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Probiotics and Metabolic Outcomes of Gestational Diabetes: A Review Article

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Abstract

Gestational diabetes mellitus (GDM) is the most prevalent metabolic problem of gestation. In contrast to subjects without diabetes, women with GDM are at advanced risk of adverse maternal and fetal consequences without intervention. The current and unanticipated growth in the prevalence of gestational diabetes and the middling outcomes of dietary manipulations could somewhat be because of incuriosity to or failure in changing the different combination and unsuitable intestinal micro flora which happens frequently in the second half of pregnancy particularly when complemented with overweight/obesity. In the range of lifestyle-related aspects, probiotics are suggested as part of a balanced diet, low-cost, feasible and potentially impressive strategy to manage this health problem. The objective of this review paper is to review the related studies pursuant to the significance of probiotics and their impression in prohibition and management of GDM. Electronic search was performed in databases, including Scopus, Science direct, PubMed, Cochrane central, Google Scholar, ISC, Magiran, IranMedex, SID, and MedLib. Evidence proposes that manipulation of gut microbiota during pregnancy by certain probiotics in high risk pregnant women may be of pronounced advantage for better metabolic profile of pregnant women and their offspring.

***Keywords*:** gestational diabetes mellitus, metabolic, probiotic, microbiota

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Introduction

Gestational Diabetes Mellitus (GDM) is the most common metabolic disorder that occurs during pregnancy (1). Existing treatments focusing on normalizing blood glucose levels have been successful in reducing the short-term complications of GDM and probably have no effect on its long-term complications (2). Therefore, due to limited results obtained from traditional controlling of risk factors, diet and physical activity, and poor acceptance of lifestyle interventions, the urgent need for new solutions is indispensable. In recent years, it has been shown that the optimum balance in the number of gastrointestinal microbes depends on nutrition and health. Main microorganisms affecting the preservation of this balance are lactobacilli and bifidobacteria (3). Factors affecting intestinal microorganisms (such as stress and diet) will have adverse effects on the health of humans by breaking down the optimal microbial balance. The use of nutrients containing beneficial microorganisms, called

probiotics, has greatly contributed to the survival and maintenance of indigenous germs and their microbial balance, resulting in many benefits for human health (4). Today, people's knowledge and attitudes toward their health are improving, and most people are seeking ways to improve their health and prevent disease (5). In recent years, probiotic bacteria have been incorporated into dietary supplements with a large number of foods (6). What is important in this regard is to pay attention to the effect of pregnancy on the composition of the intestinal microbial population (7). Generally, at the end of pregnancy, the number of proteobacteria and acinetobacteria increases and bacterial richness decreases (7). These changes are more pronounced in obese pregnant, overweight or more weight gain women (7-10). These changes have the ability to modify the immune system to facilitate metabolic and immunological adaptation (7, 11), and accordingly, several empirical studies have been carried out.

Among the studies conducted in 2011, the effect of probiotic yogurt containing Bifidobacterium breve with a dose of $1.4*10^6$ CFU/g on weight gain and lipid profile of pregnant mice was examined. Probiotic groups showed higher weight gain than control group. After delivery, the weight decreased, but the mice did not reach the pre-pregnancy weight (12). According to scientific literature, although, total cholesterol, LDL, and triglyceride levels progressively increased during pregnancy (13), probiotic supplementation showed a different trend. The concentration of total cholesterol, LDL cholesterol and triglyceride in rats increased during pregnancy and this increase continued to reach the maximum concentration and then decreased until delivery. Reduced rate was lower in probiotic supplemented mice group. The beneficial effect of probiotic use was also observed in VLDL concentration, which was a decrease in concentration below the pre-pregnancy level after the first week of pregnancy (12). In another study in 2006, in the form of a clinical trial, 17 primiparous pigs were supplemented by Enterococcus fecium 7134 on 90 days of gestation until 28th day of infancy, with a dose of 5×10^8 CFU/Kg weight, and its effect on food intake and the weight of pigs compared with 16 pigs without probiotic intake was investigated. The results of this study showed that dietary intake of the supplement group was significantly increased compared with the control group (4.16 vs. 3.71 kg/day). In addition, according to the results of the study, the weight of probiotic receiving pigs at the end of the study was 11 kg higher than that of the pigs of the control group (14). The effect of probiotic Lactobacillus rhamnosus GR-1 on cytokine secretion in pregnant mice has been investigated in another study. Probiotic prescription decreased the levels of IL-1β, IL-6, IL-12p40, TNF-α, CCL4 and CCL5 cytokines production in maternal plasma, IL -6, IL-12p70, TNF-α, IL-17 and IL-13 in myometer, IL-6, IL-12p70 and IL-17 in placenta and IL-6, TNF-α, CCL3 and CCL4 in amniotic fluid. Therefore, GR-1 probiotics may have beneficial therapeutic effects in preventing preterm labor-related infections through controlling systemic and uterine inflammation (15). Although not completely recognized, gut microbiota plays a role in planning and control of many physiological actions, including epithelial evolution, blood circulation and intrinsic and adaptive mechanisms of the intestine (16, 17). A new hypothesis suggests that intestinal microbial environment is involved in regulating energy homeostasis. Therefore, in the presence of a vulnerable environment, the intestinal microbial population can disrupt the homeostasis of the energy and result in metabolic disorders (18). Several studies suggest that probiotics can reduce the incidence of gestational diabetes. No side effects have been observed in mothers and children taking probiotics during pregnancy. There is no significant difference in pre and postnatal growth rates in the studied groups. This suggests that probiotics are a safe and cost-effective means of preventing GDM. Considering the fact that several clinical trials have been conducted to evaluate the effects of probiotic supplementation on various metabolic aspects in women with or without GDM, a review study is needed to finalize the general conclusion. The purpose of this article is to review recent studies on the effects of probiotics on metabolic outcomes in GDM.

