Combined Use of Probiotics and Vitamin D in Gestational Diabetes Mellitus

Yanqing Chen

Department of Westa College, Southwest University, Chongqing,400715, China

cyq0112@email.swu.edu.cn

Abstract. Gestational diabetes mellitus (GDM) is a common pregnancy complication with significant health implications for both mother and child. This review explores the potential of probiotics and vitamin D supplementation as therapeutic strategies for managing GDM. Probiotics, beneficial gut bacteria, have been shown to improve glucose and lipid metabolism, reduce insulin resistance, and modulate the gut microbiota in GDM patients. Essential for the regulation of calcium homeostasis and the control of immune responses, vitamin D also possesses the ability to mitigate inflammation and boost insulin sensitivity. Additionally, its deficiency is frequently observed in GDM cases. Studies indicate that combining probiotics and vitamin D supplementation yields synergistic benefits, effectively improving blood sugar control, lipid profiles, and antioxidant status in GDM patients. This review highlights the promising therapeutic potential of probiotics and vitamin D in GDM management and highlights the imperative for additional investigation to refine therapeutic approaches and enhance the health outcomes for individuals with GDM.

Keywords: Gestational diabetes mellitus, vitamin D, Probiotics.

1. Introduction

Gestational Diabetes Mellitus (GDM) refers to a condition where pregnant women with normal glucose and lipid metabolism before pregnancy or with potential impaired glucose tolerance develop varying degrees of metabolic disorders, which can significantly increase the risk of metabolic diseases in both mothers and infants in the short and long term [1]. GDM is one of the most common pregnancy complications, with over 80% of diabetic pregnancies being GDM, while less than 20% are diagnosed with diabetes before pregnancy. The global average prevalence of GDM is nearly 20%, with a prevalence rate of 14.8% in mainland China, showing a trend of increasing annually. GDM can lead to hyperglycemia in pregnant women, increasing the risk of cardiovascular diseases and adverse pregnancy outcomes such as spontaneous abortion, gestational hypertension, and macrosomia [2].

Probiotics are microorganisms that can colonize the human gut and are beneficial to health, and they can be used to improve the structure of the gut microbiota and effectively regulate the body's glucose and lipid metabolism [3]. Vitamin D (VitD) is an essential substance for maintaining normal human function. It plays a crucial role in not just facilitating the uptake of calcium and phosphorus for calcium homeostasis, but it also exerts anti-inflammatory properties. Additionally, it can decrease insulin resistance in expectant mothers, thereby enhancing insulin sensitivity and effectively managing blood glucose levels among those with gestational diabetes mellitus [4]. The main causes of GDM are insulin resistance and dysfunction of pancreatic β-cells, with insulin being the primary clinical medication; however, GDM patients may have insulin resistance, and insulin cannot regulate blood glucose in their bodies. Current studies suggest that supplementing with probiotics can regulate blood glucose during pregnancy and reduce the incidence of GDM. However, the efficacy of probiotics in lowering fasting blood glucose in GDM patients is minimal, and the issue of controlling blood glucose fluctuations in GDM patients with probiotics remains unresolved. There are few researches on the combined effect of probiotics and VitD on GDM patients' blood glucose, lipid levels, and pregnancy outcomes. Therefore, this paper aims to study the effects of probiotics used alone and in combination with VitD on the glucose and lipid metabolism and pregnancy outcomes of GDM patients.

2. The Relationship Between Pregnant Women and Gut Microbiota

2.1. The Therapeutic Mechanism of Probiotic Supplementation for GDM

Studies have shown that human health heavily relies on the role of gut microbiota. These microbial communities are crucial for participating in key physiological activities, including the metabolism of nutrients, regulation of the immune system, and maintenance of the integrity of the gut barrier. They are closely connected to our immune, nervous, and endocrine systems through symbiotic relationships, competitive mechanisms, and mutual interactions, ensuring the normal functioning of various physiological processes [5].

Probiotics may enhance metabolic health in GDM patients by various mechanisms, including the regulation of IR, boosting antioxidant levels, modulating IP, and suppressing inflammatory processes [6]. The precise cause of GDM remains elusive, but OS and inflammation are pivotal in its progression. OS and inflammation are interconnected; ROS can stimulate inflammatory cells and upregulate inflammatory mediators, which can further elevate ROS levels, creating a cycle. Inflammation can be mediated through the NF-κB pathway activation [6, 7].

