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SHORT COMMUNICATION

Gut Microbiota as Therapeutic Targets in Diabetes Management: Opportunities and Challenges

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Abstract

This article delves into the complex interplay between Type 2 Diabetes Mellitus (T2DM), gut microbiota, and dietary strategies for effective diabetes management. T2DM, characterized by insulin resistance and β-cell dysfunction, is influenced by genetic and environmental factors. The gut-brain axis and alterations in incretin functioning contribute to gastrointestinal permeability in T2DM. Plant-based diets offer substantial benefits for managing T2DM by improving emotional well-being, HbA1c levels, weight, and cholesterol. High-fiber diets positively impact gut microbiota, and serum metabolism, and emotional health in T2DM individuals. Probiotics, prebiotics, synbiotics, and postbiotics (PPSP) are emerging as pivotal interventions. Probiotics improve serum fructosamine, HbA1c, and cholesterol levels, while prebiotics like oligofructose-enriched inulin and synbiotics enhance glycemic control and lipid profiles. Insights from microbiome studies in diverse dietary populations provide personalized approaches for diabetes management. Integrating plant-based nutrition, PPSP interventions, and microbiome-focused strategies may offer a comprehensive and effective approach to T2DM management, addressing physiological aspects and empowering individuals in their health journey.

Key Words: *Type 2 Diabetes Mellitus (T2DM); Gut microbiota; diet; Probiotics; Prebiotics; Synbiotics, and Postbiotics (PPSP); Gut microbes; Metabolic pathways*

Introduction

Type 2 diabetes mellitus (T2DM) constitutes over 90% of diabetes cases in adults, primarily driven by resistance to insulin action, resulting in chronic hyperglycaemia. It stems from a cascade of pathways and factors contributing to insulin resistance and β-cell dysfunction. The development of T2DM is intricately influenced by a combination of genetic and environmental factors, which can be effectively regulated through lifestyle changes for improved diabetes management [1]. One important factor is the gut-brain axis, the gut plays a pivotal role in linking the brain with the enteric nervous system, and alterations in incretin functioning and associated pathways contribute to increased gastrointestinal permeability (Gastrointestinal

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permeability, also known as gut permeability, refers to the control of substances passing between the intestines and bloodstream. It's regulated by tight junctions in the gut lining) in type 2 diabetes mellitus (T2DM). These changes represent fundamental underlying mechanisms responsible for diabetic comorbidities during the later phases of the disease.

T2DM and Gut Microbiota

Diabetes is recognized as an intestinal disease where the gut microbiota plays a crucial role. Microflora concentration increases distally along the gastrointestinal tract, with upper intestine flora accounting for <105 cfu/mL, mid-ileum increasing to 107 cfu/mL, and colon heavily populated. Common bacteria in humans include Firmicutes (60–80%): *Ruminococcus*, *Clostridium, and Lactobacillus; Bacteroidetes* (20–30%): *Bacteroides, Prevotella, and Xylanibacter; Actinobacteria (<10%): Bifidobacterium; Proteobacteria (<1%): Escherichia and Enterobacteriaceae; and yeast Saccharomyces boulard*i. Obesity is a pivotal factor in type 2 diabetes mellitus (T2DM), correlating with increased *Staphylococcus, Enterobacteriaceae*, *Faecalibacterium prausnitzii, and E. coli* levels in obese conditions while *Bacteroides* decrease. In T2DM, *Firmicutes, Lactobacillus gasseri, Streptococcus mutans*, and *E. coli* are elevated, while *proteobacteria*, butyrate-producing bacteria, *Bacteroidetes, Roseburia, Eubacterium halii, and Faecalibacterium prauznitzii* decrease considerably. Gut microbiota alterations contribute to insulin resistance, metabolic syndrome, and low-grade inflammation associated with obesity and diabetes, affecting intestinal permeability and leading to comorbidities like gastroparesis and compromised vagal control in diabetes. These disturbances in intestinal functions can disrupt the intestinal barrier and facilitate microbial entry, contributing to diabetes progression and comorbid conditions [1].