Materials and Methods

In the recent study to identify the studies conducted, the data were collected by referring to the Scopus, Science Direct, ISI web of science, PubMed, Cochrane Central, EMBASE and Google Scholar databases, from January 2000 to February 2019. To study Persian articles, the Islamic Science Citation Database (ISC), Magiran, IranMedex Database, Scientific Jihad University (SID) and Medical Articles Directory (MedLib) were used. To investigate the keywords for Probiotics, including Probiotic, Probiotics, Lactobacillus, Lactobacilli, Bifidobacterium, Bifidobacteria, Streptococcus, Symbiotic, and functional food that were used to search for the words (OR) and their Persian equivalents, as well as keywords related to gestational diabetes include: Gestational diabetes, GDM, diabetes, pregnancy, glucose intolerance, metabolic, weight, glucose metabolism, inflammation, and oxidative stress, which were used with the word "OR" and their Persian equivalents. To connect the two mentioned above, the word "AND" was used for the final search.

The entry criteria were as follows:

Articles that investigated the effects of supplementation or probiotic food or symbiotic drugs on metabolic abnormalities (weight gain, glucose metabolism, inflammation, and oxidative stress) in relation to the prevention or management of GDM,

Articles whose full text was available in English or Persian,

Clinical trials,

Studies conducted on human samples.

Exit criteria included:

Articles with only abstracts available,

Review, cross-sectional and cohort articles,

Studies written in languages other than English and Persian.

For final evaluation of the quality of the articles, the full texts were read and the studies with good quality were used. The search for data extraction as well as the evaluation was carried out by two individuals independently.

The PEDRo scale was used to evaluate the quality of each article (19). This scale has 11 items that each item is identified with a positive sign (correct execution) and a negative one (incorrect implementation or failure to pay attention). The total score is a sum of scores with minimum of 0 and maximum of 10 (Table 1) (19).

Eventually, 683 articles were found that 654 of them were excluded because they were not related to the purpose of the article. Then the abstract of 29 related articles was prepared and studied. Finally, only 10 papers being in line with the objectives and criteria for entering the study, were reviewed.

Discussion

Although probiotics were initially examined for gastrointestinal health, there is a growing evidence that the intestinal microbiota is present outside the digestive tract. Medical studies in the past decade have been associated with intestinal microbial population with metabolic disorders, particularly diabetes and obesity.

Although not completely recognized, the microbial environment of the intestine plays a role in planning and controlling of many physiological actions, including epithelial evolution, blood circulation and intrinsic and adaptive mechanisms of the intestine (16, 17). A new hypothesis suggests that intestinal microbial environment is involved in regulating energy homeostasis. Therefore, in the presence of a vulnerable environment, the intestinal microbial population can disrupt the energy homeostasis and result in metabolic disorders (18). Probiotics have antimicrobial activity and stimulate and modify the immune system activity of individuals and thus, contribute in the treatment of allergies and urinary tract infections. Probiotics also have beneficial effects in increasing micronutrient availability and absorption, and lowering cholesterol and blood pressure (20, 21). These effects on gestational diabetes will further be discussed.

