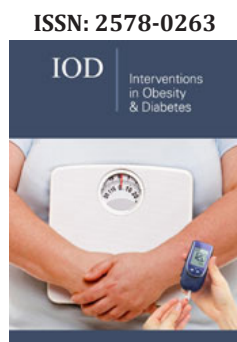


Probiotic and Prebiotic Interventions for Obesity and Diabetes

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Abstract

Gut is considered as second brain since it coordinates with all the organs. A physiological change or dysbiosis in the gut affects the body metabolism. A probiotic treatment along with a restricted diet and an appropriate prebiotic can modulate the host functioning. The mechanisms through which the probiotics improves type 1, type 2 and gestational diabetes is by modulating insulin resistance, barrier function of gut epithelium, immunomodulation, reducing appetite and upregulating genes for fatty acid breakdown. Fermentation of prebiotics in the gut produces short chain fatty acids which in turn regulates the metabolic pathways by interacting with various receptors and modulating the downstream pathways. The studies reported till date reveals that a synbiotic therapy can be an alternative as well as preventive medicine for lifestyle diseases especially diabetes and obesity.

Keywords: Obesity; Type 1 diabetes; Type 2 diabetes; Probiotics and prebiotics; Gut microbiota, Diet

Abbreviations: T1D: Type 1 Diabetes; T2D: Type 2 Diabetes; LPS: Lipopolysaccharides; TLR: Toll Like Receptor; GLP: Glucagon Like Peptide; PAMP: Pathogen Associated Molecular Patterns; GPR: G Protein Coupled Receptor; GLUT: Glucose Transporter; BMI: Body Mass Index; VFA: Visceral Fat Area; SCFA: Short Chain Fatty Acid, ITF: Inulin Type Fructan

Introduction

Diabetes and obesity are two trending metabolic disorder which leads to major complications in all cases despite of age. Both are strictly correlated and hence called diabetes. Diet is the major factor which contributes to diabetes. The microbial diversity and number in the gut environment mainly depends on the food consumed in healthy individuals. The microflora in gut profoundly affects the host metabolism through several mechanisms. There is a significant difference between the microfloral composition in diabetic and non-diabetic people as well as obese and non-obese. High fat/carbohydrate diet always promotes the establishment of putrefying and opportunistic pathogens. Supplementation of probiotics and prebiotics is a good practice to maintain a healthier gut thereby improving the host functions. The review mainly discuss about the beneficial effects of gut flora/probiotics along with prebiotics in T1D, T2D and obesity.

Discussion

Human gut harbours predominantly four phyla of bacteria *Proteobacteria*, *Firmicutes* such as *Ruminococcus*, *Lactobacillus* and *Clostridium* species, *Actinobacteria* and *Bacteroidetes* (*Bacteroidaceae* and *Prevotellaceae*). Several studies suggest the association between a dysbiosis gut with obesity and diabetes. Obesity and diabetes are clearly associated with a marked reduction in *Firmicutes* and higher proportion of *Bacteroidetes* and *Proteobacteria*. Studies in animal models showed that gut microorganisms induce diet mediated obesity by harvesting more energy from the diet and the body store them as triglycerides leading to T2D [1]. The mechanism underlying diabetes in dysbiosis includes alteration in fatty acid metabolism, modulation in gut peptide YY and GLP -1 secretion, activation of TLRs by bacterial LPS which elicits immune response thereby modulating the membrane permeability and causes insulin resistance [2]. Same mechanisms were observed in T1D children, but they are generally non obese. Their fecal microbiota of is less diverse and stable [3]. Further the PAMPs mediated inflammation lead to the destruction of beta cells of islets of langherhans thus predispose the pathogenesis of T1D [4]. A healthy and balance gut microbe along with a more vegetarian diet can improve or delay the chronic effects of both type 1 and type 2 diabetes. It also helps to maintain the glucose and fat metabolism as well as alleviates the inflammatory responses. Species of *Lactobacillus* and *Bifidobacteria* are extensively explored for their health promoting effects and they are considered as probiotics. According to WHO/

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FAO "Probiotics are live microorganisms which when administered in adequate amounts confer health benefits to the host". Probiotics have a characteristic of producing SCFAs from dietary fibers. SCFAs especially butyrate and propionate activate GPR 41 and GPR 43 which further activates GLP-1 and PYY which inhibit gut motility and reduce appetite thus reducing the energy uptake. Butyrate and Propionate also activates gluconeogenesis through cAMP dependent pathway and also decreases the permeability of intestinal barrier [5]. A metagenomic approach in T2D patients revealed a marked decrease in butyrate producing bacteria and an increase in opportunistic pathogens [6].

