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Effects of probiotic supplementation on glucose metabolism and inflammatory biomarkers in pregnant women with gestational diabetes mellitus: an integrative review

Efeitos da suplementação de probióticos no metabolismo da glicose e de biomarcadores inflamatórios em gestantes com diabetes mellitus gestacional: uma revisão integrativa

Efectos de la suplementación con probióticos sobre el metabolismo de la glucosa y los biomarcadores inflamatorios en mujeres embarazadas con diabetes mellitus gestacional: una revisión integradora

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Ribanna Aparecida Marques Braga
ORCID: https://orcid.org/0000-0003-2122-5658
Universidade Estadual do Ceará, Brazil
E-mail: ribanna.marques@gmail.com
Maria Dinara de Araújo Nogueira
ORCID: https://orcid.org/0000-0001-7843-9089
Universidade Estadual do Ceará, Brazil
E-mail: dinara.araujo@hotmail.com
Francisca Isabelle da Silva e Sousa
ORCID: https://orcid.org/0000-0001-6226-3381
Universidade Estadual do Ceará, Brazil
E-mail: isabelle_sousa@outlook.com
Alexandre Danton Viana Pinheiro
ORCID: https://orcid.org/0000-0001-9180-5514
Universidade Estadual do Ceará, Brazil
E-mail: alexandredanton@hotmail.com
Maria Raquel da Silva Lima
ORCID: https://orcid.org/0000-0002-8495-2345
Centro Universitário Estácio do Ceará, Brazil
E-mail: raquelsc@edu.unifor.br
Antoniel Rodrigues Sousa
ORCID: https://orcid.org/0000-0001-8636-2691
Escola de Saúde Pública do Ceará, Brazil
E-mail: antoniel.sousa@aluno.uece.br
Ana Clara Vital Batista
ORCID: https://orcid.org/0000-0001-7471-1663
Universidade Federal da Bahia, Brazil
E-mail: antoniel.sousa@aluno.uece.br
Ana Lúcia Hoefel
ORCID: https://orcid.org/0000-0003-0940-3263
Universidade Estácio de Sá, Brazil
E-mail: nutrianahoefel@gmail.com

Abstract
Aims: This literature review aims to investigate the effect of probiotic supplementation on glucose metabolism and inflammatory biomarkers in pregnant women with gestational diabetes mellitus. Methods: Data were collected using the National Library of Medicine (Medline), Latin American & Caribbean Health Sciences Literature (Lilacs), Virtual Health Library (BVS) and Scientific Electronic Library Online (Scielo) databases. The following descriptors were used: "gestational diabetes", "probiotic" and "inflammation". Results: The main findings emphasized the improvement in fasting glucose and insulin resistance and a lesser impact on the improvement of inflammatory markers after probiotic supplementation in pregnant women diagnosed with gestational diabetes mellitus. Conclusions: The use of probiotics in pregnant women with gestational diabetes mellitus has shown positive actions to control glucose metabolism and proinflammatory factors, which may improve serum glucose levels, insulin sensitivity and inflammation.
Keywords: Gestational diabetes; Probiotic; Inflammation.

Resumo

Objetivos: A presente revisão de literatura tem como objetivo investigar o efeito suplementação de probióticos no metabolismo da glicose e biomarcadores inflamatórios de gestantes com diabetes mellitus gestacional. Métodos: O levantamento dos dados foi realizado através das bases National Library of Medicine (Medline), Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs), Biblioteca Virtual em Saúde (BVS) e Scientific Electronic Library Online (Scielo). Os seguintes descritores foram utilizados "diabetes gestacional", "probiótico" e "inflamação". Resultados: Os principais achados enfatizaram a melhora da glicemia de jejum e resistência à insulina e um menor impacto na melhora dos marcadores inflamatórios após a suplementação de probióticos em mulheres grávidas com diagnóstico de diabetes mellitus gestacional. Conclusões: O uso de probióticos em mulheres grávidas com diabetes mellitus gestacional mostrou ações positivas de controle do metabolismo da glicose e de fatores pró-inflamatorios, podendo melhorar os níveis séricos de glicose, a sensibilidade à insulina e a inflamação.
Palavras-chave: Diabetes gestacional; Probiótico; Inflamação.

