

Progress of Research on the Effects of Intestinal Flora and Dietary Fiber on Gestational Diabetes Mellitus

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Abstract: *Gestational diabetes mellitus (GDM) is closely related to adverse pregnancy outcomes and is a common metabolic disease in pregnancy, and as the detection rate of GDM is increasing year by year in China, the prevention and treatment of GDM is of great public health significance. In the long-term research on intestinal flora and dietary fiber, although their roles in the pathogenesis of GDM cannot be fully elucidated, current studies have shown that changes in intestinal flora and increased intake of dietary fiber are helpful for glycemic control in GDM. In this paper, we review the research on the effects of intestinal flora and dietary fiber on the relevance of GDM in recent years to provide some reference for the prevention and treatment of GDM.*

Keywords: Gut flora, Gestational diabetes mellitus, Dietary fiber, Pregnancy outcome.

1. Introduction

According to the International Diabetes Federation (IDF) 2021 data, the global prevalence of gestational diabetes mellitus (GDM) is approximately 16.7%, with regional variations of 13% in Africa, 20.7% in North America and the Caribbean, and 25.9% in Southeast Asia [1]. GDM is strongly associated with adverse pregnancy outcomes, posing significant risks to maternal and fetal health. As research on GDM advances, emerging evidence suggests that the gut microbiota may play a critical role in its pathogenesis. Furthermore, dietary interventions, such as increasing the intake of high-fiber foods, have been shown to exert a beneficial effect on glycemic control in GDM.

2. Overview of Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first identified during pregnancy [2]. With the global prevalence of obesity reaching epidemic levels, the number of women diagnosed with GDM has been increasing, and these women face an elevated risk of various pregnancy-related complications [3]. A systematic review and meta-analysis by Ye et al. [4] investigated the association between GDM and adverse pregnancy outcomes. In studies where insulin was not used, after adjusting for confounding factors, women with GDM exhibited increased odds of cesarean section (odds ratio [OR] 1.16, 95% confidence interval [CI] 1.03-1.32), preterm birth (OR 1.51, 95% CI 1.26-1.80), low Apgar score at 1 minute (OR 1.43, 95% CI 1.01-2.03), macrosomia (OR 1.70, 95% CI 1.23-2.36), and large-for-gestational-age (LGA) infants (OR 1.57, 95% CI 1.25-1.97). In studies involving insulin use, women with GDM had higher odds of delivering LGA infants (OR 1.61, 95% CI 1.09-2.37), infants with respiratory distress syndrome (OR 1.57, 95% CI 1.19-2.08), neonatal jaundice (OR 1.28, 95% CI 1.02-1.62), or infants requiring admission to the neonatal intensive care unit (OR 2.29, 95% CI 1.59-3.31) compared to women without GDM. After adjusting for confounders, no

clear evidence was found to suggest differences in the odds of instrumental delivery, shoulder dystocia, postpartum hemorrhage, stillbirth, neonatal death, low 5-minute Apgar score, low birth weight, or small-for-gestational-age infants between women with and without GDM. Heterogeneity across studies of adverse pregnancy outcomes was significantly influenced by national context, adjustment for body mass index, and screening methods.

Beyond the short-term maternal and neonatal complications mentioned above, a deeper understanding of GDM has revealed long-term implications for both women with a history of GDM and their offspring [5-10]. Women with prior GDM are at a higher risk of developing type 2 diabetes mellitus (T2DM), metabolic syndrome, and cardiovascular, renal, hepatic, and retinal diseases. Their offspring face an increased risk of diabetes and obesity [11-13]. Additionally, studies using GDM animal models [14,15] have demonstrated that offspring of GDM mothers are at elevated risk of hyperglycemia, diabetes, obesity, cardiovascular disease, and structural hypothalamic changes during subsequent pregnancies. These adverse outcomes can be prevented by normalizing maternal blood glucose levels during pregnancy. Consequently, research and preventive interventions for GDM hold significant public health importance.

