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REVIEW

THE ADJUNCTIVE USE OF PROBIOTICS IN THE PERIODONTAL TREATMENT OF INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

El uso adyuvante de probióticos en el tratamiento periodontal de individuos con diabetes mellitus tipo 2: una revisión sistemática y metanálisis

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ABSTRACT

Background: Probiotics are beneficial bacteria that can promote health benefits. The aim of the present systematic review and meta-analysis was to assess the effectiveness of probiotics as an adjunct to periodontal therapy in patients with periodontitis and type 2 diabetes mellitus.

Material and Methods: The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered in the International Prospective Register of Systematic Reviews (PROSPERO). A systematic search was conducted across *PubMed, Web of Science, LILACS, Cochrane, Embase* and *Scopus* databases and *OpenGrey* and *Clinical Trials*, without language or date restrictions. Studies that investigated probiotic treatment as an adjunct to periodontal therapy in patients with periodontitis and type 2 diabetes were included. Study selection, data extraction, and risk of bias assessment were performed in duplicate. A meta-analysis was conducted, reporting the mean difference (MD) and a 95% confidence interval (CI).

Results: A total of 149 references were screened, with three studies meeting inclusion criteria. Meta-analysis from two studies revealed no significant difference between individuals undergoing probiotic treatment as an adjunct to periodontal therapy and those undergoing periodontal therapy alone for probing depth (MD=0.10, CI=-0.12–0.32, I^2=0%) and clinical attachment level (MD=-0.12, CI=-0.43 – 0.18, I^2=0%) at 3 months. Two studies were classified as low risk of bias and one was classified as moderate risk of bias.

Conclusions: The addition of probiotics to periodontal therapy in individuals with periodontitis and type 2 diabetes mellitus did not show additional benefits compared to periodontal treatment alone.

Keywords: *Probiotics; Oral health; Diabetes mellitus, type 2; Periodontitis; Glycemic control; Chronic disease*

Received: September 24, 2024. | **Accepted:** March 26, 2025. | **Published online:** April 28, 2025.

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doi:10.17126/joralres.2025.018

RESUMEN

Introducción: Los probióticos son bacterias beneficiosas que pueden promover beneficios para la salud. El objetivo de la presente revisión sistemática y metaanálisis fue evaluar la eficacia de los probióticos como complemento a la terapia periodontal en pacientes con periodontitis y diabetes mellitus tipo 2.

Material y métodos: El estudio siguió la declaración del Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) y se registró en el International Prospective Register of Systematic Reviews (PROSPERO). Se realizó una búsqueda sistemática en las bases de datos *PubMed, Web of Science, LILACS, Cochrane, Embase* y *Scopus*, así como en *OpenGrey* y *Clinical Trials*, sin restricciones de idioma ni fecha. Se incluyeron estudios que investigaron el tratamiento con probióticos como complemento a la terapia periodontal en pacientes con periodontitis y diabetes tipo 2. La selección de estudios, la extracción de datos y la evaluación del riesgo de sesgo se realizaron por duplicado. Se realizó un metaanálisis, que reportó la diferencia de medias (DM) y su intervalo de confianza (IC) del 95%.

Resultados: Se analizaron 149 referencias, y tres estudios cumplieron los criterios de inclusión. El metanálisis de dos estudios no reveló diferencias significativas entre los individuos sometidos a tratamiento probiótico como complemento de la terapia periodontal y los sometidos únicamente a terapia periodontal en cuanto a la profundidad de sondaje (DM = 0,10; IC = -0,12 – 0,32; I^2 = 0%) y el nivel de inserción clínica (DM = -0,12; IC = -0,43 – 0,18; I^2 = 0%) a los 3 meses. Dos estudios se clasificaron con bajo riesgo de sesgo y uno con riesgo moderado de sesgo.

Conclusiones: La adición de probióticos a la terapia periodontal en individuos con periodontitis y diabetes mellitus tipo 2 no mostró beneficios adicionales en comparación con el tratamiento periodontal solo.

Palabras clave: *Probióticos; Salud bucal; Diabetes mellitus tipo 2; Periodontitis; Control glucémico; Enfermedad crónica*

INTRODUCTION

Periodontitis is an inflammatory disease of the periodontal tissues, caused by bacteria, clinically characterized by loss of attachment, increased probing depth (PD), and bleeding. The interaction between dysbiosis (microbial imbalance) and the host's immune and inflammatory response is crucial in the etiopathogenesis of this multifactorial periodontal disease.[1] Periodontitis is highly prevalent worldwide and contributes significantly to tooth loss, impacting both quality of life and systemic health.[2,3] Risk factors such as smoking and diabetes mellitus (DM) increase the prevalence, extent, and severity of periodontitis.[4-7]

Periodontal therapy aims primarily to eliminate pathogenic biofilm from both supra and subgingival environments, promoting a healthy symbiotic relationship. The effectiveness of periodontal treatment in reducing inflammation and restoring oral health has been well-documented. The long-term stability of treatment outcomes relies on adequate and regular biofilm control and the evaluation of maintenance therapy.[8,9]

Type 2 DM is a prevalent chronic condition characterized by hyperglycemia, associated with insulin resistance and/or relative insulin deficiency.[10-13] Immunological and inflammatory changes resulting from elevated blood glucose levels contribute to diabetes-related complications, including ophthalmological and cardiovascular issues, renal dysfunction, and periodontitis. Moreover, individuals with diabetes may experience increased susceptibility to infections and delayed wound healing.[14-18] In this context, managing periodontal treatment in individuals with DM presents complexities and challenges.[19-20]

Probiotics are microorganisms that can be formulated into various products such as foods, medications, and supplements. They aim to prevent and treat certain disorders, particularly those affecting the digestive system.[21] Probiotics compete with pathogens for essential nutrients, restrict the adhesion capabilities of pathogens by altering the environmental pH, and produce antimicrobial substances such as lactic acid and hydrogen peroxide, which can kill or inhibit the growth of pathogens. Additionally, probiotics can modulate the host's innate and adaptive immune response, reducing the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines, as well as improving the integrity of the epithelial barrier.