Diet, Influence on Gut Microbiome and Diabetes Management

Plant-based diets, including vegetarian and vegan options, offer significant benefits for managing diabetes and improving overall health. A 2018 systematic review highlighted that these diets led to improvements in emotional and physical well-being, depression, quality of life, general health, HbA1c levels, weight, and cholesterol levels compared to control diets. Additionally, meta-analyses have shown that vegetarian diets are associated with reduced HbA1c levels, and other plant-based approaches like the Mediterranean and DASH diets also show promise in managing diabetes [2].

Recent research conducted a randomized clinical study focusing on individuals with type 2 diabetes mellitus (T2DM) to investigate the effects of a high-fiber diet on gut microbiota and emotional well-being, alongside exploring its impact on serum metabolism (Serum metabolism refers to the biochemical processes occurring within the blood serum of an organism. It contains a wide range of molecules, including glucose, proteins, lipids, hormones, electrolytes, and nutrients, crucial for various physiological functions.) The study revealed significant improvements in glucose homeostasis, serum metabolome, and emotional mood among participants following the high-fiber diet. Notably, beneficial gut microbes such as *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* increased in abundance, while opportunistic pathogens like *Desulfovibrio* and *Klebsiella* decreased. These alterations in gut microbiota induced by the high-fiber diet were associated with enhanced serum metabolism and emotional well-being in individuals with T2DM, underscoring the importance of dietary fiber in diabetes management [3].

The advantages of plant-based diets for diabetes prevention and management can be attributed to their high fiber content and inclusion of nutrient-dense foods like whole grains, legumes, nuts, green leafy vegetables, and fruits. Dietary fiber plays a crucial role in improving gut health by serving as a prebiotic for beneficial gut bacteria. This leads to the production of short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which have anti-inflammatory properties and regulate glucose and lipid metabolism. SCFAs exert their anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and promoting the generation of regulatory T cells, thus dampening inflammatory responses in the gut and systemically. Moreover, SCFAs act as signaling molecules that influence various physiological processes, including insulin sensitivity and lipid metabolism. Additionally, dietary fiber promotes satiety, aids in weight management, and helps stabilize blood sugar levels by slowing down glucose absorption. Soluble fiber forms a gel-like substance in the digestive tract, delaying gastric emptying and glucose absorption. This leads to a gradual rise in blood sugar after meals, preventing spikes and crashes, especially beneficial for individuals with diabetes. Moreover, the fermentation of dietary fiber in the colon produces SCFAs, which can directly stimulate the release of gut hormones involved in appetite regulation and satiety, further supporting weight management efforts. Overall, the influence of dietary fiber on the gut microbiome and its effects on satiety and glucose metabolism contribute to the positive outcomes of plant-based diets for diabetes management. By promoting the growth of beneficial gut bacteria and the production of SCFAs, dietary fiber exerts multifaceted effects on gut health, inflammation, and metabolic regulation, making it an essential component of a healthy diet for individuals with diabetes.

PPSP, Influence on Gut Microbiome and Diabetes Management

Before delving into the impact of PPSP (Probiotics, Prebiotics, Synbiotics, and Postbiotics) on gut health, immune function, and overall well-being, it is essential to understand the individual components that make up this holistic approach as mentioned in Table 1. Probiotics are live microorganisms that confer health benefits when consumed in sufficient quantities, commonly found in fermented foods and supplements. Prebiotics, on the other hand, are non-digestible fibers or compounds that nourish beneficial gut bacteria, promoting their growth and activity are commonly found in foods like chicory root, onions, garlic, and bananas. Synbiotics combine probiotics and prebiotics, synergistically enhancing the effectiveness of probiotics by providing them with their preferred food sources. Lastly, postbiotics refer to bioactive compounds or metabolic by-products generated by probiotics during fermentation, exhibiting diverse health-promoting effects such as supporting gut barrier function and modulating immune responses. Additionally, postbiotics contribute to metabolic health by influencing various metabolic processes. For example, SCFAs produced during fermentation have been found to regulate glucose and lipid metabolism by acting as signaling molecules that enhance insulin sensitivity, promote glucose uptake in peripheral tissues, and inhibit lipolysis in adipocytes. This helps improve glycemic control and reduce the risk of insulin resistance and dyslipidemia, which are common complications associated with metabolic disorders such as T2DM [4].