3. Association Between Gut Microbiota and Gestational Diabetes Mellitus

3.1 Overview of Gut Microbiota

Research indicates [16] that the adult human gut harbors approximately 10^{14} bacterial cells, a number tenfold greater than the total human cell count. The gut microbiota is predominantly composed of anaerobic bacteria, which outnumber aerobic and facultative anaerobic bacteria by a factor of 100 to 1,000. The gut microbial community consists of approximately 500-1,000 species. To date, the most abundant phyla in the gut are Firmicutes and Bacteroidetes, although other phyla, such as Proteobacteria,

Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria, are also present [17]. The human microbiome represents one of the most dynamic fields of contemporary research, with the gastrointestinal tract being a primary focus due to its role as the primary habitat for the majority of our microbial communities. Over the past decade, significant progress has been made in understanding the functions of gut-resident microbes and their roles in human health and disease [18]. Accumulating evidence from the past decade has linked alterations in gut microbial composition to several diseases, including inflammatory bowel disease, asthma, arthritis, obesity, and cardiovascular disease. However, further research has clarified that the normal gut microbiota also influences numerous physiological processes in healthy hosts, including organ morphogenesis, immune system development and maturation, gastrointestinal tract development, intestinal angiogenesis, tissue regeneration, carcinogenesis, bone homeostasis, metabolism, and behavior [19].

3.2 Characteristics of Gut Microbiota in Gestational Diabetes Mellitus

Research has demonstrated [20] that patients with gestational diabetes mellitus (GDM) exhibit distinct alterations in gut microbiota composition. At the phylum level, there is an increased abundance of Verrucomicrobia. At the genus level, significant reductions in the abundance of Clostridium, Prevotella, and Streptococcus are observed, alongside a marked increase in Megamonas. At the species level, notable decreases are found in Bacteroides coprophilus, Eubacterium siraeum, Bacteroides prausnitzii, Bacteroides prausnitzii, and Bacteroides korensis, while Bacteroides fragilis, unclassified Megamonas, and Ruminococcus gnavus show significant increases. Notably, Clostridium, Prevotella, and Streptococcus are capable of producing short-chain fatty acids (SCFAs) through the fermentation of dietary fiber [21]. These findings suggest that the significant reduction in the abundance of these specific gut microbes may contribute to decreased SCFA production in GDM patients. Studies [3,22] indicate that gut microbiota may mediate glucose intolerance and insulin resistance in type 2 diabetes mellitus (T2DM) through multiple mechanisms, including low-grade endotoxemia due to enhanced gut permeability, imbalances in SCFA and branched-chain amino acid production, and disruptions in bile acid metabolism. Given that GDM and T2DM share common pathophysiological features, such as pancreatic β -cell dysfunction and insulin resistance, the gut microbiota likely plays a critical role in the pathogenesis of GDM.

4. Association Between Dietary Fiber and Gestational Diabetes Mellitus

4.1 Overview of Dietary Fiber

In 2019, the World Health Organization and the Codex Alimentarius Commission defined dietary fiber as carbohydrates that are neither digested nor absorbed in the small intestine and have a degree of polymerization (DP) of ten or more monomeric units. According to the Codex definition, dietary fiber encompasses non-starch polysaccharides such as cellulose, hemicellulose, and pectin,

resistant starches, non-digestible oligosaccharides such as inulin and oligofructose, and lignin. Consequently, foods rich in dietary fiber include whole grains, legumes, vegetables, fruits, nuts, and seeds. Mechanistic studies have highlighted the diverse physicochemical properties of dietary fibers, such as solubility, viscosity, and fermentability, which determine their functionality in the upper digestive tract and lower gastrointestinal tract. Human glycemic control can be improved through mechanisms that increase the viscosity of gut contents. In rats, cellulose has been shown to influence blood glucose levels by binding to α -amylase, thereby inhibiting starch digestion [23] and reducing glucose absorption. Research indicates that the intake of viscous dietary fibers alters transit time in the upper gastrointestinal tract, including slowing gastric emptying and regulating small intestinal transit [24]. Increased luminal viscosity is considered a key mechanism in the regulatory effects of dietary fiber intake, including delayed digestion, reduced postprandial glycemia [25], lowered blood lipids [26-28], and enhanced satiety in humans [29].