This action demonstrates the plausibility of using probiotics as adjuncts in the treatment of periodontitis, an inflammatory disease of periodontal tissues with a bacterial etiology. Their action on periodontal pathogens and regulation of the inflammatory response could contribute to controlling periodontal dysbiosis and the production of inflammatory cytokines, impacting the improvement of clinical parameters such as bleeding, probing depth, and clinical attachment level. This action is particularly relevant in diabetic individuals, who present periodontitis with greater severity and extent and poorer responses to periodontal therapy.[22-24]

Considering the high prevalence of periodontitis in individuals with type 2 DM and the necessity to enhance periodontal treatment for these individuals, it is crucial to explore adjunct therapies that can contribute to restoring oral health. Probiotics show promise as adjuncts in periodontal therapy due to their potential to influence bacterial colonization and modulate the host response. However, consensus regarding the effectiveness of probiotics in periodontal treatment for individuals with type 2 DM remains elusive.

The present systematic review and meta-analysis aims to assess the current scientific evidence regarding the benefits of using probiotics as adjunctive therapy to non-surgical periodontal treatment in individuals with type 2 DM and periodontitis, compared to periodontal treatment alone.

MATERIALS AND METHODS

Registration of a protocol

In this systematic review and meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used as a reference.[25] A protocol has been registered in the International Prospective Registry of Systematic Reviews (PROSPERO). The assignment number was N°. CRD42024554325.

Eligibility Criteria

The following clinical question was applied: Treatment with probiotics as an adjunct to periodontal therapy in patients with periodontitis and type 2 diabetes presents better

clinical results than periodontal treatment alone:

Patients: Individuals with periodontitis and type 2 DM.

Intervention: Probiotic therapy associated with periodontal treatment.

Comparison: Periodontal treatment alone.

Outcomes: Clinical aspects: bleeding, probing depth, and/or clinical attachment level.

Clinical trials evaluating the clinical aspects of patients with periodontitis and type 2 DM who used probiotic therapy associated with periodontal treatment and with a control group of patients with periodontitis and type 2 DM who underwent only periodontal therapy will be eligible for inclusion. Literature review studies, systematic reviews, conference abstracts, publisher comments, and studies without data on clinical aspects were ineligible for inclusion.

Information sources

In May 2024, two researchers (RPEL and LRCC) carried out electronic searches in the *PubMed, Web of Science, Lilacs, Cochrane, Embase,* and *Scopus* databases (Appendix I). There were no language restrictions or publication date restrictions. Manual searches in the references of articles included in the present systematic review and meta-analysis and in literature reviews retrieved during electronic searches were carried out. A gray literature search was performed on OpenGrey and Clinical Trials.

Study selection

The articles found through electronic searches in the databases were evaluated according to the inclusion and exclusion criteria. The selection of studies occurred in two phases and was conducted by two independent reviewers (RPEL and LRCC).

During the first phase, the title and abstract were read, and the articles were pre-selected according to the eligibility criteria. For references to these *titles/abstracts* that did not provide sufficient information for an inclusion or exclusion decision, the full text was obtained and read by the same two reviewers who applied equal eligibility classifications.

References that met the eligibility criteria were also included. Any divergence between the reviewers during the selection of studies was discussed until a consensus was reached.

Data extraction process and extracted items

The data extracted from each included study were: name(s) of the author(s), year of publication, country, sample size, age, follow-up time, intervention protocol, bleeding on probing, pocket depth, clinical attachment level, HbA1c (glycated hemoglobin), immuno-inflammatory results, and microbiological results. Data extraction was performed by two reviewers (RPEL and LRCC) and discrepancies were resolved through discussion and consensus.

Clinical and methodological heterogeneity among the studies included in the review was assessed considering the probiotic treatment protocols and the way periodontal clinical parameters were evaluated.

Assessment of the methodological quality (risk of bias) of studies

The risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2) and for Non-Randomized Trials (ROBINS-I). The risk of bias assessment was carried out by two independent reviewers (RPEL and LRCC), considering the appropriate tool.

Synthesis of results – Meta-analysis

Meta-analyses of continuous outcomes for PD and CAL comparing the test group (probiotics and periodontal therapy) and the control group (periodontal therapy) were performed. In the meta-analyses, data on mean difference and number of participants in each group were used. For meta-analyses with the expectation that the included studies may have different effects, the random effects model was used. Results were provided as mean difference and 95% confidence interval (CI).

The statistical heterogeneity among the studies included in the meta-analysis was assessed using the I^2 test. The I^2 value ranges from 0 to 100%, with the latter corresponding to maximum heterogeneity.