Resumen

Objetivos: La presente revisión de la literatura tiene como objetivo investigar el efecto de la suplementación con probióticos sobre el metabolismo de la glucosa y los biomarcadores inflamatorios en mujeres embarazadas con diabetes mellitus gestacional. Métodos: La recolección de datos se realizó utilizando la Biblioteca Nacional de Medicina (Medline), Literatura Latinoamericana y del Caribe en Ciencias de la Salud (Lilacs), Biblioteca Virtual en Salud (BVS) y Biblioteca Científica Electrónica en Línea (Scielo). Se utilizaron los siguientes descriptores "diabetes gestacional", "probiótico" e "inflamación". Resultados: Los principales resultados destacaron la mejora de la glucosa en ayunas y la resistencia a la insulina y un menor impacto en la mejora de los marcadores inflamatorios después de la suplementación con probióticos en mujeres embarazadas con diagnóstico de diabetes mellitus gestacional. Conclusión: El uso de probióticos en gestantes con diabetes mellitus gestacional ha mostrado acciones positivas para controlar el metabolismo de la glucosa y los factores proinflamatorios, pudiendo mejorar los niveles séricos de glucosa, la sensibilidad a la insulina y la inflamación.
Palabras clave: Diabetes gestacional; Probiótico; Inflamación.

1. Introduction

The World Health Organization (WHO) characterizes Gestational Diabetes Mellitus (GDM) as an intolerance to carbohydrates that does not fulfill the diagnostic parameters of Diabetes Mellitus (DM) (World Health Organization [WHO], 2013). Complications of GDM, such as pre-eclampsia, cesarean delivery, macrosomia and neonatal hypoglycemia can compromise maternal and fetal health in the short and long term (Dickens & Thomas, 2019; International Diabetes Federation [IDF], 2015; Scientific Advisory Committee on Nutrition [SACN], 2011). The prevalence of women who develop GDM, globally and nationally, ranges from 3% to 25% (Sacks, 2012; Sociedade Brasileira de Diabetes [SBD], 2019). The incidence of this type of diabetes has grown in parallel with the increase in cases of overweight among women of reproductive age (Schoenaker et al., 2016).

Physiological metabolic changes that are present in pregnancy predispose to insulin resistance (IR) and increase in inflammatory markers such as C-reactive protein (CRP), fibrinogen (Palem & Abraham, 2015), tumor necrosis factor α (TNF-α), interleukin-6 (IL-6) and interleukin-8 (IL-8) (Murthy et al. 2018; Pantham et al., 2015). Constipation, for example, is common in pregnant women due to the action of progesterone (Zhang et al., 2019), which promotes dysregulation of the intestinal microbiota, exacerbating inflammation and contributing to IR (Bock et al., 2021; Lim et al., 2007).

Evidence suggests positive effects of the use of probiotics, including in the dysbiosis scenario, for the control of inflammatory markers. However, studies are still limited as to their effects on IR (Barrett et al., 2012; Gomes et al., 2014; Lee et al., 2013; Panwar et al., 2013). In 2002, the Food and Agriculture Organization of the United Nations (FAO) defined probiotics as live microorganisms that, when administered in an adequate manner and in adequate amounts, bring beneficial effects to the health of the host. (Redman et al., 2014).

Given what has been presented, it is demonstrated the importance of investigating the relationship between the use of probiotics in the improvement of changes in glucose metabolism and inflammation found in GDM. Thus, this literature review

aims to investigate the effect of probiotic supplementation on glucose metabolism and inflammatory biomarkers in pregnant women with GDM.

2. Methodology

The integrative review was the method chosen to achieve the objective of this study, as it is characterized as a research method that allows a more comprehensive synthesis of published studies on a given subject, analyzing their results in a systematic and orderly manner, contributing to the deepening of the knowledge about the researched topic (Souza, Silva & Carvalho, 2010).

For the application of the method, the following steps were followed: elaboration of the guiding question; literature search for studies; categorization of studies; evaluation of the studies chosen for the review; interpretation of results; synthesis of knowledge and presentation of the review (Mendes et al., 2008).

The search for studies was based on the following guiding question: “Does supplementation with probiotics in pregnant women with GDM produce beneficial effects on glucose metabolism and on inflammation biomarkers?”. Data collection was carried out through the National Library of Medicine (Medline) and the Latin American & Caribbean Health Sciences Literature (Lilacs) databases, through Virtual Health Library (BVS) and Scientific Electronic Library Online (Scielo). The descriptors used were determined according to the Health Science Descriptors (DECs): "gestational diabetes", "probiotic" and "inflammation", combined with each other through the boolean operator "AND".

