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The Potential Role of Probiotic Supplementation in Glycemic Management of Adults with Type 2 Diabetes Mellitus

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Abstract. Type 2 diabetes mellitus (T2DM) is a common metabolic disease, and long-term glycemic control can help reduce the risk of complications. Probiotic supplementation has been studied as a complementary approach in T2DM, though its effects on glycemic control have varied across studies. This paper evaluates the effects of probiotic supplementation on glycated hemoglobin (HbA1c), fasting blood glucose, fasting insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) in patients with T2DM, and explores the potential mechanisms underlying these effects and possible reasons for the inconsistent findings across studies. Existing evidence suggests that probiotics may modestly improve fasting blood glucose, HbA1c, and markers of insulin resistance, but the magnitude of these effects appears limited. However, variations in study findings may be related to factors like probiotic intervention protocols, subject characteristics, and research methodologies. Thus, probiotic supplementation may support glycemic management in patients with T2DM, but it cannot replace established treatments. Larger, longer-term, and standardized randomized controlled trials are needed to clarify its clinical significance and long-term effects.

Keywords: Probiotic supplementation, Type 2 diabetes mellitus, Glycemic control, HbA1c, Insulin resistance

1. Introduction

Type 2 diabetes mellitus (T2DM) is mainly characterized by insulin resistance and relative insulin secretion deficiency [1]. Chronic hyperglycemia can damage the kidneys, eyes, and other organs, increasing the risk of diabetes-related complications [2]. Thus, improving and maintaining glycemic control is a key objective in the management of T2DM [3]. The gut microbiota of individuals with T2DM differs from that of healthy individuals [4, 5]. This difference may affect glucose metabolism by altering intestinal permeability, inter-organ signaling, and microbial metabolites [6]. Therefore, targeting the gut microbiota has gained attention as a potential approach to T2DM management. Prior studies suggested that probiotic supplementation may improve glycemic biomarkers and could serve as an adjunctive intervention for glycemic control [7]. However, study results have varied, with certain clinical trials failing to observe significant improvements in glycemic indicators [8]. Thus, the efficacy of probiotic supplementation in glycemic management in patients with T2DM requires further evaluation. This study evaluated the effects of probiotic supplementation on fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), fasting insulin, and the homeostatic model

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assessment of insulin resistance (HOMA-IR) in adult patients with T2DM, and explored the potential mechanisms of these effects as well as the factors that might lead to differences in the results. By reviewing evidence from mechanistic studies, randomized controlled trials (RCTs), and systematic reviews and meta-analyses, this study examines existing evidence to assess the potential value of probiotics as an adjunctive intervention and provide recommendations for future research.

2. Potential mechanisms underlying the effects of probiotics on glycemic control

2.1. Regulation of gut microbiota and intestinal function

Prior studies have shown that certain probiotics may regulate the gut microbiota by competitively excluding pathogens or producing antimicrobial substances after entering the gastrointestinal tract [9]. Beyond their impact on the microbiota, probiotics may also contribute to maintaining intestinal barrier function. The intestinal barrier, primarily composed of the mucus layer, intestinal epithelial cells, and intercellular tight junctions, serves as a key defense against harmful substances from the gut lumen. Some studies suggest that certain probiotics may promote mucin production, supporting the protective role of the mucus layer and helping maintain intestinal barrier integrity [10]. In turn, improved barrier function could potentially reduce translocation of bacterial components such as lipopolysaccharides (LPS) into the bloodstream, providing a foundation for subsequent modulation of inflammatory responses. However, much of the mechanistic evidence comes from animal or in vitro studies, and whether probiotics can consistently modulate the gut microbiota and ameliorate barrier function in individuals with T2DM remains to be confirmed by further clinical studies [10].