Figure 1. Flowchart of the systematic review and meta-analysis depicting the search and the selection of the included articles.

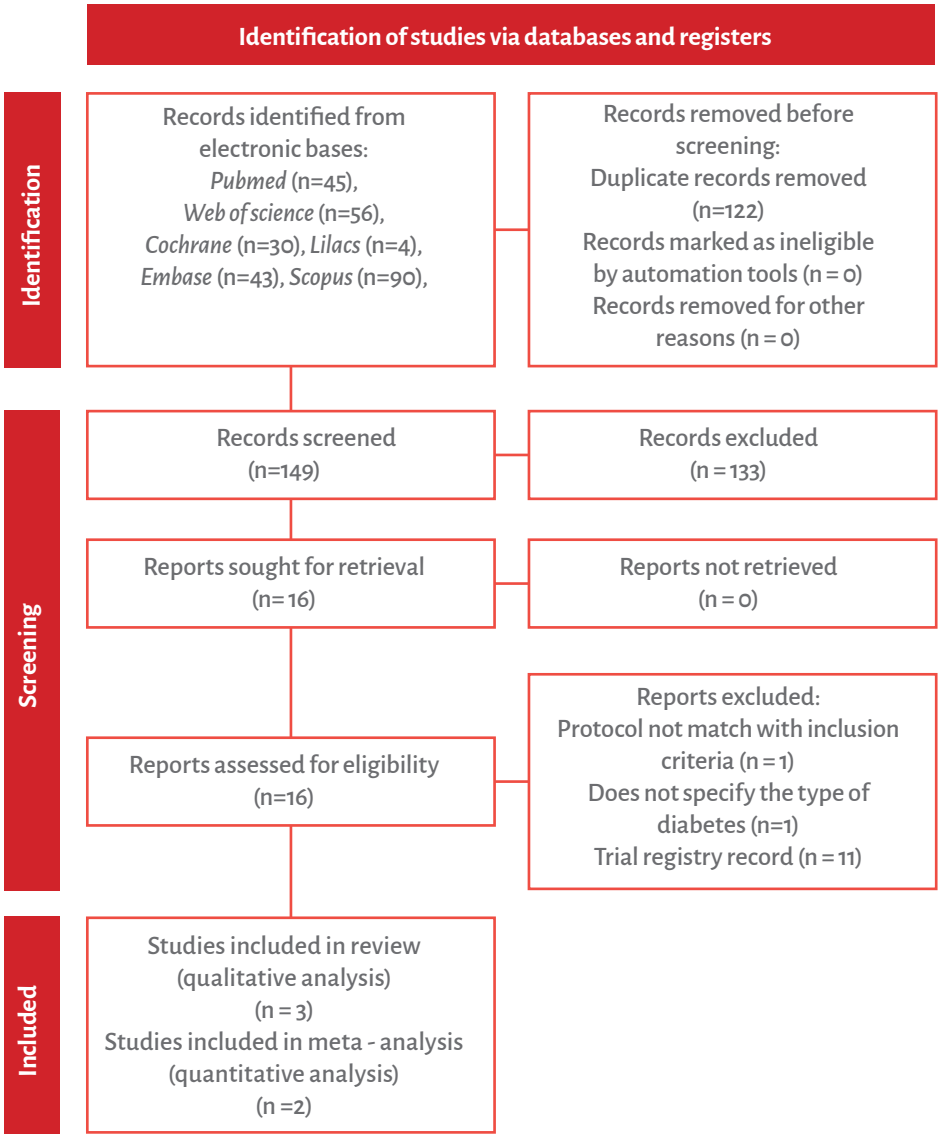
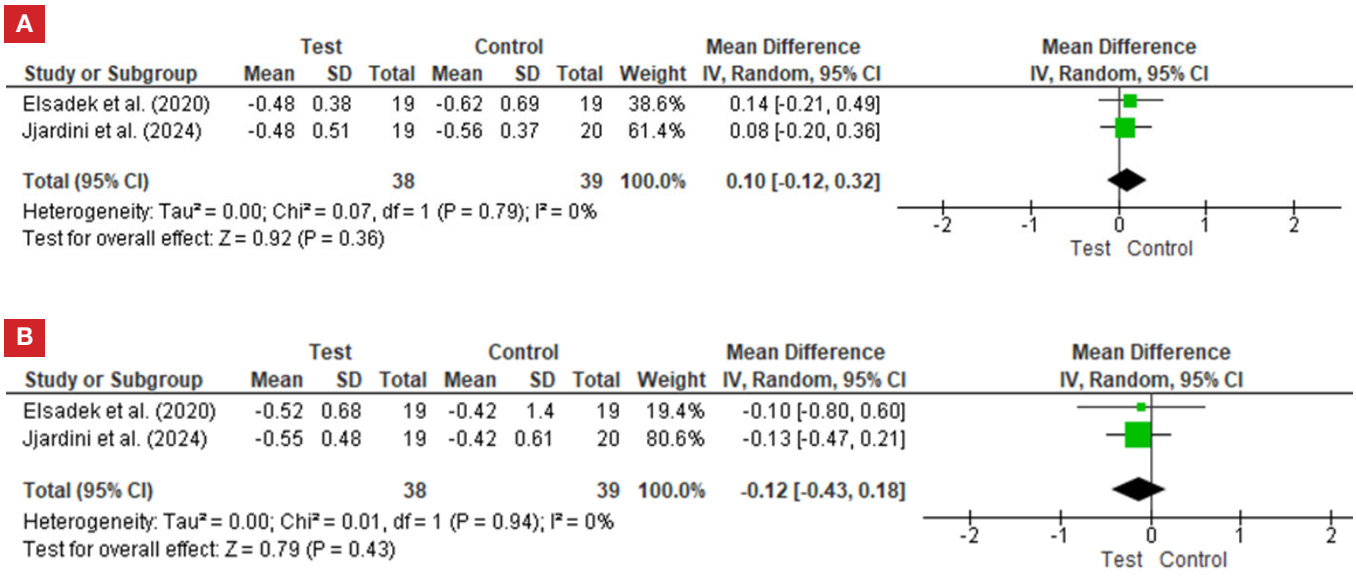


