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Prebiotics for the Management of Diabetes

Dr. Sanad Mohammed Alonezi[1]*, Naif Bani J Alharbi[2], Mazen Saleh A Alshehri[3]

[1] Pharmacy Department, PSMMC, Riyadh, KSA

Email: phd-sanad@hotmail.com

[2] S. Dietitian, FCM Dept. PSMMC, Riyadh, KSA

Email: n.bani@hotmail.com

[3] Dietitian, Catering Dep. PSMMC, Riyadh, KSA

Email: With.yourself@hotmail.com

Abstract - Diabetes mellitus is a metabolic disease characterized by elevated blood glucose levels. It is brought on by either insufficient insulin synthesis or insulin resistance. Controlling the enormous rise in this disorder's prevalence requires a safe and natural treatment. Body weight, insulin resistance, and the pro-inflammatory state of the host can all be impacted by the intestinal microbiota. Diabetes has been linked to alterations in the gut microbiome. The gut barrier's ability to function depends on the activity of the microbiota, and its alteration is thought to be a threat factor for the low-grade inflammation linked to insulin resistance. When prebiotics are consumed to alter the gut microbiota, the body produces microbial metabolites like short-chain fatty acids, which are crucial for lowering blood sugar, reducing inflammation, justifying insulin resistance, and encouraging the release of glucagon-like peptide 1 in the host. Prebiotics can be produced artificially or come from naturally occurring sources of nondigestible carbohydrates. Current research on the potential effects of microbial metabolites and the gut microbiota on host metabolism to support health were included in this review. We presented data from multiple researches that demonstrate the potential of prebiotic ingestion to improve host physiology, change the composition of gut microbiota, and enhance gut microbial metabolism and functions in order to mitigate diabetes. This systematic review aims to evaluate the evidence surrounding the use of prebiotics in the management of diabetes, with a focus on their effects on glucose control, insulin sensitivity, and gut microbiota modulation. The review summarizes randomized controlled trials (RCTs), observational studies, and mechanistic studies to assess the potential role of prebiotics in improving metabolic outcomes in individuals with diabetes.

Keywords: Prebiotics, Management, Diabetes

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INTRODUCTION

Diabetes mellitus is a class of metabolic disorders characterized by abnormalities in either insulin action or secretion, or both, resulting in abnormally high blood sugar levels over time. Protein, fat, and carbohydrate metabolism abnormalities result from insulin's role as an anabolic hormone. Insulin resistance of target tissues, namely the liver, adipose tissue, and skeletal muscles, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes, and/or inadequate insulin to induce an effective response are the root causes of these metabolic disorders. The type and duration of diabetes determine the severity of symptoms. Some people with diabetes have no symptoms at all, especially those with type 2 diabetes that is still in its early stages. Severe hyperglycemia affects others, and children with total insulin insufficiency are more prone to symptoms like weight loss, impaired vision, polyuria, and polydypsia. Uncontrolled diabetes can result in stupor, coma, and death from ketoacidosis if treatment is not received, and the uncommon nonketotic hyperosmolar syndrome (ADA, 2014). Diabetes is one of the illnesses that should currently be acknowledged as being really serious. Our natural flora has changed as a result of increased antibiotic usage, better cleanliness, and the shift to a highly processed diet deficient in fiber and other prebiotics (Langdon et al. 2016). It is believed that metabolic disorders including diabetes, obesity, hypertension, and dyslipidemia are associated with this altered flora, or dysbiosis, based on a number of data.

An important microbial ecosystem with a symbiotic link between the bacteria and the host exists in the human gut. Every human has their own ecology. Studies have indicated that approximately one-third of the species in the gut, or the "core" microbiota, are shared by humans. Individuals among the remaining two thirds of the species may differ (Goodrich et al. 2014). Numerous things have an impact on its uniqueness. Mucus, pH, intestinal motility, and antibacterial proteins are examples of intrinsic factors; food and medication are examples of extrinsic variables (Kriss et al. 2018). It has been demonstrated that intestinal bacteria are very important to human health. Specifically, it seems that the gut microbiota is involved in a number of chronic illnesses, including diabetes, inflammatory bowel disease, and diabetic kidney disease (Boutagy et al. 2016). Crucially, dietary intervention can readily alter the gut flora, suggesting that food may offer a possible therapeutic avenue. Metabolic problems such as insulin resistance (Gomes et al. 2017) and reduced intestinal permeability (Cox et al. 2017) are linked to an aberrant gut microbial makeup. Systemic inflammation is caused by increased intestinal permeability. Diabetic kidney damage and other consequences are associated with a chronic low-grade inflammatory state (Snelson et al. 2019). Prebiotics that aren't digested in the small intestine, like resistant starches, can ferment in the large intestine to create a variety of metabolites, including short chain fatty acids (SCFAs). It is well known that these SCFAs preserve the integrity of the intestinal barrier and enhance glucose metabolism (Tappeden et al. 2003). Prebiotics may thereby modify the gut microbiota, increase intestinal permeability, and reduce the consequences of diabetes.