4.2 Dietary Fiber and Gestational Diabetes Mellitus

A systematic review and meta-analysis by Reynolds et al. [30] demonstrated that a high-fiber diet is a critical component of diabetes management, contributing to improved glycemic control, lipid profiles, body weight, and inflammation markers, as well as reduced premature mortality. These benefits are not limited to specific fiber types or diabetes subtypes and are evident across a range of intake levels. Based on these findings, increasing daily fiber intake by 15g or 35g may be a reasonable target to reduce the risk of premature mortality in adults with diabetes. It is recommended that all individuals with diabetes be encouraged to consume adequate dietary fiber. A prospective cohort study by Zhang et al. [31] involving 13,110 eligible women found that a 10g/day increase in total fiber intake was associated with a 26% reduction in GDM risk (95% CI: 9-49%). Similarly, a 5 g/day increase in cereal or fruit fiber was linked to a 23% (95% CI: 9-36%) and 26% (95% CI: 5-42%) risk reduction, respectively. Dietary glycemic load was positively correlated with GDM risk, with a multivariate relative risk of 1.61 (95% CI: 1.02-2.53; P for trend = 0.03) for the highest versus lowest quintile. These findings suggest that pre-pregnancy dietary patterns may influence GDM risk, with low fiber intake and high glycemic load associated with increased risk. Multivariate regression coefficients comparing the highest and lowest quintiles were 0.70 (95% CI: 0.52-0.96; P = 0.02), 0.77 (95% CI: 0.59-1.01; P = 0.03), and 0.68 (95% CI: 0.52-0.88; P = 0.02) for total dietary fiber and specific fiber types analyzed as continuous variables. Multivariate analyses showed that a 10 g/day increase in total fiber reduced GDM risk by 26%, while a 5 g/day increase in cereal or fruit fiber reduced risk by 23% and 26%, respectively. In this large prospective study, pre-pregnancy intake of total fiber, cereal fiber, and fruit fiber was significantly negatively correlated with GDM risk, whereas dietary glycemic load was positively correlated.

A nested case-control study [32] identified a cholesterol-rich dietary pattern characterized by high intake of livestock, poultry, and eggs but low consumption of cereals. After multivariate adjustment, the odds ratios (ORs) for GDM were

1.24 (95% CI: 1.06-1.44) and 1.28 (95% CI: 1.09-1.49). Genetic analysis utilizing 28 cholesterol metabolism-related single nucleotide polymorphisms (SNPs) revealed significant associations between CYP7A1 variants (rs3808607 G→T, rs8192871 G→A, rs7833904 A→T) and GDM risk, as well as between the AGGG and tGA haplotypes spanning CYP7A1 and GDM. For combined effects, the OR for individuals with the highest dietary pattern score and genetic risk score (GRS) was 3.53 (95% CI: 1.71-7.31) compared to those in the lowest category, with no significant interaction ($P < 0.101$). Both a cholesterol-rich dietary pattern and genetic variations in cholesterol metabolism genes were associated with GDM risk. Adherence to a cholesterol-rich dietary pattern in early pregnancy increased the likelihood of developing GDM, particularly in women with high GRS. The GRS, derived from 28 cholesterol metabolism-related SNPs, was also associated with GDM, with higher GRS linked to increased risk. A significant joint relationship was observed between the cholesterol-rich dietary pattern and GRS in relation to GDM.

Using Cox proportional hazards analysis and linear mixed-effects regression, Zhang et al. [33] investigated outcome variables including GDM risk, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR). Women with the highest dietary glycemic index (GI) or glycemic load (GL) levels before pregnancy, in early pregnancy, or in mid-pregnancy had a 12% (15%), 25% (23%), or 29% (25%) higher GDM risk, respectively, compared to those with the lowest levels (all $P = 0.02$). Women with the highest pre-pregnancy dietary fiber intake had an 11%, 17%, or 18% lower GDM risk in the first or second month of pregnancy (all P for trend = 0.03). Additionally, during pregnancy (months 1-3), increases in GI or GL and reductions in fiber intake were independently associated with adverse concurrent changes in FPG, HbA1c, and HOMA-IR ($P < 0.03$). These findings indicate that pre-pregnancy and pregnancy dietary GI, GL, and fiber intake influence glycemic homeostasis in Chinese pregnant women. The benefits of a low-GI diet combined with high fiber intake were additive in preventing GDM. These results confirm the role of dietary fiber in glycemic homeostasis, particularly during pregnancy. Collectively, this study suggests that dietary GI, GL, and fiber intake before and during pregnancy significantly impact glycemic homeostasis in Chinese pregnant women.