Figure 2. Meta-analysis comparing the test group.



A. Meta-analysis comparing the test group (probiotic and non-surgical periodontal therapy) and the control group (non-surgical periodontal therapy) for probing deep before and 3 months after treatment.
B. Meta-analysis comparing the test group (probiotic and non-surgical periodontal therapy) and the control group (non-surgical periodontal therapy) for clinical attachment level before and 3 months after treatment.

RESULTS

Study selection

Through the electronic search, 271 studies were found. Of these, 16 studies were selected for full reading. After this reading, 3 studies were included in this systematic review and meta-analysis. The references and the reason for exclusion of the 13 excluded studies are available in Appendix 2.

No additional references were found when searching the references of the articles included in our study, other literature reviews, and Open Grey. Figure 1 describes a flowchart representing the steps for selecting studies.

Characteristics of the studies

Table 1 shows the characteristics of the 3 included studies. These studies were carried out in Iran, Saudi Arabia, and Brazil, and were published in English. The number of participants in each study ranged from 38 to 47 individuals.

The follow-up time for individuals was no longer than 6 months after the intervention, which consisted of periodontal therapy associated with the use of probiotics or periodontal therapy alone. The study with the longest follow-up period after the intervention was that of Jardini *et al.*,[26] with 6 months, followed by the study by Elsadek *et al.*,[28] with 3 months, and the study by Bazyar *et al.*,[27] with 2 months of follow-up.
In addition to the variation in follow-up time, the included studies presented distinct probiotic therapy protocols. All studies assessed periodontal clinical parameters through periodontal probing of all present teeth.

Table 1. Results of included studies and their characteristics.

Author, Year Country	Sample (n)	Age Follow-up time	Test protocol	Probing depth attachment	Clinical probing	Bleeding on probing
Bazyar et al. 2020, Iran	Control: n=24 Test: n=23	Control: 50.1 Test:n= 4 8.6 *p* = 0.28 2 months	Test: 500 mg/d synbiotic + 100 mg fructo-oligoss-accharide per day for 8 weeks + NSPT. Control: 500 mg/d place-bo per day for 8 weeks + NSPT. Synbiotic supplement contained: *Lactobacillus acidophilus, L. casei, L. rhamnousus, L. bulg-aricus, Bifidobacterium breve, B. longum, Strep-tococcus thermophilus.*	Baseline: Control: 4.50 ± 0.97 Test: 4.30 ± 0.76 *p* = 0.45 2 months. Control: 4.04 ± 1.04 Test: 3.47 ± 0.79 *p* = 0.04	Baseline: Control: 3.08 ± 0.77 Test: 3.26 ± 0.61 *p* = 0.39 2 months Control: 2.95 ± 0.75 Test: 2.73 ± 0.75 *p* = 0.32	Baseline: Control: 24 Test: 23 *p* = 0.35 2 months Control: 22 Test: 19 *p* = 0.04
Elsadek et al. (2020) Saudi Arabia	Control: n=19 Test: n=19	Control: 52.9 Test: 51.9 3 months	Test: Probiotic + RSD Control: RSD alone Probiotic: tablets containing two strains *L. reuteri.* Two lozenges for over 24 hours for 3 weeks.	Baseline: Control: 3.36 ± 0.62 Test: 3.29 ± 0.47 3 months Control: 2.74 ± 0.75 Test: 2.81 ± 0.25 Proportion of PD ≥4mm Baseline Control: 0.26 ± 0.20 Test: 0.28 ± 0.21 3 months Control: 0.15 ± 0.16 Test: 0.14 ± 0.06 Proportion of PD ≥5mm Baseline Control: 0.15 ± 0.15 Test:0.15 ± 0.12 3 months Control: 0.09 ± 0.12 Test:0.09 ± 0.04	Baseline: Control: 4.71 ± 1.35 Test: 4.06 ± 0.83 3 months Control: 4.29 ± 1.44 Test: 3.54 ± 0.48	Baseline: Control: 0.69 ± 0.25 Test: 0.83 ± 0.13 3 months Control: 0.45 ± 0.27 Test: 0.63 ± 0.33
Jardini et al. (2024) Brazil	Control: n=20 Test: n=19	Control: 54.3 Test: 63.8 *p* = 0.004 6 months	Test: SRP + Probiotic Control: SRP + Placebo Probiotic or placebo was administered twice a day for 21 days. Probiotic: tablets containing *Lactobacillus reuteri*	Baseline Control: 3.31 ± 0.31 Test: 3.6 ± 0.54 *p*= 0.23 1 month Control: 3.00 ± 0.43 Test: 3.15 ± 0.57 *p* = 0.29 3 months Control: 2.75 ± 0.43 Test: 3.12 ± 0.47 *p* = 0.05	Baseline Control: 3.57 ± 0.40 Test: 4.00 ± 0.61 *p* = 0.02 1 month Control: 3.28 ± 0.55 Test: 3.57 ± 0.63 *p* = 0.12 3 months Control: 3.02 ± 0.54 Test: 3.58 ± 0.61 *p*= 0.002	Baseline Control: 88 ± 19 Test: 93 ± 17 *p*= 0.11 1 month Control: 41 ± 23 Test: 42 ± 26 *p*= 0.98 3 months Control: 29 ± 21 Test: 35 ± 27 *p*= 0.40