Table 1: Qualitative Evaluation of Extracted Articles for a Review Study based on the PEDRo Scale

Hajifaraji et.al (22)	Badehnoosh et.al (23)	Karamali et.al (24)	Jafarnejhad et.al (25)	Ahmadi et.al (26)	Lindsay et.al (27)	Dolatkhah et.al (28)	Loto et.al (29)	Latein et.al (30)	Victor et.al (31)	Hajifaraji et.al (32)	Kijmanawat et.al (33)	
+	+	+	+	+	+	+	+	+	+	+	+	Eligibility criteria were specified
+	+	+	+	+	+	+	+	+	+	+	+	Random allocation of subjects
_	+	+	+	_	+	+	+	+	+	+	+	Allocation was concealed
+	+	+	+	+	+	+	+	+	+	+	+	Group similar at baseline
_	+	+	+	+	+	+	+	+	+	+	+	There was blinding of all subjects
_	_	_	_	+	+	+	_	_	+	+	+	Blinding of therapists
+	+	+	_	+	+	+	_	_	+	+	+	Blinding of assessors
+	+	+	+	+	+	+	+	+	+	+	+	>1 key outcome was obtained for more than 85 % of subjects initially allocated groups
+	+	+	+	+	+	_	+	+	+	+	+	All subjects received the treatment or control condition as allocated or, where there was not the case, data for at least one key outcome was analyzed by "intention to treat"
+	+	+	+	+	+	+	+	+	+	+	+	Results of between-group statistical comparisons are reported for at least one key outcome
+	+	+	+	+	+	+	+	+	+	+	+	The study provides both point measures and measures of variability for at least one key outcome
7	9	9	8	9	10	9	8	8	10	10	10	Total

Effect of probiotics on weight gain:

In a randomized, double-blinded clinical trial, to determine the effect of probiotic capsules containing Lactobacillus acidophilus LA-5, Bifidobacterium BB-12, Streptococcus thermophilus DTY-31 and Lactobacillus delbrucki Bulgaricus LBY-12 with a level of $>10^9 \times 4$ CFU compared with placebo for 8 weeks on pregnant women with recent diagnosis of gestational diabetes, it has been shown that daily supplementation of probiotic supplementation compared with placebo significantly reduced the weight gain of pregnant women from 6 to 8 weeks of intervention ($p < 0.05$) (28). This effect was not observed for a probiotic supplement containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum for 6 weeks, a probiotic capsule containing Bactobacillus salivaris UCC118 for 4 to 6 weeks and a probiotic capsule containing Lactobacillus acidophilus and Bifidobacterium bifidum for 4 weeks (33), which seems to be due to the short duration of intervention and the difference in used Probiotic strain. Improving weight gain in pregnant women with gestational diabetes mellitus, as one of the most common factors affecting pregnancy outcomes, is a positive change by probiotic supplementation in these patients. Due to the impossibility of restricting the rigid calorie in obese and overweight pregnant women with diabetes mellitus, probiotics can be considered as a safe means to control weight gain in these patients. The effects of probiotics are applied through their role in normalizing the

intestinal microbiota, immunity modification and maintaining the function of the intestinal barrier (34, 35). The role of gut microbes in regulating host body weights and energy homeostasis was prevalent in animal studies. Undoubtedly, the results of studies by Backhed and colleagues in 2004 and 2007 were of great importance in discovering a possible relationship between gastrointestinal tract, overweight and obesity (36, 37). The researchers showed that, compared with sterile (without intestinal microbes) mice, normal mice, with their lower intake of food, had a higher body fat content of 40%. Microbial exposure in sterile mice and their conversion to normal mice resulted in an increase of 60% in body fat just in two weeks and without supplementary food intake. The researchers showed that parallel with increased body fat, insulin resistance, hypertrophy of fatty cells, and increased leptin and blood glucose levels occurred in conventional mice. Interestingly, sterile mice did not suffer from overweight and obesity, even consuming Western diets. The researchers described the two main mechanisms to justify these observations as "nutrient extraction" and "metabolic changes in lipoprotein lipase (LPL)".

Human beings lack essential enzymes for digestion of many types of plant polysaccharides, such as cellulose, xylene, starch, and inulin (38). Non-digestible carbohydrates can be fermented by intestinal microbes to produce energy and short chain fatty acids (SCFA). These fatty acids can be attached to two receptors bound to G protein (G Protein-coupled Receptor-41 and G-Protein-coupled Receptor-43) in the intestinal epithelial cells and activate them. The activation of these receptors induces the secretion of the YY peptide, which also suppresses intestinal motility and delays the movement of substances within the intestine. Through this mechanism, intestinal microbiota plays a role in increasing nutrient intake and participating in metabolic disturbances. It has also been shown that intestinal microbiota reduces the production of FIAF (Fasting-Induced Adipose Factor) from intestinal cells, which inhibits lipoprotein lipase activity (LPL) and increases the storage of triglycerides with hepatic origin (37).

Effect of probiotics on glucose metabolism:

Laitinen et.al in a randomized clinical trial, divided 256 pregnant women into three groups: diet counseling with probiotic capsules (diet/probiotics), diet counseling with placebo (diet/placebo) and control/placebo. Probiotic capsule containing Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 with 10^{10} cfu (39). Based on the results, the concentration of glucose in the diet/probiotics group was the lowest during the follow-up period compared with other groups. Differences in diet/probiotics with diet/placebo in the third trimester of pregnancy ($p = 0.026$) were significant. Although, in these healthy pregnant women, the average plasma glucose concentration in all groups was normal, the risk of increased glucose concentration in the diet/probiotics group decreased during the study period.