The antiobesity effect of *Lactobacillus gasseri* is well known. It reduces the adipose tissue weight in high sucrose fed rat and reduce glucose level in T2D mice. In mice the same strain significantly increased the mRNA levels of fatty acid oxidation and lowers the expression of genes involved in synthesis of fatty acids and also elevated the glucose transporter GLUT-4 [7]. Probiotic supplementation with low calorie diet can reduce the BMI in adults. A 12-week administration of *L. gasseri* SBT2055 was enough to reduce BMI, hip circumference and abdominal VFA in Japanese adults [8]. The strain *Lactobacillus plantarum* reduces the subcutaneous and mesenteric fat mass in high fat fed mice [9]. The probiotic fermented soya and flaxseed milk increased insulin production and thereby reduced blood glucose level in alloxan induced T1D rat [10]. Administration of *Bifidobacterium breve* reduces the accumulation of epididymal fat in a dose dependent manner [11]. *L. acidophilus*, *L. casei*, *B. lactis*, *S. thermophilus* and *E. faecium* are other probiotics with antiobesity activity. *L. acidophilus* and *B. lactis* in yogurt reduced fasting blood sugar, total cholesterol and low-density lipoprotein in T2D patients [12]. Administration of probiotic *L. rhamnosus* GG and *B. lactis* in pregnant women from early pregnancy helps in reduction of weight and waist circumference after postpartum [3]. Another study reported a reduction in chance of gestational diabetes mellitus [13]. Probiotics can exert their effect only when they colonize the gut. The non-dietary non digestible components in food can be fermented and utilized by probiotics as energy sources. These components are collectively called prebiotics. It is defined by FAO/WHO as "Non digestible food ingredients that beneficially affect the host by selectively stimulating the growth and activity of one or a limited number of bacterial species already established in the colon, and thus improve the host health [14]. Since they are non-digestible, reaches the distal part of GI tract where the resident bacteria utilize it as nutrients. Galacto oligosaccharides, Fructo oligosaccharides, Soybean oligosaccharides, Inulin, Coclodextrins, Gluco oligosaccharides, Xylo oligosaccharides, Lactulose, Lactosucrose and Isomalto oligosaccharides are commonly used for the enriched growth and establishment of probiotics [15]. A study in obese women treated with ITF showed a selective change in gut flora that is increased *Bifidobacterium* and *Faecalibacterium prausnitzii* which have a negative impact on serum LPS, fat mass and plasma phosphatidyl choline levels [16]. Arabinoxylan oligosaccharide from wheat bran improves the physiological and metabolic impairments caused by high fat diet in obese mice. It reduces the high fat induced hyperinsulinemia, metabolic endotoxemia, weight

gain and fat mass also upregulated the alterations in tight junction [17]. The synergistic form of prebiotic and probiotic called synbiotic selectively and effectively modulate specific microbes of the gut. Dietary ITF consumption selectively modulated *Bifidobacterium* spp. and decreased fecal SCFA levels in obese women [18]. FOS supplementation in healthy individuals promote satiety, reduce hunger and food ingestion [19] whereas FOS administration in obese resulted in weight loss [20]. In high fed mice FOS restored *Bifidobacterium* sp. numbers and normalize the LPS level, glucose tolerance and insulin secretion [21]. Antiobesogenic effect of cyclodextrins can be explained by increased level of lactic acid and SCFA in obese mice through the expression of genes involved in lipid metabolism (PPAR and PPAR γ) [22]. Likewise, obese rat fed with prebiotic insulin and oligofructose showed elevated level of circulating GLP-1 and enhanced expression of pro-glucagon and Peptide YY genes [23]. The synbiotic effect of *Lactobacillus acidophilus* ATCC 4962, fructo-oligosaccharide, inulin, and mannitol in hypercholesteremia was showed in high fat fed pigs. It was observed that total cholesterol, low density lipoprotein and triglycerides were reduced [24]. The synbiotic *Bifidobacterium animalis* subsp. lactis BB-12 and oligofructose improved glycemic condition in obese rat [25]. Daily administration of insulin or maltodextrose in T2D women modulated inflammation and metabolic endotoxemia [26]. Recent studies explain that the enteroendocrine peptides like GLP-1, PYY, and ghrelin which plays important role in glucose homeostasis can be modulated by inulin [27]. ITF can stimulate GLP-1 and GLP-2 synthesis by increasing endocrine L cells in rodents. GLP-1 reduce appetite, fat mass and insulin resistance and GLP-2 decreases the permeability of intestine and reduce endotoxemia related to diabetes [28]. A four-week administration of FOS reduces hepatic glucose synthesis whereas in T2D patients, oligofructose showed a significant decrease in blood glucose after 6 weeks of administration [29]. The decrease in intestinal low-grade inflammation, correlated with improved gut barrier integrity and reduced proinflammatory cytokines levels, provides an improvement in glucose tolerance and insulin sensitivity [21]. All these findings highlight the use of prebiotics in improving glycemic control and diabetes.

Conclusion

In vivo studies in animals and humans proved the importance of maintaining a healthy gut in metabolism and homeostasis. Supplementation of probiotics and prebiotics improve the health of the host. A single probiotic cannot satisfy all the health requirements rather they can be used as personalized or occupation-based medicine. Synbiotic therapy is a promising strategy for lifestyle disease like obesity and diabetes. It can prevent the pathogenesis and to some extent can cure these types of metabolic dysfunctions. However more human trails are required to extensively use probiotics in medical practice.

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