2.2. Regulation of inflammation and insulin sensitivity

As gut microbiota dysbiosis and impaired intestinal barrier function develop, intestinal permeability may increase, and the levels of pro-inflammatory cytokines, chemokines and inflammatory proteins in patients with T2DM will also rise. In particular, certain gut microbes and their related products, particularly LPS, can induce metabolic endotoxemia and low-grade inflammation, and the resulting chronic low-grade inflammation may disrupt insulin signaling in major metabolic organs such as the liver, muscle, and adipose tissue, reducing tissue insulin sensitivity [11]. Thus, gut microbiota-associated inflammation may link gut microbiota changes to insulin resistance. In turn, probiotics may reduce this inflammatory process by inflammatory signaling in immune cells and reducing the release of pro-inflammatory cytokines. For example, Sun et al. reported in vitro that Lactobacillus paracasei treatment attenuated LPS-induced TNF-α and IL-1β secretion while reducing NF-κB translocation to the nucleus. The study further indicates that this effect is related to the increased expression of negative regulatory factors of NF-κB signaling pathway [12]. This reveals the anti-inflammatory effects of certain probiotics. However, since this study did not directly examine the changes in insulin sensitivity in adults with T2DM, further validation is still needed through relevant clinical studies to determine whether these anti-inflammatory effects can further improve the insulin resistance of patients.

2.3. Role of microbial metabolites in glucose metabolism

Gut microbes make short-chain fatty acids (SCFAs) by fermenting indigestible carbohydrates, such as dietary fiber, mainly producing acetate, propionate, and butyrate. Beyond their role as microbial metabolites, SCFAs also act as signaling molecules in host metabolism. By activating receptors on

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enteroendocrine cells, SCFAs promote the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). GLP-1 delays gastric emptying and promotes glucose-dependent insulin secretion, increasing insulin secretion by pancreatic β-cells in response to elevated blood glucose levels [13]. These effects may help regulate postprandial glycemia and explain how gut microbial metabolites influence glucose homeostasis. By modulating gut microbiota composition and metabolic activity, some probiotics may alter SCFA production. For example, Li et al. found in a mouse model of T2DM that supplementation with Lactobacillus casei CCFM419 restored SCFA levels, along with modulation of the gut microbiota and improved insulin sensitivity [14]. This suggests that SCFA metabolism may be involved in the metabolic effects. Yet, these changes occur simultaneously and are insufficient to prove that SCFAs are the direct cause of the observed effects, nor can they show that all probiotics produce the same effects. Beyond influencing gut hormone secretion, SCFAs may also affect inflammatory responses and insulin sensitivity. For instance, Chang et al. found that butyrate inhibits histone deacetylase activity and reduces inflammatory mediators such as IL-6 and IL-12 released by macrophages following LPS stimulation [15]. However, not all inflammatory mediators decreased, suggesting that butyrate may have differential effects. Gao et al. found in mice fed a high-fat diet that butyrate supplementation improved insulin sensitivity [16]. These findings show that butyrate may have anti-inflammatory and metabolic effects, although whether probiotics can exert similar effects by altering butyrate levels in adults with T2DM remains unclear.

3. Effects of probiotic supplementation on glycemic control in T2DM

3.1. Effects of probiotic supplementation on fasting blood glucose

In the systematic review by Hejazi et al., 32 randomized controlled trials were included to assess the effects of probiotic supplementation on glycemic indicators in adults with T2DM [7]. Compared with the controls, probiotic supplementation lowered FBG by an average of 13.27 mg/dL (95% CI: −18.31 to −8.22), equivalent to around 0.74 mmol/L. As the confidence interval did not include 0, the reduction was statistically significant, suggesting a modest glucose-lowering effect. However, this represents the average effect of multiple studies, but it does not mean that every patient will experience the same degree of improvement.

Similarly, Li et al. reported lower FBG levels in the probiotic group in a meta-analysis of 30 randomized controlled trials involving 1,827 patients. FBG was lower in the probiotic group than in the placebo group (SMD = −0.331, 95% CI: −0.424 to −0.238) [17]. However, because Li et al. used standardized mean differences rather than the original units, the effect size cannot be directly compared numerically with the reduction reported by Hejazi et al. [7, 17]. While both meta-analyses support a reduction in fasting blood glucose, statistical significance does not necessarily indicate a clear clinical benefit. Notably, Hejazi et al. reported substantial heterogeneity among the included studies and rated the overall evidence as low quality. Thus, probiotic supplementation may serve as an adjunct to T2DM management, but the consistency, long-term benefits, and clinical applicability of these effects remain uncertain and require confirmation in higher-quality clinical trials.