Table 1 continues on the next page →

Author, Year Country	Sample (n)	Age Follow-up time	Test protocol	Probing depth attachment	Clinical probing	Bleeding on probing
Jardini et al. (2024) Brazil	Control: n=20 Test: n=19	Control: 54.3 Test: 63.8 *p* = 0.004 6 months	Test: SRP + Probiotic Control: SRP + Placebo Probiotic or placebo administered twice a day for 21 days. Probiotic: tablets containing *Lactobacillus reuteri*	6 months Control: 2.69 ± 0.41 Test: 2.87 ± 0.51 *p* = 0.27 PD 5 and 6 mm Baseline Control: 5.4 ± 0.24 Test: 5.34 ± 0.18 *p* = 0.40 1 month Control: 4.32 ± 0.61 Test: 4.43 ± 0.66 *p* = 0.57 3 months Control: 3.9 ± 0.68 Test: 4.14 ± 058 *p* = 0.16 6 months Control: 3.75 ± 0.63 Test: 3.81 ± 0.59 *p* = 0.74 PD ≥ 7mm Baseline Control: 8.53 ± 1.33 Test: 7.95 ± 0.44 *p*= 0.32 1 month Control: 5.32 ± 1.73 Test: 6.50 ± 1.51 *p* = 0.10 3 months Control: 4.99 ± 1.46 Test: 6.23 ± 1.0 *p* = 0.02 6 months Control: 4.83 ± 1.38 Test: 5.05 ± 1.65 *p* = 0.79 Number of sites with PD 5 and 6mm Baseline Control: 10.00 ± 5.33 Test: 13.55 ± 10.3 *p*= 0.33 1 month Control: 3.35 ± 3.00 Test: 6.05 ± 5.64 *p* = 0.16	6 months Control: 2.96 ± 0.47 Test: 3.32 ± 0.57 *p* = 0.024 CAL 5 and 6 mm Baseline Control: 5.38 ± 0.19 Test: 5.06 ± 1.2 *p* = 0.43 1 month Control: 4.51 ± 0.56 Test: 4.5 ± 1.14 *p*= 0.72 3 months Control: 4.21 ± 0.65 Test: 4.35 ± 1.14 *p* = 0.66 6 months Control: 4.08 ± 0.65 Test: 4.11 ± 1.08 *p* = 0.08 CAL ≥ 7mm Baseline Control: 6.56 ± 3.53 Test: 7.51 ± 1.99 *p* = 0.73 1 month Control: 4.65 ± 3.09 Test: 6.69 ± 2.01 *p* = 0.03 3 months Control: 4.49 ± 2.77 Test:6.47 ± 1.94 *p* = 0.02 6 months Control: Test:5.89 ± 1.84 Control: 4.35 ± 2.62Aa *p* = 0.04	6 months Control: 29 ± 27 Test:24 ± 26 *p* = 0.31

Table 1 continues on the next page →

Author, Year Country	Sample (n)	Age Follow-up time	Test protocol	Probing depth attachment	Clinical probing loss	Bleeding on probing
Jardini et al. (2024) Brazil	Control: n=20 Test: n=19	Control: 54.3 Test: 63.8 *p* = 0.004 6 months	Test: SRP + Probiotic Control: SRP + Placebo Probiotic or placebo administered twice a day for 21 days. Probiotic: tablets containing *Lactobacillus reuteri*	3 months Control: 2.5±2.54 Test: 6.15±6.52 *p* = 0.06 6 months Control: 2.55±2.21 Test: 5.30±6.41 *p* = 0.38 Number of sites with PD≥ 7mm Baseline Control: 4.08±2.06 Test: 8.38±6.78 *p*= 0.03 1 month Control: 1.31±1.03 Test: 4.31±4.70 *p* = 0.18 3 months Control: 0.92±0.86 Test: 3.85±3.89 *p* = 0.05 PD (6 months) Control: 0.85±0.90 Test: 3.00±3.42 *p* = 0.22 PISA Baseline Control: 907.11±279.28 Test: 992.71±360.28 *p* =0.49 1 month Control: 433.03±271.66 Test: 455.15±320.15 *p* = 0.95 3 months Control: 245.25±243.65 Test: 391.56±341.31 *p* = 0.04 6 months Control: 181.93±232.07 Test: 262.82±337.35 *p* = 0.38		

RPISA: Periodontal Inflamed Surface Area. **NSPT:** Non Surgical Periodontal Therapy. **RSD:** Root Surface Debridement. **SRP:** Scaling and Root Planing.