TABLE 1
Summarizes the definitions, roles, and differences between Probiotics, Prebiotics, Synbiotics, and Postbiotics (PPSP)

Component	Definition	Role	Difference in mode of action
Probiotics	Live microorganisms are found in fermented foods and supplements that offer health benefits.	Colonize the gut, support beneficial bacteria, and promote gut and immune health.	Live microorganisms; support existing gut flora.
Prebiotics	Non-digestible fibers are found in certain foods like onions and bananas, nourishing gut bacteria.	Act as food for beneficial gut bacteria, promoting their growth and activity.	Non-living fibers; support existing gut flora by providing nourishment.
Synbiotics	Combination of probiotics and prebiotics synergistically, enhancing their effectiveness.	Pair live beneficial microorganisms with their preferred food sources.	The combined approach; aims to improve the survival and activity of probiotics with prebiotic nourishment.
Postbiotics	Bioactive compounds, produced by probiotics during fermentation, promote gut health.	Include substances like short-chain fatty acids and enzymes.	Metabolic by-products; do not involve live microorganisms or fiber, but help in promoting gut health.

In summary, PPSP plays a vital role in promoting metabolic health by supporting gut barrier function, modulating immune responses, and regulating metabolic processes such as glucose and lipid metabolism. Their diverse health-promoting effects make them promising targets for therapeutic interventions aimed at preventing and managing metabolic disorders.

According to the results from experimental studies and clinical trials, probiotics, prebiotics, synbiotics, and postbiotics (PPSP) have shown alleviated effects on obesity, type 2 diabetes mellitus, and other metabolic diseases in most cases.

A study involving 8574 adults found that consuming yoghurt was associated with a lower risk of type 2 diabetes mellitus (HR: 0.73; 95% CI: 0.61, 0.88). However, concerns have been raised about the potential adverse effects of sugar-sweetened yoghurt. To explore the benefits of probiotics for type 2 diabetes, researchers are investigating new approaches. For example, using monk fruit extract as a sweetener in yoghurt may improve serum lipid levels more effectively than yoghurt alone, while avoiding the health risks linked to sugar. Additionally, certain prebiotic foods, such as *Lactobacillus* plantarum-fermented Momordica charantia juice, show promise in enhancing the anti-diabetic effects compared to their original forms. Given the role of gut bacterial metabolites in type 2 diabetes treatment, postbiotics are being considered as an alternative therapeutic option to probiotics, prebiotics, and faecal microbiota transplants [5].

In a clinical trial involving 50 patients with type 2 diabetes mellitus, daily consumption of 120 g of fermented milk containing *Bifidobacterium lactis BB-12* and *Lactobacillus acidophilus La-5* (109 CFU each) for 6 weeks resulted in improved serum levels of fructosamine, haemoglobin A1c

(HbA1c), and IL-10 [6]. Additionally, in a study with 68 patients, both *Lactobacillus reuteri ADR-1* and *ADR-3* strains were found to decrease serum levels of HbA1c and cholesterol, while regulating the abundances of *Bacteroidetes* and *Bifidobacterium*. The ADR-3 strain showed superior effects on reducing blood pressure and Firmicutes abundance compared to the ADR-1 strain [7]. Furthermore, in a study involving 70 patients, consumption of fermented milk processed by *Lactobacillus casei Shirota* for 16 weeks inhibited the translocation of gut bacteria into the bloodstream, leading to increased abundances of *Clostridium coccoides*, *Clostridium leptum*, and *Lactobacillus* in faecal samples [8]. Several meta-analyses also supported the benefits of probiotic treatment in improving HbA1c and fasting insulin levels [9,10].

Prebiotics have demonstrated potential in preventing type 2 diabetes by rebalancing gut microbiota [4]. In a randomized placebo-controlled trial with 46 patients, consuming 10 g/day of oligofructose-enriched inulin for 2 months resulted in improved glycemic status, lipid profiles, and immune biomarkers [11]. Additionally, synbiotic supplementation, particularly with Coix lacryma-jobi, has garnered attention for its ability to enhance the effects of probiotic yoghurt, leading to reductions in body weight and fasting blood glucose levels in individuals with type 2 diabetes mellitus [12].