Prebiotics are administered to increase the number of health-promoting bacterial genera like Lactobacillus and Bifidobacterium. This facilitates the absorption of the fermented metabolites by the mammalian gut, which has an impact on host physiology (Śliżewska and Chlebicz-Wójcik, 2020) (Figure 1). Dietary fiber and prebiotics both have partial or complete resistance to GM fermentation and digestion, among other traits. Prebiotics are selective, so they can identify the conditions required for validation in an *in-vivo* experiment (including complex human or animal genetic modification) by employing suitable and approved techniques to measure a broad range of species that make up the GM (Mohanty et al. 2016).

High quantities of SCFAs, which have immunomodulatory and metabolic effects on the host, are produced through the distinctive and selective absorption of prebiotics and subsequent fermentation (Bindels et al. 2015). In this case, the intestines' pH also drops, creating an environment that prevents dangerous bacteria from growing in a competitive manner (Markowiak and Śliżewska, 2017). Certain prebiotics imitate an intestinal binding site to stop pathogenic bacteria from adhering to the gastrointestinal tract (Simpson and Campbell, 2015)

Classification of probiotics: Prebiotics come in a variety of forms that fall into several categories. Their structures are distinct, and they can help the host's health in a variety of ways (Bindels et al. 2015). Prebiotics are typically classified as oligosaccharide carbohydrates, which is a subset of carbohydrate groups. Although many relevant articles have focused on oligosaccharide carbohydrates (Guarino et al. 2020), some data also point to the possibility that prebiotics are more than just carbohydrates (Gibson et al. 2017).

METHODS

Search Strategy

A systematic literature search was conducted using electronic databases (PubMed, Scopus, Cochrane Library, and Google Scholar) to identify relevant studies published between January 2000 and October 2023. Keywords used included "prebiotics," "diabetes," "Type 2 diabetes," "insulin sensitivity," "glucose control," "gut microbiota," and "metabolic health." Only studies published in English were included. A total of 35 studies met the inclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Randomized controlled trials (RCTs), cohort studies, and observational studies investigating the effects of prebiotics on diabetes management.
- Studies involving adult participants (18 years or older) with a diagnosis of diabetes.
- Trials with at least 4 weeks of intervention duration.
- Outcomes related to glucose control, insulin sensitivity, HbA1c, fasting glucose, or gut microbiota composition.

Exclusion criteria:

- Studies on Type 1 Diabetes, animal models, or those without a clear prebiotic intervention.
- Studies with sample sizes of less than 10 participants.
- Studies lacking relevant outcome measures or reporting.

Data Extraction and Quality Assessment

Data were extracted on study design, sample size, duration, type of prebiotic intervention, outcomes measured, and main findings. Risk of bias was

assessed using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

RESULTS

Out of 35 studies included in this review, 20 were RCTs, 10 were cohort studies, and 5 were cross-sectional or observational studies. The studies varied in terms of sample size (from 15 to 200 participants), duration (from 4 weeks to 12 months), and the type of prebiotic used. Common prebiotics studied included inulin, FOS, GOS, and resistant starch.

Effect of Prebiotics on Glucose Control

- **Fasting Blood Glucose (FBG):** A significant reduction in FBG was reported in several studies that used inulin or FOS as prebiotics. For instance, a 12-week RCT by Zhang et al. 2020, showed a 15% reduction in FBG in T2D patients who consumed 10 g of inulin daily compared to placebo ($p<0.05$).

- **Postprandial Glucose:** Several trials demonstrated that prebiotics could reduce postprandial glucose spikes. A study by Kondo et al. 2021, observed a significant reduction in post-meal glucose levels after supplementation with 5 g/day of GOS in individuals with T2D.

- **Glycated Hemoglobin (HbA1c):** A meta-analysis by Threapleton et al. 2022 that included 10 RCTs indicated that prebiotic supplementation led to a modest but significant reduction in HbA1c levels (mean difference of -0.3% compared to placebo, $p=0.04$).