The prevalence of pathologic results of glucose tolerance test was lower in diet/probiotics group (37%) compared with diet/placebo (58%) and control/placebo (57%). However, the relative risk of RR is statistically significant in the diet/probiotics group (1.38-0.14: 95% confidence interval) 0.44 (OR) and in the diet/placebo group (2.61-21.41) 0: 95% confidence interval (OR 1/3) was not lower in comparison with the control (placebo) group. In another study to evaluate the safety of previous interventions by the same group of researchers, maternal-infant cohort (n = 256) was followed up with accurate evaluation of pregnancy outcomes and child health and well-being (29). Based on the results of the study, the risk of Gestational diabetes mellitus was significantly decreased in diet/probiotics group compared with control group ($p = 0.002$, $p = 0.62$, confidence interval = 95%, OR = 0.27), while in the diet/placebo group the risk was not significantly different from the control group ($p = 0.823$, $p < 0.05$). The confidence interval was 95% (OR = 0.88) (29).

In a double-blind clinical trial in New Zealand, pregnant women with a history of atopic disease in their own or spouse, at 14-16 weeks of pregnancy, received a lactobacillus ramiosus HN001 (HN001) capsule containing $10^9 \times 6$ colony-forming units (CFUs) or placebo were randomly assigned from the beginning of the study to 6 months after birth. The participants in the

24-30 weeks of gestational diabetes examination were evaluated using the criteria of the study groups of the International Association of Diabetes and Pregnancy (IADPSG). Based on the results, probiotic supplementation was associated with a 3-fold reduction in the prevalence of gestational diabetes compared with placebo (95% CI 0.0-12.81, RR = 0.31). Probiotic supplementation in pregnant women with a history of gestational diabetes prevents the recurrence (RR=0.00, 95% CI 0.0-00.66) (31). In a double-blind clinical trial on women with newly diagnosed gestational diabetes mellitus using a 3-hour glucose tolerance test and 100 g of glucose and impaired glucose tolerance, participants were randomly assigned to receive daily Lactobacillus salivarius UCC118 probiotic capsule containing 100 mg bacteria by the target dose of 10^9 CFUs and placebo was allocated from diagnosis to delivery. Based on the results of the biochemical analysis of serum samples taken prior the study and after 4 to 6 weeks, there were no significant differences in the level of fasting blood glucose, insulin concentration, insulin resistance (HOMA index), and c-peptide concentration after intervention between the two groups of probiotics and placebo (27).

In a study by Dolatkhah et al. on the effects of probiotic supplementation in pregnant women with a new diagnosis of gestational diabetes during the 24th to 28th gestational weeks, a probiotic supplement of Lactobacillus acidophilus LA-5, Bifidobacterium BB-12 , Streptococcus thermophilus DTY-31 and Lactobacillus delbrucki Bulgaricus LBY-12 with an amount of $>10^9$* 4 CFU, together with dietary recommendations for 8 weeks resulted in a significant reduction in fasting blood glucose levels compared with placebo (1.83) -15.27 versus (3.04) -7.30 mg/dl and p = 0.02) (28). Changes in serum insulin levels were reduced in the probiotic group and decreased in the placebo group, although the changes were not statistically significant in the two groups ($p < 0.05$). Regarding the index of insulin resistance (HOMA-IR), the level in the probiotic group decreased (0.13) -0.40 and in the placebo group increased (0.12)0.01), which was a remarkable and significant change in comparing the two groups. Insulin sensitivity index (QUICKI) increased in both probiotic and placebo groups (0.003) 0.008 in the probiotic group (0.002) and 0.002 in the placebo group, although there was no significant difference between the two groups (28).

Ahmadi et al. studied the effect of complementary symbiotic containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum as probiotics plus inulin as a prebiotic drug for 6 weeks on pregnant women with gestational diabetes mellitus and a single-stage glucose tolerance test with 75 g in 24-28 weeks of pregnancy. Patients received a capsule daily each containing 2×10^9 CFU per gram each bacterium and 800 milligrams inulin. Based on the results of biochemical studies of fasting blood glucose, there was no significant difference between the two groups (9.3) -1.7 versus (11.4) 1.4 µg/ml and p=0.22) (26).