In addition, insights from microbiome studies among non-Western diet populations have elucidated key changes in gut bacteria composition that correlate with conditions like obesity and type 2 diabetes mellitus. Concerning microbiomes in non-Western diet populations, a Japanese population study identified a similar rise in the percentage of *Firmicutes* to *Bacteroidetes* in the obese subjects and also identified five *Firmicutes* species associated with obese subjects and five *Bacteroidetes* species associated with non-obese subjects [13]. Combining probiotics with berberine significantly improved glycemic control in newly diagnosed type 2 diabetes patients compared to individual treatments or placebo. Understanding these microbiome shifts and their implications for metabolic health provides valuable insights into personalized approaches for diabetes management [14,15].

Gut Microbes, Metabolic Pathways and Diabetes Management

The gut microbiota is intricately involved in both the development and management of diabetes and hyperglycaemia, influencing various pathways crucial for glucose regulation. Dysbiosis, characterized by an imbalance in gut bacteria, can lead to reduced production of short-chain fatty acids (SCFAs), exacerbating insulin resistance and systemic inflammation. Targeting these pathways involves dietary interventions, such as increasing fiber intake and incorporating prebiotics to promote SCFA-producing bacteria. Probiotics containing strains like *Lactobacillus* and *Bifidobacterium* can improve gut barrier function and reduce inflammation. Furthermore, a deficiency in SCFA production, particularly in individuals with type 2 diabetes mellitus (T2DM), has been observed. A randomised clinical study highlighted that specific SCFA-producing strains, promoted by dietary fibers, led to improved outcomes in T2DM patients, partly through increased glucagon-like peptide-1 (GLP-1) production. This approach not only improved haemoglobin A1c levels but also reduced the production of metabolically detrimental compounds, suggesting that targeted restoration of SCFA producers offers a novel ecological approach for managing T2DM and underscores the potential of dietary interventions in modulating gut microbiota composition to enhance metabolic health [13]. Furthermore, the gut microbiota influences glucose metabolism through bile acid metabolism, regulation of enteroendocrine cells [16], and the metabolism of dietary components. Modulating the composition of gut bacteria can affect bile acid metabolism, with certain probiotic strains demonstrating promising effects in this regard. Modulating the composition of gut bacteria with probiotics or dietary interventions can affect bile acid metabolism. For example, certain probiotic strains like *Lactobacillus rhamnosus GG* have been shown to influence bile acid metabolism [17].

Conclusion

In conclusion, the interplay between diet, gut microbiome, and innovative PPSP interventions offers a multifaceted approach to diabetes management. Leveraging the synergistic benefits of plant-based diets, probiotics, prebiotics, and postbiotics holds immense promise in enhancing overall health and well-being while empowering individuals in their journey towards optimal diabetes control. Plant-based diets, rich in fiber, vitamins, and antioxidants, contribute significantly to improved glycemic control, weight management, and overall cardiovascular health. Probiotics, prebiotics, and postbiotics further enhance these benefits by promoting a healthy gut environment, optimizing nutrient absorption, and modulating metabolic processes.

Probiotics, such as *Lactobacillus* and *Bifidobacterium* strains, have demonstrated the ability to improve insulin sensitivity, reduce inflammation, and support immune function. Prebiotics like inulin and oligofructose serve as fuel for beneficial gut bacteria, aiding in the production of short-chain fatty acids that play a crucial role in glucose regulation and energy metabolism. Postbiotics, including metabolites and microbial components, exert direct therapeutic effects on metabolic pathways, contributing to improved glycemic control and reduced risk of diabetic complications.

By adopting a comprehensive approach that combines plant-based nutrition with targeted PPSP interventions, individuals with diabetes can experience significant improvements in their overall health and well-being. This integrated approach not only addresses the physiological aspects of diabetes management but also empowers individuals to make informed dietary choices and lifestyle modifications that support long-term health outcomes.

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