An imbalance between ROS production and antioxidant defenses results in OS. Inflammation is a defense mechanism against infections and other harmful stimuli. OS can trigger apoptosis, damage ATP channels, and inhibit transcription factors like PDX1 and MAFA, as well as disrupt mitochondrial function, all of which can decrease insulin secretion. Conversely, OS can impair insulin signaling, leading to decreased insulin sensitivity in peripheral tissues. ROS and OS can also activate serine kinases, reducing IR and IRS family tyrosine phosphorylation in response to insulin, thus weakening its effect. Furthermore, OS can decrease Glut-4 expression and content in AT and SM, reducing cellular glucose uptake and causing IR. OS can also disrupt insulin production and signaling by exacerbating inflammatory responses. Research indicates that eight weeks of probiotic intake can lower serum hs-CRP, TNF-α, erythrocyte GPX, and MDA levels, while increasing GR content, suggesting that probiotics work by inhibiting the NF-κB pathway to alleviate OS [8].

2.2. Gut Microbiota Characteristics in GDM Patients

The gut microbiota is closely related to human health, maintaining a dynamic balance and playing an important role in metabolism. Insulin resistance and metabolic disorders during pregnancy may lead to an imbalance in the gut microbiota of pregnant women. In a randomized controlled study of 175 pregnant women, the GDM group had higher rates of Enterobacteriaceae and yeast positivity than the control group, and lower rates of Bifidobacteria, Lactobacillus, and Bacteroides positivity [2]. In the third trimester of pregnancy, the GDM group showed an increase in the ratio of Firmicutes to Bacteroidetes at the phylum level compared to the non-GDM group. Research has shown that an elevated Firmicutes to Bacteroidetes (F/B) ratio correlates with obesity and intensified chronic low-grade inflammation. This implies that the gut microbiome in gestational diabetes mellitus (GDM) patients might be disrupted, featuring a surge in detrimental microbes (including Enterobacteriaceae and yeast) and a decline in advantageous species (such as Bifidobacteria, Lactobacillus, and Bacteroides). This alteration in bacterial composition may affect the host's metabolic and immune state, leading to an increase in inflammatory responses that may contribute to the development of metabolic diseases such as diabetes. Moreover, beneficial bacteria like Bifidobacteria and Lactobacillus typically participate in carbohydrate metabolism and help maintain stable blood sugar levels. The reduction of these bacteria may lead to decreased blood sugar regulation and trigger GDM [9, 10].

2.3. The Therapeutic Effect of Probiotic Adjunct Therapy on GDM's Glucose and Lipid Metabolism

Probiotic intervention has shown significant benefits for the metabolic health of patients with GDM. In a randomized controlled study of 104 GDM patients conducted over one year, the control group received insulin pump therapy, while the observation group received probiotic treatment in

addition to the control group's therapy. The observation group demonstrated significantly better blood sugar control than the control group, as illustrated by the data presented ($P<0.05$) [11]. Compared to the control group without probiotic intervention, the patients receiving probiotic intervention showed better results in blood sugar control, lipid levels, and antioxidant indicators. Specifically, the probiotic intervention group experienced significant reductions in fasting blood glucose, postprandial blood glucose, and glycosylated hemoglobin levels, indicating effective control of blood sugar levels and a reduced risk of diabetes in GDM patients. Additionally, the probiotic intervention group showed advantages in lipid levels, with decreases in triglycerides, total cholesterol, and low-density lipoprotein cholesterol, and an increase in high-density lipoprotein cholesterol, which is beneficial for improving lipid profiles and reducing the risk of cardiovascular disease. In terms of insulin resistance and antioxidant indicators, the probiotic intervention group also showed better results, with decreases in fasting insulin and insulin resistance index, and increases in glutathione and superoxide dismutase levels, suggesting improved insulin sensitivity and enhanced antioxidant capacity. These results indicate that probiotic intervention may be an effective adjunctive treatment for GDM patients, helping to improve their metabolic health, reduce the risk of complications, and promote the health of both mother and infant.