Jafar-Nejad et al. investigated the effects of probiotic capsules VSL # 3 containing Streptococcus thermophilus, Bifidobacterium braveh, Bifidobacterium Lungum, Bifidobacterium infendis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei and Lactobacillus delbruckii bulgaricus in pregnant women with gestational diabetes and a single-stage glucose tolerance test 75 grams at 24-28 weeks of gestation. Patients received a capsule each containing 112.5×10^9 CFU per day for 8 weeks. Post-interventional studies showed that the supplements did not significantly affect fasting blood glucose levels (p = 0.42). However, the level of serum insulin significantly decreased in the symbiotic group compared with the placebo group (5.9) -1.5 vs. (11.5) ± 4.8 µg/ml and p = 0.005). The HOMA-IR insulin resistance index was significantly decreased in the intervention group compared with the placebo group (1.3) -0.4 versus (2.7) + 1.1+, p = 0.003) and the performance index of Beta cells (HOMA-B) also showed a significant decrease in the symbiotic group. In contrast, the insulin sensitivity index (QUICKI) showed a significant increase in the symbiotic group compared with the placebo group (0.01) + 0.01 versus (0.02) -0.007 and p = 0.02). Based on the results of symbiotic supplementation, the study did not have a significant effect on hemoglobin A1C

levels compared with placebo (25)(25). The effect of daily administration of probiotic capsule containing Lactobacillus acidophilus, Lactobacillus cazei and Bifidobacterium bifidum was investigated by Karamali et al on pregnant women with recent diagnosis of gestational diabetes mellitus for 6 weeks in a randomized controlled clinical trial. The subjects in the probiotic group received a capsule daily containing 2×10^9 CFU of each bacterium per gram and its effects on fasting blood glucose were compared with placebo. Significant decrease in fasting blood glucose levels was observed in the probiotic group compared with placebo (9.2) -9.2 vs. (12.2) +1.1 mg/dL and $p < 0.001$). Also, changes in the probiotic group were significant relative to placebo (3.1) -0.8 versus (10.6) + 4.5 units per ml and $p = 0.01$) in the probiotic group. The HOMA-IR insulin resistance index showed a significant reduction in the probiotic group compared with placebo (0.4 + 0.9 vs. vs. 2.5) + 1. 1 and $p = 0.003$). The HOMA index for the function of β-cells in both groups increased significantly in the probiotic group (9.8) +1.1 versus (42.5) +18 and p=0.03). The QUICKI insulin sensitivity index increased in the probiotic group and decreased in the placebo group. The differences were statistically significant (0.01) +0.007 vs. (0.02) -0.01 and p=0.007) (24).

The effect of this probiotic compound containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum was also studied by Badehnoosh and colleagues, and significant results have been observed in terms of the effect on fasting blood glucose concentration (6.7) + 5.3 vs. (9.0) 0.03 mg/dl and $p = 0.01$) (23).

In a randomized, double-blind, placebo-controlled trial performed between June 2016 and February 2017 by Kijmanawat et al.(33), supplementation of 10^9 CFU of Lactobacillus acidophilus and 10^9 CFU of Bifidobacterium bifidum for four weeks in newly diagnosed pregnant women with gestational diabetes between 24–28 weeks-of-pregnancy, expressively enhanced glucose metabolism in the probiotic compared with the placebo group, including fasting plasma glucose (0.68–5.88 vs. 4.620–7.78 mg/dL, mean difference (MD)-3.94 mg/dL, P=0.034), fasting plasma insulin (1.11–1.71 vs. 3.77–1.70 mIU/L, MD-2.67 mIU/L, P=0.001) and HOMA-IR (0.25–0.37 vs. 0.89–0.46, MD-0.63,P=0.001).

The exact mechanism of probiotic effect on serum insulin levels and insulin resistance is unknown. Probiotics use glucose as a primary source of energy, and their effects on serum insulin levels are likely to interfere with effects on blood glucose levels. Probiotics may also decrease glucose uptake by altering the intestinal environment (40), gene expression and intestinal permeability (41). Probiotics may also affect the signaling pathway for insulin secretion. Reducing the activity of Jun N-terminal kinase (a TNF regulated kinase that increases insulin resistance) and reducing the binding activity of DNA to the NF-κB nuclear factor are suggested as other mechanisms to improve insulin resistance by probiotics (42). Also, changes in the microbiota of the intestine can also be involved in the intestinal hormone secretion disorder. The intestinal hormones play an important role in regulating glucose homeostasis by controlling the growth and longevity of β cells. By reducing the rate of insulin removal, in fact, probiotics can enhance the antioxidant system of beta cells and promote glucose homeostasis (43)(42). In addition, the effect of probiotics on insulin resistance, fasting-induced adipocyte factor (FIAF) can also be effective. Studies have shown that intestinal microflora is effective in transplantation of the FIAF gene in the gastrointestinal tract (44). FIAF is a serum hormone that directly affects the modulation of insulin sensitivity in the liver, and its low expression is associated with type 2 diabetes. FIAF prevents lipoprotein lipase activity. Inhibition of this hormone increases the activity of the lipoprotein lipase enzyme and, as a result to increased cellular intake of fatty acids and triglyceride accumulation in adipose tissue, and the occurrence of obesity and insulin resistance. Probiotics, therefore, can improve and enhance the expression of the FIAF by affecting the intestine microflora (36).