Study results

All included studies compared periodontal clinical parameters between the control and test groups. One study, Bazyar *et al.*,[27] demonstrated a significant difference between the two groups and improvement in probing deep (PD) and bleeding on probing (BOP) after 2 months in individuals who underwent probiotic therapy as an adjunct to periodontal treatment compared to individuals who only underwent periodontal therapy.

There was no difference between the groups in relation to clinical attachment loss (CAL). Another study, Elsadek *et al.*,[28] showed significant improvement in clinical and microbiological parameters within 3 months of intervention in both groups. In the group that used probiotics as an adjunct to periodontal treatment, there was a significant reduction in the frequency of Porphyromonas gingivalis and Tannerella forsythia compared to the control group. In the study by Jardini *et al.*,[26] a significant difference between the groups was observed for PD at 3 months and CAL at 3 and 6 months, with benefits for the test group.

However, no difference between groups was observed for BOP at the times evaluated. Immuno-inflammatory results were observed in two studies. The study by Bazyar *et al.*,[27] showed that after 2 months, in the group where periodontal therapy associated with probiotics was performed, there was a significant reduction in serum levels of Interleukin (IL) 1β, but this average change was significantly lower in the test group compared to the control.

In another study, Jardini *et al.*,[26] showed significant differences in intergroup analysis for IL-8 at the beginning of the study, IL-1β in months 1 and 3, and IL-10 and IL-12 in the third month. Levels of cytokines IL-13, IL-6, and tumor necrosis factor alpha (TNF-α) did not change significantly in intergroup comparisons. Interferon gamma (IFN-γ), IL-4, IL-8, IL-10 showed a decrease, and levels of IL-12 and IL-1β showed an increase in the probiotic intervention group. In the control group, cytokines IL-10 and IL-8 were reduced and IL-12 increased after periodontal treatment. The results of the included articles are described in Table 1.

Assessment of the methodological quality (risk of bias) of studies

The results of the risk of bias assessment for the randomized studies and the non-randomized study are described in Appendix 3 and Appendix IV, respectively. The randomized studies[26,27] were classified as low risk of bias, and the non-randomized study[28] was classified as moderate risk of bias.

Synthesis of results - meta-analysis

In the analysis comparing the test group (probiotic and non-surgical periodontal therapy) and the control group (non-surgical periodontal therapy) for PD before and 3 months after treatment, data from two studies[26,28] were combined. The results demonstrated no significant difference between individuals undergoing probiotic treatment as an adjunct to periodontal therapy and those in the control group for PD 3 months after treatment (MD= 0.10, CI=-0.12 – 0.32, I^2=0%) (Figure 2A). In the analysis comparing the test group (probiotic and non-surgical periodontal therapy) and the control group (non-surgical periodontal therapy) for CAL before and 3 months after treatment, data from two studies[26,28] were also combined.

The results showed no significant difference between individuals undergoing probiotic treatment as an adjunct to periodontal therapy and those in the control group for CAL 3 months after treatment (MD=-0.12, CI=-0.43 – 0.18, I^2=0%) (Figure 2B).

DISCUSSION

Type 2 DM is one of the risk factors contributing to the progression and increased complexity of periodontitis.[4-6] In light of this, improving periodontal treatment for these individuals is important to enhance clinical parameters and restore oral health.

In this regard, adjunctive treatments such as probiotics have been studied for their potential to affect bacterial colonization and modulate the host's immune response.
This systematic review and meta-analysis evaluated the benefits of using probiotics as an adjunctive treatment to periodontal therapy in type 2 DM. Results from individual studies demonstrated benefits at specific times for PD and BOP, while at other times, additional benefits were not observed.
However, the meta-analysis showed no significant difference between the test and control groups in PD and CAL parameters three months after intervention.

A scoping review conducted by De Brito Avelino *et al.*,[29] gathered data from six articles and demonstrated that probiotics can improve clinical parameters of PD and BOP in patients with type 2 DM. However, this review included individuals with gingivitis and periodontitis, not just periodontitis.

Furthermore, differences in glycemic control, as well as the severity and extent of periodontal diseases, may influence the results, in addition to differences in the diagnosis of periodontitis and probiotic therapy.
Other studies also indicated improvements in periodontal parameters when periodontal therapy was combined with other adjunctive treatments in patients with type 2 DM.[29,30,31,32] Each adjunctive therapy presents a different mechanism of action and varying degrees of plausibility regarding its impact on periodontal therapy, which should be considered when comparing the various treatment alternatives. Moreover, probiotic therapy, in particular, lacks a defined protocol, and the heterogeneity among studies regarding this topic is quite significant.

In this context, the systematic review and meta-analysis by Da Silva-Junior *et al.*,[30] evaluated the effects of antimicrobial photodynamic therapy as an adjunct to periodontal treatment in individuals with type 2 DM and demonstrated improvements in PD and BOP parameters. The meta-analysis by Freire *et al.*,[31] analyzed the effects of photobiomodulation as an adjunct to periodontal therapy in individuals with type 2 DM and demonstrated improvements in reducing PD and CAL. The clinical study by Gullapelli *et al.*,[32] showed that the adjunctive use of tetracycline in individuals with controlled type 2 DM yielded better clinical results than in those with uncontrolled type 2 DM and demonstrated that probiotics provide better results than periodontal treatment alone.