Only clinical trials available in full in the last 10 years and in Portuguese or English were included. The exclusion criteria adopted were: review studies; cross-sectional studies; case studies; animal studies; theses; dissertations; studies that did not answer the guiding question; and duplicate articles. After reading the titles and abstracts, the full reading was taken, where studies that did not have free access were excluded.

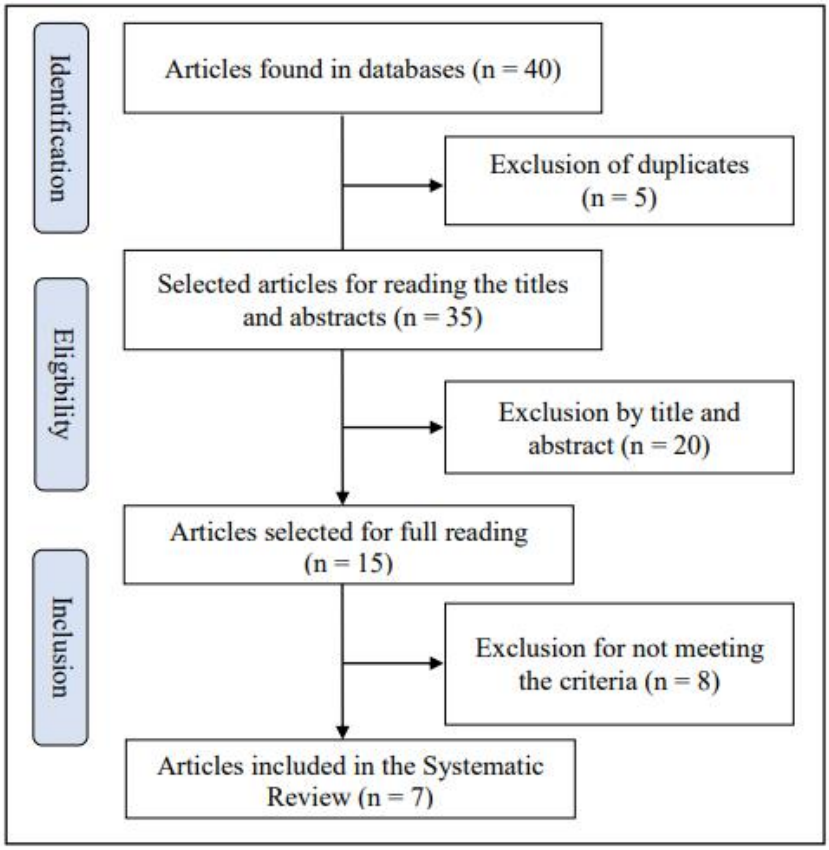
3. Results

According to the inclusion criteria, 40 articles were found in the search. After reading the titles and abstracts, 15 studies were read in full. Eight studies had no full text available, therefore, seven articles were selected to compose this review. The flowchart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used to detail the article selection process (Figure 1). The article selection steps are shown in Figure 1. The characteristics of the study, as well as the main results, can be seen in Table 1.

It was possible to observe similarities between the studies, such as the chosen gestational age (most opted for the period of 24 to 28 weeks of gestation to test the effect of probiotics), the maximum age (which was 45 years) and the duration of the intervention (which ranged largely from 6 to 8 weeks).

The great distinction observed occurred in relation to the strains used, which included between one and eight types of probiotics, varying their classes of *Lactobacillus*, *Streptococcus* and *Bifidobacterium*. It is also noted that despite some positive impacts on the lipid profile and inflammatory markers, the main findings emphasized the improvement in fasting glucose and IR.

Figure 1. Flowchart of the bibliographic research process.



Source: Author's own authorship.

Table 1. Synthesis of the effect of probiotic supplementation on glucose metabolism and inflammatory biomarkers in pregnant women with gestational diabetes mellitus **(to be continued)**.