3. The Relationship Between Pregnant Women and Vitamin D Nutrition

3.1. The Physiological Functions of Vitamin D

Vitamin D is a group of compounds with a cyclopentanophenanthrene ring structure that have the biological activity of calcitriol. The active form of vitamin D, 1,25-(OH)2-D, acts on target organs such as the small intestine, kidneys, and bones, participating in the regulation of extracellular and intracellular calcium concentrations and calcium and phosphorus metabolism, as well as having immunomodulatory and anti-inflammatory effects. About 80%-90% of vitamin D is synthesized from the skin, with a smaller portion obtained from dietary intake [12]. For the assessment of vitamin D levels in pregnant women, the same criteria as for the general population are used. Serum 25-(OH)D levels are measured to evaluate vitamin D status, with levels of 75 nmol/L or higher considered sufficient for normal physiological function; levels between 50 and 75 nmol/L indicate vitamin D insufficiency; and levels below 50 nmol/L indicate vitamin D deficiency. Studies have shown that when vitamin D is insufficient, it may reduce peripheral tissue sensitivity and impair the secretory function of pancreatic β-cells, playing a key role in the occurrence and development of GDM [9].

3.2. The Therapeutic Mechanism of Vitamin D Supplementation for GDM

Vitamin D is capable of modulating blood glucose metabolism, and research has verified that reduced concentrations of serum 25-hydroxyvitamin D3 [25-(OH)D3] serve as an autonomous risk factor for the onset of gestational diabetes mellitus (GDM). Vitamin D is involved in the regulation of insulin secretion and can improve insulin resistance. Therefore, supplementing with vitamin D can enhance blood glucose metabolism in GDM patients and increase insulin sensitivity [9]. Animal models suggest that vitamin D can enhance pancreatic exocrine function and insulin sensitivity. Early pancreatic cells express vitamin D receptors (VDRs), and vitamin D may play a role in the regulation of insulin secretion as a modulator. Vitamin D can increase VDRs, maintain calcium balance, and improve pancreatic paracrine cell dysfunction caused by iron overload [12].

Current research implies a connection between vitamin D insufficiency and the onset of insulin resistance-related conditions. Besides its established role in promoting bone health, the addition of vitamin D to one's diet is crucial for ameliorating issues of insulin resistance. Insulin resistance during pregnancy can lead to a weakened response of body tissues to insulin, preventing glucose from effectively entering cells for energy metabolism, which is a key factor in the development of GDM. Adequate vitamin D levels not only have an effect on inflammation control but also reduce oxidative stress, which in turn can alleviate insulin resistance and play a role in controlling blood sugar levels in GDM patients [11].

The mechanism between vitamin D and insulin resistance (IR) involves multiple levels. Firstly, vitamin D protects pancreatic β-cell function and insulin sensitivity by reducing oxidative stress levels, which is crucial for maintaining normal blood glucose homeostasis. High blood glucose leads to increased production of reactive oxygen species, causing oxidative stress, and vitamin D can improve mitochondrial structure and function, reduce the expression of nuclear factor E2-related factor 2, and thus lower oxidative stress [12]. Additionally, vitamin D has immunomodulatory effects, can suppress the expression of inflammatory factors, and reduce chronic low-grade inflammation, which is an important cause of IR. Increased levels of inflammatory factors, such as C-reactive protein, interleukins, and tumor necrosis factor, can interfere with insulin signaling, and adequate levels of vitamin D help suppress these inflammatory factors, reduce mitochondrial dysfunction, prevent the decline in glucose utilization and lipid accumulation, thereby alleviating IR [11]. Therefore, vitamin D is pivotal in the avoidance and treatment of insulin resistance through the modulation of oxidative stress and inflammatory reactions.

4. The Therapeutic Effect of Combined Probiotic and Vitamin D Supplementation on Glucose and Lipid Metabolism in GDM

The combined intervention of probiotics and vitamin D shows significantly better therapeutic effects for GDM than vitamin D intervention alone. In a randomized controlled study, 90 GDM patients were randomly assigned to two groups: the control group received conventional treatment combined with vitamin D, while the observation group received the same treatment as the control group plus probiotics. Before treatment, there were no significant differences in fasting blood glucose (FBG), 2-hour postprandial blood glucose (2 h PG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR), and pancreatic β-cell function index (HOMA-β) between the two groups [4]. The results of this randomized controlled study indicate that the combined intervention of probiotics and vitamin D significantly improved blood sugar control and pancreatic β-cell function in GDM patients, while vitamin D alone showed some positive effects, but the results were not as significant as the combined intervention. The decrease in fasting blood glucose, 2-hour postprandial blood glucose, and insulin resistance index in the combined intervention group was greater than that in the control group, and the increase in the pancreatic β-cell function index was also more significant. This suggests that the combined intervention may effectively improve the metabolic health of GDM patients through mechanisms such as regulating the gut microbiota, increasing the production of short-chain fatty acids, reducing inflammation, and lowering oxidative stress. Therefore, the combined intervention of probiotics and vitamin D may become a more effective adjuvant treatment for GDM patients, helping to improve their metabolic health, lower the likelihood of complications and enhance the well-being of mothers and offspring.