3.2. Effects of probiotic supplementation on HbA1c

Regarding long-term HbA1c, the meta-analysis conducted by Hejazi et al. indicated that probiotic supplementation reduced HbA1c levels in adults with T2DM by 0.44 percentage points compared with controls (95% CI: −0.59 to −0.28) [7]. This suggests that probiotics may modestly improve long-term glycemic control. However, individual clinical trials have shown inconsistent results. For

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example, a 12-week randomized controlled trial by Cuthill et al. reported that after supplementing with probiotics, there was no significant improvement in HbA1c or other metabolic indicators [8]. Based on current evidence, probiotics may modestly reduce HbA1c levels in adults with T2DM, but the clinical significance of this reduction remains uncertain. These differences among studies may be related to variations in probiotic strains, participant characteristics, and intervention protocols. Further well-designed clinical trials are needed to determine whether probiotic supplementation can produce meaningful and sustained improvements in long-term glycemic control.

3.3. Effects of probiotic supplementation on insulin resistance

Regarding insulin resistance-related outcomes, fasting insulin and HOMA-IR are commonly used surrogate measures related to insulin resistance. Evidence from a meta-analysis of 32 randomized controlled trials showed that probiotic supplementation significantly reduced both fasting insulin and HOMA-IR, by 1.33 μIU/mL (95% CI: −2.57 to −0.08) and 0.95 (95% CI: −1.71 to −0.18), respectively, compared with controls [7]. Similarly, Li et al. observed reductions in fasting insulin (SMD = −0.185, 95% CI: −0.313 to −0.056) and HOMA-IR (SMD = −0.224, 95% CI: −0.342 to −0.105) [17]. The evidence for HOMA-IR was further supported by Ding et al., who reported a significant reduction across 10 studies involving 523 participants (SMD = −0.36, 95% CI: −0.62 to −0.10), although moderate heterogeneity was present across studies (I^2 = 53%) [18].

Despite these findings, the magnitude and interpretation of the observed effects warrant careful consideration. The available evidence suggests that probiotic supplementation may exert a modest beneficial effect on markers of insulin resistance. However, the reduction in fasting insulin appears limited, and HOMA-IR, as an indirect measure based on fasting glucose and insulin levels, may not fully reflect tissue-specific insulin sensitivity. Thus, although probiotic supplementation shows potential for improving insulin resistance in adults with T2DM, the stability and clinical relevance of these effects require confirmation through larger and well-designed clinical trials.

4. Factors influencing the findings and limitations of the available evidence

4.1. Intervention-related factors

Differences in probiotic strains may partly explain the variability in findings across studies. This may be consistent with the strain-specific nature of probiotic effects, as even strains within the same species can differ in metabolic activity and interactions with the host. In a subgroup analysis, Li et al. found different response patterns in studies using bifidobacteria compared with other probiotic preparations [17]. However, these differences cannot be attributed to strain selection alone, given the variation in baseline characteristics, co-interventions, and other study conditions, as well as the limited number of trials in some subgroups. Thus, observed differences between probiotic strains should be interpreted in the context of these potential sources of variation.

Beyond strain selection, variability in intervention intensity and delivery may provide additional explanations for differences between studies. Dose and intervention duration varied across trials, yet subgroup analyses have not shown a consistent dose-response or duration-response pattern. Li et al. found no significant differences between high- and low-dose interventions or between interventions lasting more or less than 8 weeks, while Hejazi et al. found that longer interventions were linked to greater reductions in FBG [7, 17]. Such differences may reflect variations in probiotic preparations, populations, outcomes, or assessment timing, thus making the effects of dose or duration difficult to isolate. Moreover, the form of probiotic delivery may introduce similar complexity. For instance, Li

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et al. reported differences between food-based and non-food-based interventions [17]. However, food-based preparations also contain nutrients and other components that may affect the observed response, and differences in the control food may further affect between-group comparisons. Thus, variation in the delivery form may reflect differences in the overall intervention composition rather than the probiotic vehicle itself.