Author	Objectives	Sample/Age/gestational week	Intervention/ Duration	Outline	Main results
Lindsay *et al*., 2015	To investigate the effects of a probiotic capsule intervention on maternal metabolic parameters in pregnant women with GDM	100 patients › 18 years old ‹ 34 weeks	Group 1(=48) - Probiotic: 100mg of *Lactobacillus salivarus* Group 2(=52): Placebo 8 weeks	Clinical trial, controlled, double-blind	Supplementation had no impact on glycemic control. There was an increase in cholesterol (LDL) at the end of pregnancy in the probiotic group.
Dolatkhah *et al*., 2015	To verify the effect of probiotic supplements on glucose metabolism and weight control in women newly diagnosed with GDM	56 patients 18 - 45 years old 24-28 weeks	Group 1(=29) - Probiotic: *Lactobacillus acidophiluus, Bifidobacterium, Streptococcus thermoplhilus, Lactobacillus delbrueckii* Group 2(=27) - Placebo 8 weeks	Clinical trial, controlled, double-blind	Fasting blood glucose and insulin resistance (HOMA-IR index) significantly decreased in the probiotic group compared to placebo after the intervention. There was no significant difference between groups regarding insulin sensitivity (QUICKI index).
Jafarnejad *et al*., 2016	To examine the effects of a probiotic mixture on glycemic status and inflammatory markers in women with GDM	72 patients Group 1: 32,4 ± 3,1 years old Group 2: 31,9 ± 4.0 years old Group 1: 26,4 weeks Group 2: 26,6 weeks	Group 1 (n=37) - Probiotic mixture: *Streptococcus Thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii* Group 2 (n=35) - Placebo 8 weeks	Clinical trial, controlled	There was a significant reduction in fasting insulin, insulin resistance (HOMA-IR index) and inflammatory markers (CRP, IL-6 and TNF-α) in group 1 compared to 2 after the intervention. However, for fasting glucose and HbA1c the results did not show statistical differences between groups 1 and 2 after the intervention.
Karamali *et al*., 2016	To determine the effects of probiotic supplementation on glycemic control and lipid profile in patients with GDM	60 patients 18-40 years old 24-28 weeks	Group 1(n=30) - Probiotics: *Lactobacillus acidophiluus, Lactobacillus casei, Bifidobacterium Bifidum* Group 2(n=30) - Placebo 6 weeks	Clinical trial, controlled, double-blind	In group 1, supplementation with probiotics reduced fasting glucose, serum insulin levels, insulin resistance (HOMA-IR), TGL and VLDL compared to placebo. In addition, there was an increase in insulin sensitivity (QUICKI) in group 1 compared to 2 after probiotic supplementation.

Table 1. Synthesis of the effect of probiotic supplementation on glucose metabolism and inflammatory biomarkers in pregnant women with gestational diabetes mellitus **(conclusion)**.

Babadi *et al*., 2018	Evaluate the effects of probiotic supplementation on the genetic and metabolic profiles of patients with GDM without the use of oral hypoglycemic agents	48 patients with DMG 18-40 years old 24-28 weeks	Group 1(n=24) - Probiotic capsule: *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus Fermetum, Bifidobacterium bifidum* Group 2 (n=24) - Placebo 6 weeks	Clinical trial, controlled, double-blind	Group 1 significantly decreased fasting plasma glucose, serum insulin levels, insulin resistance (HOMA-IR index), TGL, VLDL and total cholesterol compared to placebo. There was an increase in insulin sensitivity (QUICKI index), HDL-c, plasma nitric oxide and total antioxidant capacity, reducing inflammation and oxidative stress in groups 1 compared to 2 after intervention.
Kijmanawat *et al*., 2018	Evaluate the effect of probiotic supplementation on insulin resistance in pregnant women with diet-controlled GDM	57 patients 18-45 years old 24-28 weeks	Group 1 (n=28) - Probiotic: *Lactobacillus acidophilus e Bifidobacterium bifidum.* Group 2(n=29) - Placebo 4 weeks	Clinical trial, controlled, double-blind	The group that received the supplementation with probiotics had lower levels of fasting blood glucose, fasting insulin and insulin resistance (HOMA-IR index) compared to the placebo group.
Hajifaraji *et al.*, 2018	Measuring the effect of a probiotic supplement capsule on inflammation and oxidative stress biomarkers in women with newly diagnosed GDM	56 patients 18-45 years old 24-28 weeks	Group 1(n=29) - Probiotic (*Lactobacillus acidophiluus, Bifidobacterium BB-12, Streptococcus thermoplhilus, Lactobacillus delbrueckii)* Group 2(n=27) - Placebo 8 weeks	Clinical trial, controlled, double-blind	Serum levels of C-reactive protein and Tumor Necrosis Factor-α improve in the probiotic group compared to placebo. In addition to the levels of malondialdehyde, glutathione reductase, and glutathione peroxidase.