It is also important to highlight that studies have demonstrated the benefit of using probiotic therapy as an adjunct to periodontal treatment in non-diabetic individuals. In clinical studies conducted by Ghasemi *et al.*,[33] and Grusovin *et al.*,[34] the use of probiotics associated with periodontal therapy not only promoted improvement in BOP and CAL, but also contributed to a significant reduction in PD compared to periodontal therapy alone. The meta-analysis by Hu *et al.*,[35] which included 24 clinical studies, demonstrated that within 3 months, the adjunctive use of probiotics significantly improved PD, BOP and CAL compared to periodontal therapy alone.

In contrast, some studies showed divergent results where the adjunctive use of probiotics did not lead to significant positive changes in clinical parameters. In the study by Pudgar *et al.*,[36] the adjunctive use of probiotics resulted in a greater number of residual periodontal pockets greater than 4 mm and increased BOP. In the study by Kumar *et al.*,[37] the use of probiotics did not show significant differences in PD and BOP compared to periodontal treatment alone.

Regarding microbiological aspects, positive results were found associated with the use of probiotics as an adjunct to periodontal treatment in individuals with and without type 2 DM. De Brito Avelino *et al.*,[28] found a significant reduction in the frequency of pathogenic periodontal bacteria in individuals with type 2 DM, while Gheisary *et al.*,[38] found a reduction in the counts of bacteria Porphyromonas gingivalis, Tannerella forsythia and Fusobacterium nucleatum in individuals without type 2 DM.

Considering the relationship between periodontitis and diabetes, studies have also been conducted to verify whether periodontal treatment alone impacts glycemic control, contributing to a reduction in HbA1c levels. Several studies[39-43] have demonstrated that periodontal therapy has a positive impact on improving glycemic control in patients with periodontitis and DM, within a range of 3 to 12 months. Furthermore, it has been shown that the use of antibiotics as an adjunct to periodontal treatment in individuals with type 2 DM provides additional benefits in terms of their glycemic control.[44-46]

Therefore, it is possible to infer that periodontal treatment combined with other adjunctive therapies can be beneficial for improving clinical parameters and HbA1c levels in patients with type 2 DM.

It is then up to the dental surgeon to assess the necessity of combining treatments, as studies demonstrate that periodontal treatment alone effectively improves periodontal parameters and glycemic control.[47-51]

It is important to highlight that this systematic review and meta-analysis has limitations that should be considered when interpreting the results, including the small number of studies and the divergence among them regarding the probiotic therapy protocol. The limited number of studies is due to the scarcity of research on the topic, particularly in this specific sample of individuals with type 2 diabetes. The divergence of one study, for example, compared to the others, carries different weight depending on the final number of studies. The heterogeneity among the studies, particularly regarding probiotic treatment, may limit the comparison and pooling of results. Additionally, the differences in glycemic control could impact the results.

The need for additional clinical trials is evident. Future research should include larger sample sizes to allow for subgroup analysis considering the glycemic control level of the sample, proper randomization, appropriate blinding with placebo use, longer follow-up periods, standardization of periodontitis diagnosis considering the classification of periodontal diseases, and, most importantly, a rigorous definition of the probiotic treatment protocol, taking into account biological plausibility, scientific evidence, and methodological reproducibility.

The present systematic review and meta-analysis demonstrated that probiotic therapy, as an adjunct to periodontal therapy, does not show benefits in individuals with type 2 DM, particularly regarding periodontal clinical parameters.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

ETHICS APPROVAL

Does not apply

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

Laís Rezende Carvalho Chaves: Conceptualization, Methodology, Investigation, Writing- Original draft, Writing- Reviewing and Editing, Visualization.

Rafael Paschoal Esteves Lima: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original draft, Writing- Reviewing and Editing, Visualization, Super-vision.

ACKNOWLEDGEMENTS

None.

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PUBLISHER'S NOTE

All statements expressed in this article are those of the authors alone and do not necessarily represent those of the publisher, editors, and reviewers.

PEER REVIEW

This manuscript was evaluated by the editors of the journal and reviewed by at least two peers in a double-blind process.

PLAGIARISM SOFTWARE

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ISSN Print 0719-2460 - ISSN Online 0719-2479
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Appendix I.

Search strategy employed to identify articles in six databases.