5. Conclusion

Based on the above, The administration of probiotics, either independently or alongside vitamin D supplementation, has been shown to successfully modulate glucose and lipid metabolism in individuals suffering from gestational diabetes mellitus (GDM).Compared to insulin treatment alone, the supplementation of probiotics and vitamin D significantly improves blood sugar control, lipid profile, and antioxidant status in GDM patients, while also improving the insulin resistance index and islet cell function index. This indicates a synergistic effect of probiotics and vitamin D in the management of GDM. Subsequent studies ought to concentrate on executing extensive, multicentric clinical trials to more thoroughly substantiate the effectiveness and safety of probiotics used as a monotherapy and in conjunction with vitamin D for the treatment of gestational diabetes. This will provide valuable insights for optimizing GDM treatment and preventing metabolic diseases in susceptible populations. Moreover, focus is needed on aspects like the choice of probiotic strains, the

refinement of dosage, and the timing of probiotic intake to develop more targeted and efficacious treatment strategies for individuals with gestational diabetes.

References

[1] Zheng W L, Li L, Wang K, et al. Effects of gut microbiota transplantation and probiotic supplementation on anti-inflammation, antioxidation and pregnancy outcomes in gestational diabetes mellitus rats [J]. Chinese Journal of Microecology, 2024, 36 (6): 657–664+670.

[2] Zhou H Y, Qing Y, Zhou C M, et al. Research progress on the correlation between gestational diabetes mellitus and gut microbiota [J]. Chinese Journal of Diabetes, 2022, 30 (6): 459–461.

[3] Liang F J, Jiao L L, Liu M Y. Effects of probiotic supplements on inflammatory and oxidative stress biomarkers in patients with gestational diabetes mellitus [J]. Hainan Medical Journal, 2022, 33 (6): 754–757.

[4] Yang Y, Ye J, Yang M, et al. Effects of probiotics combined with vitamin D on glycolipid metabolism and insulin resistance in gestational diabetes mellitus [J]. Medical & Pharmaceutical Journal of Chinese People's Liberation Army, 2020, 32 (11): 71–74.

[5] Zhong J, Wu H M, Zhang H, et al. Research progress on the relationship between gut microbiota and its metabolites with gestational diabetes mellitus [J]. Translational Medicine Journal, 2024, 13 (3): 495–498.

[6] Saucedo R, Ortega-Camarillo C, Ferreira-Hermosillo A, et al. Role of oxidative stress and inflammation in gestational diabetes mellitus [J]. Antioxidants, 2023, 12 (10): 1812.

[7] Zheng J, Feng Q, Zheng S, et al. The effects of probiotics supplementation on metabolic health in pregnant women: An evidence based meta-analysis [J]. PLOS ONE, 2018, 13 (5): e0197771.

[8] Huang L, Thonusin C, Chattipakorn N, et al. Impacts of gut microbiota on gestational diabetes mellitus: a comprehensive review [J]. European Journal of Nutrition, 2021, 60 (5): 2343–2360.

[9] Das B P, Das S K, Bhuyan A K, et al. Relationship between vitamin D level and gestational diabetes mellitus: a cross-sectional study[J]. Journal of Obstetrics and Gynaecology of India, 2023, 73 (Suppl 1): 83–87.

[10] Liang W, Feng Y, Yang D, et al. Oral probiotics increased the proportion of Treg, Tfr, and Breg cells to inhibit the inflammatory response and impede gestational diabetes mellitus [J]. Molecular Medicine (Cambridge, Mass.), 2023, 29 (1): 122.

[11] Wu L X, Luo R K, Wang W B. Therapeutic effect of probiotics combined with insulin pump on patients with gestational diabetes mellitus [J]. Maternal and Child Health Care of China, 2024, 39 (16): 3007–3011.

[12] Motamed S, Anari R, Motamed S, et al. Vitamin D and biomarkers of inflammation and oxidative stress among pregnant women: a systematic review of observational studies [J]. BMC Immunology, 2023, 24 (1): 41.