Caption: GDM: gestational diabetes mellitus; HOMA-IR: homeostasis assessment model for insulin resistance; QUICKI: quantitative index for checking insulin sensitivity; CRP: C-reactive protein; IL-6: interleukin 6; TNF-α: tumor necrosis factor α; HbA1c: glycated hemoglobin; VLDL: very low density lipoprotein; HDL: high density lipoprotein; LDL: low density lipoprotein; TGL: triglycerides. Source: Authors.

4. Discussion

From the studies that were part of this review, it was possible to observe, mainly, findings of improvement in fasting glucose and IR. However, some studies have also shown positive impacts on the lipid profile and inflammatory markers.

Most of the studies analyzed in the current review identified improvement in fasting glucose and IR with the use of probiotics, in addition, two studies also demonstrated benefits from the use of these beneficial bacteria in improving insulin sensitivity. The mechanisms by which probiotics alter glucose homeostasis are not fully understood. A proposed method is based on the production of short-chain fatty acids (SFAs), by-products of bacterial fermentation of dietary fibers. AGCs stimulate, in the intestine, the expression of hormones that decrease appetite, reducing intestinal transit time and increasing insulin sensitivity (Kellow et al., 2014). Thus, these bacteria can improve the control of GDM (Dallanora et al., 2018).

Another action of AGCs is to promote the integrity of the intestinal barrier, minimizing the concentration of circulating lipopolysaccharides (Jayashree et al., 2014) a structural component of gram-negative bacterial cell walls that induces an immune cell response, stimulating the production of pro-inflammatory cytokines and the onset of IR and hyperglycemia (Cani et al., 2007). The current review found studies in which the modulation of the microbiota showed positive effects in controlling blood glucose, improving insulin sensitivity, as well as reducing inflammatory markers and increasing antioxidant capacity in women with GDM.

In a study carried out with 91 pregnant women, it was possible to observe significant changes in the composition of the intestinal microbiota from the first to the third trimester of pregnancy. Probiotics act positively on inflammatory processes (Bai et al., 2004; Lee et al., 2013). For such desired treatment effects, it is important to consider the genera and strains provided in probiotics. *Lactobacillus* and *Bifidobacterium*, for example, have effects related to the modulation of inflammatory and hypersensitivity processes (Reid et al., 2003). The strains chosen in the studies were mostly *Lactobacillus* and *Bifidobacterium*.

Hormonal actions are remarkable during pregnancy. Progesterone reduces intestinal motility, creating a condition of constipation present in most pregnant women (Zhang et al., 2019). In this scenario, dysregulation of the intestinal microbiota occurs mainly due to the proliferation of commensal bacteria, which exacerbate systemic inflammation and contribute to IR (Lim et al., 2007; Bock et al., 2021). Due to changes in maternal metabolism to meet fetal demands, as circulating maternal glucose is an essential nutrient for the fetus, especially during the second trimester, IR becomes more present. (Lain & Catalano, 2007). Thus, the use of the 24–28-week period is justified in most of the studies analyzed in the current review.

The intestinal microbiota is among the many changes that take place during pregnancy, especially in the third trimester (Crusell et al., 2018; Koren et al., 2012; Ponzo et al, 2019). When comparing the microbiota of women with GDM and healthy pregnant women between 21 and 29 weeks of gestation, findings demonstrated the presence of intestinal dysbiosis in pregnant women with GDM (Kuang et al., 2017). Dysbiosis is associated with inflammation, adiposity, glucose intolerance, high serum levels of lipopolysaccharide and body weight gain (Caricilli & Saad, 2013; Hasain et al., 2020). Therefore, finding alternatives to improve this microbiota is essential, and probiotics have shown positive effects in terms of glycemic control, IR and inflammation.

5. Conclusion

The use of probiotics in pregnant women with GDM showed positive actions to control glucose metabolism and proinflammatory factors, which may improve serum glucose levels, insulin sensitivity and inflammation. Future studies may investigate the effect of probiotic use on oxidative stress in women with GDM, as few studies have specifically addressed the redox context these women's bodies are experiencing.

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