression of baseline inflammatory markers and the systemic inflammatory response were observed, thereby, indicating ineffectiveness of the probiotic therapy in diabetic patients [23]. However, this inconsistency in results could be attributed to heterogenicity with regard to probiotic strain.

Conclusion

The published studies support the fact that changing the gut microbiota by probiotics may be effective towards prevention and management of DM. There is a good reason to believe from the interesting leads that emerged from extensive *in vitro* cell line and animal studies that probiotics do have the potential to prevent and reduce the severity of DM and other metabolic syndromes possibly through modifying the intestinal microbiota. Future research should be focused on functional properties of probiotics to ensure optimal health benefits.

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