Study	Reason for exclusion
PubMed Library of Medicine)	*"probiotic"* OR *probiotics"* OR *"probioticsupplements"* AND *"periodontal (National treatment"* OR *"periodontal therapy"* OR *"periodontitis"* OR *"periodontal pocket"* OR *"periodontal disease"* OR *"chronicperiodontitis"* OR *"aggressiveperiodontitis"* AND *"diabetes"* OR *"diabetes mellitus"* OR *"diabetes mellitus, type2"* OR *"type 2 diabetes mellitus"* OR *"hyperglycemia"*
Web of Science (Thomson Reuters)	*"probiotic"* OR *"probiotics"* OR *"probiotic supplements"* AND *"periodontal treatment"* OR *"periodontal therapy"* OR *"periodontitis" OR "periodontal pocket"* OR *"periodontal disease"* OR *"chronicperiodontitis"* OR *"aggressive periodontitis" AND "diabetes OR diabetes mellitus"* OR *"diabetes mellitus, type 2"* OR *"type 2 diabetes mellitus"* OR *"hyperglycemia"*
Lilacs (Virtual Library on Health)	*"probiotic"* OR *"probiotics"* OR *"probiotic supplements"* AND "periodontal treatment" OR "periodontal therapy" OR *"periodontitis"* OR *"periodontal pocket"* OR *"periodontal disease"* OR *"chronicperiodontitis" OR "aggressive periodontitis"* AND *"diabetes"* OR *"diabetes mellitus" OR "diabetes mellitus, type 2"* OR *"type 2 diabetes mellitus" OR "hyperglycemia"*
Cochrane Library (Cochrane)	*"probiotic"* OR *"probiotics"* OR *"probiotic supplements"* AND "periodontal treatment" OR "periodontal therapy" OR *"periodontitis"* OR *"periodontal pocket"* OR *"periodontal disease"* OR *"chronicperiodontitis" OR "aggressive periodontitis"* AND *"diabetes"* OR *"diabetes mellitus" OR "diabetes mellitus, type 2"* OR *"type 2 diabetes mellitus" OR "hyperglycemia"*
Scopus (Elsevier)	*"pericyte"* OR *"rouget cell" OR "NG2 antigen" OR "NG2 proteoglycan"* OR *"platelet derived growth factor beta receptor"* OR *"platelet derived growth factor beta receptor"* OR *"CD 140b antigen"* OR *"PDGFRB OR PDGFR1"* OR *"PDGFR beta"* OR *"PDGF beta receptor"* OR *"PDGFRβ" OR "ACTA 2"* OR *"alpha-SMA"* OR *"alpha SMA"* OR *"α-SMA"* OR *"α SMA"* OR *"alpha 2 actin"* OR *"α-2 actin"* OR *"alpha-smooth muscle actin"* OR *"alpha smooth muscle actin"* OR *"α-smooth muscle actin"* AND *"squamous cell carcinoma"* OR *"epidermoid carcinoma"*
Embase (Elsevier)	*"probiotic"* OR *"probiotics"* OR *"probiotic supplements"* AND *"periodontal treatment"* OR *"periodontal therapy"* OR *"periodontitis"* OR *"periodontal pocket"* OR *"chronicperiodontitis"* OR *"aggressive periodontitis"* AND *"diabetes"* OR *"diabetes mellitus" OR "diabetes mellitus, type 2"* OR *"type 2 diabetes mellitus" OR "hyperglycemia"*

Appendix II.

Studies excluded after full text analysis and reasons for exclusion.

Study	Reason for exclusion
ChiCtr. The effects of probiotic supplementation in chronic periodontal patients with Type 2 diabetes: a randomized controlled trial. 2020. Ref ID: 30	Trial registry record.
ChiCtr. Clinical and microbiological efficacy of Lactobacillus reuteri as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis with type 2 diabetes: a randomized controlled clinical trial. 2022.	Trial registry record.
Ctri. Additional use of Probiotics in Diabetics for treatment of gum disease. 2020.	Trial registry record.
Ctri. Benefits of two locally delivered agents on cytokine level in diabetic patients with chronic periodontitis. 2021.	Trial registry record.
Irct20161104030694N. Impact of probiotic supplementation in treatment of periodontal patients with type 2 diabetes mellitus. 2018.	Trial registry record.
Nct. A Clinical Trial to Evaluate the Effectiveness of Lactobacillus Reuteri for Periodontitis in a Chinese Population. 2019.	Trial registry record.
Nct. Non Surgical Therapy of Periodontitis in Diabetes Patients: the Adjunctive Use of Probiotics. 2019.	Trial registry record.
Nct. Effects of a Probiotic on Oral Microbiota and Glycemic Control in Type 2 Diabetics; A Randomized Clinical Trial. 2021.	Trial registry record.
Nct. Lactobacillus Reuteri for Non-surgical Periodontal Treatment of Chronic Periodontitis With Type 2 Diabetes Patients. 2022.	Trial registry record.
z3w3n RBR. Effects of probiotic use in diabetic patients with periodontal disease. 2020.	Trial registry record.
Umin. A study on the significance of probiotic treatment for type 2 diabetes patients with periodontal disease. 2018	Trial registry record.
Gullapelli P, Koduganti RR. Efficacy of Probiotics Versus Tetracycline Fibers as Adjuvants to Scaling and Root Planing on Interleukin 1Î² Levels in Type 2 Diabetic Patients With Periodontitis: A Clinical and Biochemical Study. 2023	Comparison with tetracycline.
Hu B, Qu JC, Han TL, Leng J. Effect of Basic Periodontal Therapy Combined with Probiotics on Oral Microecology and Blood Sugar Control in Patients with Diabetes and Periodontitis. 2023; 55(3):1109-1114.	Does not specify which type of diabetes.

Appendix III.

Risk of bias assessment of studies randomizeds included in the systematic review.

References	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported outcome	Risk of bias judgment
Bazyar et al. 2020	Low	Low	Low	Low	Low	Low
Jardini et al. 2024	Low	Low	Low	Low	Low	Low

Appendix IV.

Risk of bias assessment of study non-randomized included in the systematic review.

References	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Risk of bias judgment
Elsadek et al. 2020	Low	Moderate	Low	Low	Low	Low	Low	Moderate