5. Summary and Outlook

With the development of China's economy, changes in dietary patterns, and the standardization of prenatal screening, the detection rate of gestational diabetes mellitus (GDM) has been steadily increasing. GDM is closely associated with adverse pregnancy outcomes, underscoring the critical importance of its prevention and management. Although the precise mechanisms underlying GDM pathogenesis remain incompletely elucidated, current research has confirmed that the gut microbiota plays a significant role. Dietary intervention is one of the primary strategies for glycemic control in GDM patients, and improving dietary patterns, particularly by increasing the intake of high-fiber foods, has demonstrated notable efficacy in managing blood glucose levels. High fiber intake is correlated with alterations in gut

microbiota composition, which may contribute to GDM prevention, though further research is needed to substantiate this relationship. In conclusion, more in-depth studies are required to explore the mechanisms linking gut microbiota to GDM pathogenesis and to investigate the impact of gut microbiota on maternal-fetal transmission. Such research has the potential to mitigate adverse pregnancy outcomes and promote maternal and infant health.

References

- [1] Global diabetes data report 2000 — 2045 [Z].
- [2] KJOS S L, BUCHANAN T A. Gestational diabetes mellitus [J]. *The New England Journal of Medicine*, 1999, 341(23): 1749-1756.
- [3] MCINTYRE H D, CATALANO P, ZHANG C, et al. Gestational diabetes mellitus [J]. *Nature Reviews Disease Primers*, 2019, 5(1): 47.
- [4] YE W, LUO C, HUANG J, et al. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis [J]. *BMJ*, 2022, 377: e067946.
- [5] DALY B, TOULIS K A, THOMAS N, et al. Increased risk of ischemic heart disease, hypertension, and type 2 diabetes in women with previous gestational diabetes mellitus, a target group in general practice for preventive interventions: A population-based cohort study [J]. *PLoS medicine*, 2018, 15(1): e1002488.
- [6] CHEUNG N W, BYTH K. Population health significance of gestational diabetes [J]. *Diabetes Care*, 2003, 26(7): 2005-2009.
- [7] LAUENBORG J, MATHIESEN E, HANSEN T, et al. The prevalence of the metabolic syndrome in a danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population [J]. *J Clin Endocrinol Metab*, 2005, 90(7): 4004-4010.
- [8] RETNAKARAN R. Hyperglycemia in pregnancy and its implications for a woman's future risk of cardiovascular disease [J]. *Diabetes Research and Clinical Practice*, 2018, 145: 193-199.
- [9] RETNAKARAN R, SHAH B R. Role of Type 2 Diabetes in Determining Retinal, Renal, and Cardiovascular Outcomes in Women with Previous Gestational Diabetes Mellitus [J]. *Diabetes Care*, 2017, 40(1): 101-108.
- [10] KRAMER C K, CAMPBELL S, RETNAKARAN R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis [J]. *Diabetologia*, 2019, 62(6): 905-914.
- [11] SILVERMAN B L, RIZZO T, GREEN O C, et al. Long-term prospective evaluation of offspring of diabetic mothers [J]. *Diabetes*, 1991, 40 Suppl 2: 121-125.
- [12] DABELEA D, HANSON R L, LINDSAY R S, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships [J]. *Diabetes*, 2000, 49(12): 2208-2211.
- [13] FRASER A, LAWLOR D A. Long-term health outcomes in offspring born to women with diabetes in pregnancy [J]. *Current Diabetes Reports*, 2014, 14(5): 489.
- [14] HARDER T, AERTS L, FRANKE K, et al. Pancreatic islet transplantation in diabetic pregnant rats prevents