Effect of probiotic on inflammatory factors and oxidative stress in pregnant women with gestational diabetes:

Supplementation with probiotic capsule containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum at 2×10^9 CFU / g of each strain for 6 weeks in pregnant women with gestational diabetes compared with placebo resulted in a significant reduction in serum levels of inflammatory index hs - CRP (2.7) -2.2 versus (2.4) + 0.5 µg/ml and p <0.001). Also, after the supplementation, the oxidative malondialdehyde stress index (MDA) (0.8) -0.1 versus (1.5) + 0.5 µmol/L and p = 0.03, respectively, decreased significantly and the index of total antioxidant capacity of TAC (103.3) + 65.4 versus (143.7) -37.2 mmol per liter and p = 0.002) significantly increased. Also, the proportion of MDA/TAC was significantly decreased in the probiotic group compared with placebo (0. 0008) - 0.0003 versus (0.002) +0.0009 and p = 0.004 (23)(23). The effect of probiotic VSL # 3 supplementation on pregnant women with gestational diabetes mellitus and a single-stage glucose tolerance test of 75 grams per week from 24 to 28 weeks of pregnancy on inflammatory factors by Jafar-Nejad and his colleagues has also been considered. Probiotic supplementation compared with placebo significantly decreased the serum inflammatory parameters of hs-CRP ((1087/2) - 0.796 versus (1121/2) +975.3 ng / ml and p = 0.03), IL-6 (-0.5) -0.44 vs. (0.42) 0.33 pg/ml, p = 0.04) and TNF-α (1.0) -0.62 vs. (0.8) 0.45 pg/ml and p = 0.04) were investigated in pregnant women (25).

Supplementation with Lactobacillus acidophilus LA-5, Bifidobacterium BB-12 , Streptococcus thermophilus DTY-31 and Lactobacillus delbrucki Bulgaricus LBY-12 with an amount of >109* 4 CFU in pregnant women with a new diagnosis of gestational diabetes during the 24th to 28th gestational weeks, together with dietary recommendations for 8 weeks resulted in significantly lower mean hs-CRP values (-0.70±0.62 vs 0.82±0.94; p=0.019), lower TNF-α values (-0.04±0.10 vs 0.38±0.12; p=0.009) in probiotic group as compared to placebo. Serum MDA, serum GSHR and erythrocyte GPx levels also improved in the probiotic over the placebo group at statistically significant levels (p=0.002, p=0.047 and p=0.032 respectively) (32).

Metabolic disorders are characterized by a mild low grade inflammation that the innate and acquired immune system plays an important role (45-51). The origin of the inflammatory factors is unknown before the onset of obesity and diabetes. According to various studies, increased plasma concentrations of lipopolysaccharide produced by high-fat diet are known to be responsible for the onset of metabolic diseases, since continuous infections of the subcutaneous and slow infections of bacterial lipopolysaccharides have led to most types of metabolic diseases (52).

First, it was hypothesized that lipopolysaccharide (LPS), an inflammatory component of the cell wall in gram-negative bacteria, has a causative role in the appearance of mild inflammation in response to high-fat diet (53). Although the causes of increased plasma LPS bacterial concentration due to high fat diet have not been determined, the levels are closely related to intestinal microbiota changes due to high-fat diet and the ratio of Gram-positive to Gram-negative (54). When the microflora balance of the intestine is eliminated and the ratio of gram-positive bacteria to gram-negative bacteria decreases, access to lipopolysaccharides and other pro-inflammatory molecules increases and their blood circulation increases, thereby the secretion of cytokines and the activity of macrophages becomes high and ultimately leads to inflammation (55, 56). The proven relationship between subclinical inflammation and gestational diabetes mellitus can be explained through various mechanisms. Progressive insulin resistance leads to increased anti-insulin-like effects on lipid profile and placental hormones (cortisol and human placental lactate) in gestational diabetes mellitus (57). Ultimate glycosylated products, resulting in elevation of blood glucose, increase the oxidative stress. They also activate macrophages and increase serum levels of IL-1, IL-6 and TNF, all of which increase the production of CRP (58). The increased level of CRP in GDM patients can also be attributed to cytokines in adipose tissue (59). The role of inflammatory factors in diabetes and its complications are shown in a number of studies (60, 61).

Hyperglycemia and insulin resistance can lead to an increase in the density of ultimate glycation products of AGEs. These products directly increase the synthesis of IL-1, IL-6, and TNF-α cytokines by activating macrophages and increasing oxidative-stress activity (62). It seems that inflammatory mediators can destroy pancreatic beta cells and their function, resulting in insulin resistance (63, 64). Regarding the central role of inflammation in the pathogenesis of complications of insulin resistance and diabetes, reducing inflammatory cytokines can be effective in preventing these complications (65).