4.2. Participant-related factors

Differences in participant characteristics may partly explain the variability in responses to probiotic interventions. Li et al. found in a subgroup analysis that participants with obesity (BMI ≥ 30 kg/m^2) showed greater changes in FBG and HbA1c than those with lower BMI [17]. They suggested that this difference might be related to obesity-associated gut microbiota dysbiosis; but this explanation remains hypothetical and may also reflect differences in baseline metabolic characteristics between subgroups. Similarly, the ethnicity-stratified analysis showed a comparable pattern, in which the White subgroup showed greater changes in FBG and HbA1c than the Asian subgroup, but also had a substantially higher mean BMI [17]. Thus, the observed differences cannot readily be attributed to ethnicity alone, as BMI and other metabolic characteristics may partly explain the variation in response. Besides, baseline glycemic status, diabetes duration, and the severity of insulin resistance may likewise influence probiotic responses and should be considered when comparing findings across study populations.

In addition, differences in participants' concomitant medication use and dietary background may partly underlie the variability between studies. Notably, metformin, a commonly used antidiabetic medication, has been shown to alter the composition and function of the gut microbiota, potentially modifying the host environment in which probiotic interventions act [19]. Accordingly, differences in antidiabetic medication regimens or changes in medication use during follow-up may influence metabolic outcomes and obscure the effects attributable to probiotic supplementation. Dietary patterns may have similar effects, particularly when habitual diets or concurrent dietary guidance differ between study populations. When medication use and dietary background are inadequately reported or poorly controlled, their contribution to differences in probiotic responses cannot be clearly separated from that of the intervention itself.

4.3. Study design-related factors

The current evidence base is characterized by limitations in sample size, intervention duration, and participant representativeness, which may restrict conclusions regarding the long-term effects of probiotic supplementation. Though Li et al. included a total of 30 randomized controlled trials and 1,827 participants, some individual trials included relatively small sample sizes, which may have limited statistical power and increased uncertainty in the findings. Furthermore, most trials lasted between 4 to 24 weeks, with only one reaching 36 weeks, making it difficult to assess whether the observed improvements in glycemic control can be sustained long-term [17]. Besides, the included studies were geographically unevenly distributed, with certain populations underrepresented, which may restrict the applicability of the findings to diverse populations of adults with T2DM.

Meanwhile, differences between studies also increase the difficulty of interpreting the results. Indeed, Hejazi et al. pointed out that the included studies exhibited significant heterogeneity and low-quality evidence [7]. Therefore, although the pooled results suggest that probiotics may have certain auxiliary effects, caution is still needed to observe the stability and long-term significance of these effects. Future studies should involve larger and more diverse populations, longer study

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durations, and more standardized randomized controlled trials to determine whether the effects of probiotic supplementation can be sustained over time and whether these findings are generalizable to broader patient populations.

5. Conclusion

Based on the current research evidence, probiotic supplementation can have a certain improvement effect on FBG, HbA1c, fasting insulin, and HOMA-IR in adult patients with T2DM. However, the overall effect is relatively small, and there is considerable heterogeneity among different studies. Thus, probiotics may have a potential adjunctive role in glycemic management, but they should not be considered a substitute for standard diabetes treatment. Existing studies show that the effects of probiotics may be related to regulating the intestinal microbiota, improving the intestinal barrier function, influencing inflammatory signaling pathways, and regulating microbial metabolites like short-chain fatty acids. However, most mechanistic evidence comes from animal and in vitro studies, and these mechanisms require further clinical validation in adults with T2DM. In addition, differences in probiotic strains, intervention protocols, and participant characteristics may underlie variations in treatment responses. It is not clear whether the improvement effect produced by probiotics is durable and can be transformed into clinically significant benefits. Future randomized controlled trials should use larger samples, longer follow-up periods, and standardized protocols to clarify the optimal probiotic strains, doses, and intervention durations and their clinical significance.

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