- acquired malformation of the ventromedial hypothalamic nucleus in their offspring [J]. *Neuroscience Letters*, 2001, 299(1-2): 85-88.
- [15] AERTS L, VAN ASSCHE F A. Animal evidence for the transgenerational development of diabetes mellitus [J]. *The International Journal of Biochemistry & Cell Biology*, 2006, 38(5-6): 894-903.
- [16] CLEMENTE J C, URSELL L K, PARFREY L W, et al. The impact of the gut microbiota on human health: an integrative view [J]. *Cell*, 2012, 148(6): 1258-1270.
- [17] CONSORTIUM H M P. Structure, function and diversity of the healthy human microbiome [J]. *Nature*, 2012, 486(7402): 207-214.
- [18] SCHMIDT T S B, RAES J, BORK P. The Human Gut Microbiome: From Association to Modulation [J]. *Cell*, 2018, 172(6): 1198-1215.
- [19] SOMMER F, BÄCKHED F. The gut microbiota—masters of host development and physiology [J]. *Nature Reviews Microbiology*, 2013, 11(4): 227-238.
- [20] YE D, HUANG J, WU J, et al. Integrative metagenomic and metabolomic analyses reveal gut microbiota-derived multiple hits connected to development of gestational diabetes mellitus in humans [J]. *Gut Microbes*, 2023, 15(1): 2154552.
- [21] KOH A, DE VADDER F, KOVATCHEVA-DATCHARY P, et al. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites [J]. *Cell*, 2016, 165(6): 1332-1345.
- [22] CANFORA E E, MEEX R C R, VENEMA K, et al. Gut microbial metabolites in obesity, NAFLD and T2DM [J]. *Nature Reviews Endocrinology*, 2019, 15(5): 261-273.
- [23] DHITAL S, GIDLEY M J, WARREN F J. Inhibition of alpha-amylase activity by cellulose: Kinetic analysis and nutritional implications [J]. *Carbohydr Polym*, 2015, 123: 305-312.
- [24] MÜLLER M, CANFORA E, BLAAK E. Gastrointestinal Transit Time, Glucose Homeostasis and Metabolic Health: Modulation by Dietary Fibers [J]. *Nutrients*, 2018, 10(3).
- [25] CHUTKAN R, FAHEY G, WRIGHT W L, et al. Viscous versus nonviscous soluble fiber supplements: mechanisms and evidence for fiber-specific health benefits [J]. *J Am Acad Nurse Pract*, 2012, 24(8): 476-487.
- [26] VUKSAN V, JENKINS A L, ROGOVIK A L, et al. Viscosity rather than quantity of dietary fibre predicts cholesterol-lowering effect in healthy individuals [J]. *Br J Nutr*, 2011, 106(9): 1349-1352.
- [27] David L. Topping, David Oakenfull, et al. A viscous fibre (methylcellulose) lowers blood glucose and plasma triacylglycerols and increases liver glycogen independently of volatile fatty acid production in the rat [J]. *British Journal of Nutrition*, 1988, 59(1):21-30.
- [28] Anderson J W, Allgood L D, et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials [J]. *The American journal of clinical nutrition*, 2000, 71(2):472-479.
- [29] Bergmann J F, Chassany O, et al. Correlation between echographic gastric emptying and appetite: influence of psyllium. [J]. *Gut*, 1992, 33(8):1042-1043.
- [30] Reynolds Andrew N, Akerman Ashley P, et al. Dietary fibre and whole grains in diabetes management: Systematic review and meta-analyses [J]. *PLoS medicine*, 2020, 17(3):e1003053.
- [31] ZHANG C, LIU S, SOLOMON C G, et al. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus [J]. *Diabetes Care*, 2006, 29(10): 2223-2230.
- [32] CUI N, LI Y, HUANG S, et al. Cholesterol-rich dietary pattern during early pregnancy and genetic variations of cholesterol metabolism genes in predicting gestational diabetes mellitus: a nested case-control study [J]. *Am J Clin Nutr*, 2023, 118(5): 966-976.
- [33] ZHANG X, GONG Y, DELLA CORTE K, et al. Relevance of dietary glycemic index, glycemic load and fiber intake before and during pregnancy for the risk of gestational diabetes mellitus and maternal glucose homeostasis [J]. *Clin Nutr*, 2021, 40(5): 2791-2799.