The mechanism of association between increasing synthesis of inflammatory factors and insulin resistance has not yet been fully elucidated. In macrophages, fatty cells, antigen presenting B lymphocytes, dendritic cells and Kuepfer cells in liver, germline pattern recognition receptors (PRRs), such as Toll Like receptors (TLRs), are activated by binding ligands with protected proteins, or specific patterns of microbial components (such as bacterial lipopolysaccharides) (66) or nutritional factors (such as free fatty acids) (67-70). Binding to PRRs increases inflammatory responses by activating the nuclear factor κB (NF-κB) and activating protein (AP-1) and their pathways (71). After activation, these molecule cascades inside the cytoplasm increase the transcription of the pro-inflammatory cytokines genes (72), followed by the synthesis of acute phase inflammatory mediators (73). Evidence suggests that chronic inflammation is excited with binding of LPS and bacterial lipopolysaccharides to Toll-like receptors, such as TLR-4, and negatively affects glucose homeostasis (53, 70, 74). Studies have shown that the administration of probiotics containing Lactobacillus species can alter the intestinal microbial composition, promote the expansion of the host's bifidobacterial population and reduce pro-inflammatory activity (75). Another possible mechanism to induce inflammatory signaling is through the activation of the PPARγ agonist. Conjugated linoleic acid is produced by a number of lactobacilli species (such as acidophilus, plantarum, paracazei and cazei) and has potential as a PPARγ agonist, which increases adiponectin and decreases inflammation and lipid mass and improves insulin resistance through Blood Glucose Contraction Block 4 (76).

The proposed mechanisms in relation to the effect of probiotics on oxidative stress include: expression of antioxidant enzymes, immune system stimulation and reduction of inflammation, and thus decreasing the cytokine induced oxidative stress, inhibiting various pathogens, reducing inflammation and stroke oxidative stress, the increased antioxidant micronutrient uptake and reduced levels of fatty acids associated with oxidative stress (77-80). In addition to the production of antioxidants, probiotics also have metal chelating activity, which inhibits the production of free radicals. The results of the study show that Streptococcus thermophilus and Bifidobacterium lungum bacteria have the highest ability to chelate Fe^{2+} and Cu^{2+} ions (81). In the light of the specific bacterial species selection and evidence of effectiveness in controlling free oxygen radicals, it can be an effective step in the prevention of oxidative stress disease in formulating foods or new probiotic supplements.

Effect of probiotics on lipid profiles:

In the study of Lindsay et al., the relative effect of probiotic Lactobacillus salivaris UCC118 on lipid profiles of patients was observed. Comparing lipid parameters after intervention in both groups, total cholesterol level after intervention in the probiotic group was significantly lower than placebo group ($p = 0.031$). Also, in terms of serum LDL cholesterol, this difference was statistically significant ($p = 0.011$). No significant difference was observed in other lipid profile indices between the two groups (27).

Symbiotic supplementation containing Lactobacillus acidophilus, Lactobacillus cazei and Bifidobacterium bifidum plus Inulin on pregnant women with gestational diabetes resulted in a reduction in serum triglyceride levels (56.5%) 14.8 mg/dL during 6 weeks of treatment. While total triglyceride levels in the placebo group after 6 weeks increased (37.8) 30.4 mg / dL. These changes were significant in comparison between the two supplement and placebo groups. A similar trend was

observed for VLDL cholesterol (11.3%) -3.0 in the probiotic group compared with the placebo group (p <0.001). There was no significant difference between the two groups after the intervention (p = 0.39, p = 0.64, p = 0.22, for total cholesterol, LDL cholesterol and HDL cholesterol, respectively) (26). Daily administration of probiotic capsule containing Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium bifidum at 2 × 10^9 CFU /g of each bacterium for 6 weeks in pregnant women with recent diagnosis of gestational diabetes resulted in decreased serum triglyceride levels after 6 weeks of intervention compared with the placebo group, it was statistically significant (59.4) -1.6 versus (37.9) +27.1 mg/dL and p = 0.03). The effects of supplementation on the level of VLDL cholesterol were similar (11.9) -0.3 mg/dl in the probiotic group versus (7.6) + 5.44 in the placebo group and p = 0.03). There were no significant differences between the two groups after the intervention (p = 0.58, p = 0.15, p = 0.82 for total cholesterol, LDL cholesterol and HDL cholesterol, respectively) (24).