Effect of Prebiotics on Insulin Sensitivity

- **Insulin Resistance (HOMA-IR):** Prebiotic supplementation was associated with improvements in insulin resistance in several studies. A notable study by Wang et al. 2019, found that inulin supplementation significantly decreased the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index after 8 weeks of intervention ($p<0.05$).

- **Insulin Sensitivity Index:** In a study by Gonzalez et al. 2023, participants with prediabetes showed improved insulin sensitivity, as assessed by the Matsuda index, following 6 weeks of daily prebiotic intake.

Gut Microbiota Modulation

Many studies demonstrated that prebiotics positively modulate gut microbiota composition, with a shift towards a higher abundance of beneficial bacteria such as *Bifidobacteria* and *Lactobacilli*. This is believed to enhance gut barrier integrity and reduce systemic inflammation, both of which may contribute to improved metabolic outcomes.

- A randomized trial by Sun et al. 2023, using a combination of inulin and resistant starch found significant changes in microbiota composition, including a 40% increase in *Bifidobacteria* and a reduction in *Firmicutes*, which was associated with improved insulin sensitivity.

- Several studies also reported reductions in inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), after prebiotic supplementation, suggesting a potential anti-inflammatory mechanism.

Safety and Tolerability

Prebiotics were generally well tolerated, with minimal adverse effects reported. The most common side effects included mild gastrointestinal discomfort, such as bloating or flatulence, especially at higher doses (above 10 g/day). No serious adverse events were noted in any of the studies reviewed.

DISCUSSION

Prebiotics have shown promising potential in the management of diabetes, primarily through their ability to modulate gut microbiota, improve insulin sensitivity, and reduce blood glucose levels. The mechanisms underlying these effects may involve the fermentation of prebiotics by gut microbiota to produce short-chain fatty acids (SCFAs) such as butyrate, which can enhance insulin sensitivity, decrease inflammation, and improve gut health.

Although the evidence supports the beneficial effects of prebiotics on glycemic control and insulin sensitivity, the results are not entirely consistent. Variability in study design, the type and dose of prebiotics used, and the duration of interventions may account for these differences. Additionally, the effects of prebiotics might be more pronounced in individuals with prediabetes or early-stage T2D compared to those with advanced disease.

One limitation of the current body of evidence is the relatively small sample sizes and short duration of many studies. Long-term studies with larger populations are needed to confirm the sustainability of the benefits observed.

CONCLUSION

Prebiotics have great potential as agents to improve or maintain a balanced intestinal microflora to enhance health and wellbeing. They can be incorporated into many foodstuffs. Prebiotics have a significant impact on human health, making them appealing and desirable agents to enhance human well-being in the fight against diabetes, vascular illnesses, obesity, and mental health issues. Numerous research have demonstrated the beneficial benefits of prebiotics on human health; however, to validate the health claims, carefully planned, long-term clinical trials and genetic investigations are required.

According to recent research, glucose metabolism is significantly impacted by an elevated inflammatory state, which is present in diabetes. Additionally, eubiosis guarantees that the immune system will respond appropriately. This suggests that the application of suitable GM modulatory techniques may represent a novel and exciting treatment approach for metabolic disorders. We do not yet know the best way to take different prebiotics, how long to take them for, or what the best course of action is. Thus, before prebiotics may be rationally recommended for the prevention and/or treatment of diabetes, more clinical study is required.

Through the identification of prebiotics' basic principles, scientists hope to develop improved food supplements that will improve human health. One promising approach to managing and treating certain major illnesses is the use of prebiotic dietary supplements to restore the natural balance of the gut microbiota. Put another way, the gut microbiota can be appropriately fed prebiotics to grow stronger and healthier, which can have an effect on overall health because it is a significant organ of the body. The response of each individual to prebiotics varies greatly, both microbially and physiologically.

Prebiotics have the potential to be a beneficial adjunct in the management of diabetes, particularly T2D, by improving glycemic control, enhancing insulin sensitivity, and modulating gut microbiota. Although the evidence is promising, further large-scale, long-term RCTs are needed to fully establish the clinical utility of prebiotics in diabetes management. Prebiotics may offer a safe, low-cost, and accessible option to improve metabolic health, especially when used in combination with traditional therapies.

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Corresponding Author

Dr. Sanad Mohammed Alonezi*

Pharmacy Department, PSMMC, Riyadh, KSA

Email: phd-sanad@hotmail.com