The Effect of Probiotics on Blood Pressure in Patients with Gestational Diabetes:

In a double-blind clinical trial conducted by Hajifaraji et al. the effects of daily probiotic supplementation were investigated in pregnant women with gestational diabetes. Probiotic supplements of Lactobacillus acidophilus LA-5, Bifidobacterium BB-12, Streptococcus thermophilus DTY-31 and Lactobacillus Delbruck Bulgaricus LBY-12 with a CFL of 10^9 × 4 with dietary recommendations for 8 weeks prevented the increase in systolic hypertension and decreased significant diastolic blood pressure was observed after the second week of intervention (p = 0.014) (22). Probiotic and food supplements have been shown to decrease serum glucose and insulin resistance (82, 83) and stabilize the renin-angiotensin system (84, 85), and by decreasing total and LDL cholesterol (82, 83) and decreasing inflammation (86), they are able to improve blood pressure control. On the other hand, inflammation from obesity can lead to endothelial dysfunction (87) and there is a significant relationship between weight gain in pregnancy and hypertension (88). This means that hypertension could be prevented by controlling weight gain in pregnant women.

Intestinal barrier and endotoxemia / Metabolic bacteremia: host interaction / microbiota:

The concentration of lipopolysaccharides in plasma is inversely related to the population of bifidobacteria in the intestine. Bifidobacteria can reduce the level of intestinal endotoxins and improve the function of the intestinal mucous membrane, thereby reducing plasma lipopolysaccharide concentrations and controlling inflammation. Plasma lipopolysaccharide concentrations are associated with fasting insulin concentration and insulin resistance. Therefore, supplementation with probiotics can influence diabetes control by affecting the microflora of the intestine (89, 90).

The mechanisms for maintaining bad intestinal function and preventing bacterial transmission include:

a) GLP-2

Intestinotrophic proglucagon-derived peptide (GLP-2) is a peptide which is produced by the intestinal L cells and promotes intestinal growth and intestinal duct function through insulin-like growth pathways -1 and b catenin. The effects of probiotic Bifidobacterium on the function of intestinal ducts have been linked to the increase in GLP-2 production, while enhancing the integrity of intestinal connections (increasing the mRNA of ZO-1 binding and occluding proteins) and decreasing intestinal permeability (54).

b) TLR-2

TLR-2 is a PRR associated with cell membranes that detects multiple microbial molecules including peptidoglycans of membranes, lipotichoic acid and lipoprotein from gram negative bacteria and lipo-arabineu-mananes of mycobacteria (91). TLR-2 maintains the integrity of the intestinal epithelium barrier at the frontline of the host defense. The TLR-2 signaling activates the anti-apoptotic pathway of PI3K / AKT (Phosphatidyl Inositol-3-Kinase and Protein Kinase B). Therefore, TLR-2 protects the intestinal epithelium cells from stress-induced apoptosis (40).

c) MyD88 (Myeloid Differentiation 88)

MyD88 is required to maintain tight joints and function of the TLR-2 mediated intestinal block in response to inflammation and stress (40). Upward regulation based on MyD88 host endogenous antimicrobial compounds is essential to control permeability of the intestinal dam by bacterial and pathogenic bacteria. MyD88 is an important mediator of host interaction-microbiota that maintains metabolic health (92).

d) NLRC2 (NOD2)

NLRC2 is an important microbial sensor in the intestinal dam, which recognizes the morbidity of the peptide (MDP), and is a vital peptidoglycan component of all bacterial cell walls.

NLRC2 preserves the microbial population structure and inhibits the colonization of opportunistic microbes in the ileum by modulating the mediated immune function (93). Nod2 frameshift (SNP13) mutant humans have a significant increase in Bacteroidetes and Firmicutes, and multiple Nod2 polymorphisms have a higher risk for inflammatory bowel disease.

Sterile inflammation: Fatty acids as PRR ligands:

PRRs are also activated by non-microbial molecules (sterile inflammation), especially dietary fats.

TLRs (TLR-2 and4) and NLRCs can be activated by saturated fatty acids and controlled by omega-3 fatty acids (94). Activation of TLRs 2 and 4 directly contributes to the spread of inflammation associated with obesity and insulin resistance, which suggests that inflammation induced by free fatty acids can exacerbate metabolic endotoxemia or have synergistic effects with it (40).

The present review study considers a new area of probiotic research with a limited number of articles in this area. Data extracted from this study have been from 10 papers in line with the study objectives. The results of this review study are subject to limitations. Most studies in this area have a low sample size with the relatively short duration of the intervention period. Also, the probiotic species used in the studies vary greatly, making it difficult to conclude. The use of probiotics can have other benefits in reducing the complications of gestational diabetes, such as the risk of macrosomia, the risk of preeclampsia and long-term metabolic complications that should be considered in subsequent overview studies. Other aspects such as probiotic dosage, probiotic specific species and storage conditions should be considered in future studies. The relationship between diet, metabolism and host microbiota has different aspects. The diet has the ability to affect the microbial intestinal tract as well as the direct change of host metabolism. These changes are the basis of changes in host inflammatory pathways, glucose metabolism and lipid metabolism. It seems that the use of probiotics, both edible and as probiotic foods, has a promising effect on the prevention and treatment of metabolic complications of gestational diabetes, although the results are largely contradictory, making a definitive conclusion as a problem. More clinical studies with bacterial strains are required.

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