Effect of Adjunctive Probiotic Therapy on the Treatment of Peri-implant Diseases – A Systematic Review

Alexandre Pires Silva, Thaís Oliveira Cordeiro, Raíssa Afonso da Costa, Ana Rafaela Luz de Aquino Martins, Euler Maciel Dantas, Bruno César de Vasconcelos Gurgel and Ruthineia Diógenes Alves Uchoa Lins

Federal University of Rio Grande do Norte, Department of Dentistry. Natal, Brazil

Abstract

Aim: The aim of this study was to determine the effects of probiotics on peri-implant diseases.

Materials and Methods: PubMed-MEDLINE, Scopus, Literature in the Health Sciences in Latin America and the Caribbean (LILACS) and Science Direct were searched until September 2019. Three authors independently carried out this search, using the following search algorithm to explore databases using Boolean operators ("peri-implant diseases" OR "dental implants") AND ("probiotics" OR "lactobacillus"). Randomized clinical trials were included. No limits were applied to the year and articles were restricted to those in the English, Spanish and Portuguese languages. Review articles, reports of clinical cases and works without mention of the topic were excluded.

Results: Five randomized clinical trials were analyzed in the final review process. For the primary outcomes - Periodontal probing depth (PPD) and bleeding on probing (BOP); and for the secondary outcames - plaque index, gingival index, gingival crevicular fluid and microbiological tests - no significant clinical effects of probiotics were observed.

Conclusion: Probiotics could be used during the treatment of peri-implant diseases. However, the most appropriate form of probiotic administration or the effectiveness of this approach are still unclear. There is currently insufficient evidence to demonstrate the benefits of the use of probiotics as an adjunctive therapy in patients with peri-implant diseases

Keywords. Dental Implants; Lactobacilus reuteri; Peri-implantitis; Probiotics

Introduction

The placement of dental implants has become a routine procedure in the oral rehabilitation of totally or partially edentulous patients. However, the number of individuals affected by peri-implant diseases is increasing and microbial infection is the major etiological factor of these pathologies (Heitz-Mayfield and Lang, 2010; Jepsen *et al.*, 2015). Peri-implant diseases are classified as peri-implant mucositis and peri-implantitis. The prevalence of peri-implant mucositis is high, varying from 19% to 65%, with an average of 42.9%; while peri-implantitis varies from 1% to 47%, with an average of 21.7% (Derks and Tomasi, 2015).

The key parameter for the diagnosis of peri-implant mucositis is bleeding on probing. Peri-implant mucositis is presumed to be the precursor of peri-implantitis, as is gingivitis for periodontitis. However, unlike periodontitis, there are currently no established and predictable approaches for the treatment of peri-implantitis. Therefore, primary prevention is important and management of peri-implant mucositis is considered a preventive measure to avoid its progression to peri-implantitis (Jepsen *et al.*, 2015).

Due to the lack of consensus of clinical protocols for the treatment of peri-implant diseases, there exists a need to investigate alternative preventive therapies in order to avoid development of peri-implant lesions and to perform effective long-term therapies once diseases have been established (Schwarz *et al.*, 2015).

As such, the use of probiotic microorganisms with immunomodulatory and antimicrobial properties in the

Correspondence to: Alexandre Pires Silva, 1787 Senador Salgado Filho Avenue – Lagoa Nova – Natal – RN – Brazil. 59056-000
Email: alexandrepiress@gmail.com

host organism has been studied, with a view to evaluate their capacity to control pathogenic bacterial colonization and favor the emergence of microbiota that support peri-implant health (Galofré *et al.*, 2018).

Probiotics are defined as live microorganisms that confer health benefits when administered in sufficient doses (Reid *et al.*, 2003). These microorganisms generally belong to the genus bifidobacterium and lactobacillus; however, other genera, such as bacillus, enterococcus and streptococcus, have also been classified as probiotics (Boyle *et al.*, 2011). The mechanisms of action by which probiotics induce health benefits in the oral cavity can be divided into; direct and indirect. Direct mechanisms are: a) competition with other microorganisms via cellular adhesion and nutrients production, b) production of antimicrobial agents (eg bacteriocins and acids), and c) interaction with microbial pathogenicity factors such as suppressing the inflammatory cascade. Indirect mechanisms include activation of the host's immune system (eg, stimulation of IgA production), the induction of non-immunological defense mechanisms and maintenance of homeostasis in the oral cavity (Jain and Sharma, 2012).

Different clinical studies have demonstrated that the oral administration of probiotics as an adjunctive treatment to non-surgical mechanical periodontal therapy of gingivitis or periodontitis, improves the following clinical parameters; plaque index, gingival bleeding index, bleeding at probing and depth of probing (Krasse *et al.*, 2006; Vicario *et al.*, 2013). Reductions in the concentrations of some periodontopathogens (Vivekananda *et al.*, 2010; Teughels *et al.*, 2013) and the levels of proinflammatory cytokines (Szkaradkiewicz *et al.*, 2014; Twetman *et al.*, 2009) have also been reported following probiotic administration. However, there is limited literature on the efficacy of probiotics in the health of peri-implant tissues and controversies about this subject remain (Hallström *et al.*, 2016; Mongardini *et al.*, 2017).

Thus, this systematic review aimed to analyze and clarify the scientific evidence of the proposed benefits and effects of probiotic microorganisms when administered in combination with mechanical treatments for peri-implant mucositis and peri-implantitis, in comparison to other conventional therapies and to the administration of placebos. Our main question was "What is the clinical impact of probiotic therapy, versus conventional or placebo treatment, on the prevention or treatment of peri-implant diseases?"

Materials and Methods

Focused Question

This systematic review was conducted according to the guidelines of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). For this, the following focused question was developed in accordance with the recognized patient, intervention, comparison, and outcome (PICO) format: What is the clinical effect of the use of probiotics as an adjuvant therapy on the non-surgical treatment of peri-implant diseases, when compared to mechanical therapy and the use of other chemical agents, for the reduction of bleeding at probing and depth of probing?

Search strategy

The following databases were searched until September 2019: PubMed-MEDLINE, Scopus, Literature in the Health Sciences in Latin America and the Caribbean (LILACS) and Science Direct. Articles were restricted to those in the English, Spanish and Portuguese languages. Three authors independently carried out this search using the following search algorithm using Boolean operators to explore databases ("peri-implant diseases" OR "dental implants") AND ("probiotics" OR "lactobacillus"). In addition, a manual search of the following dental journals from the earliest record until September 2019 was performed: *Journal of Clinical Periodontology, Journal of Periodontology, 2000, Journal of Periodontal Research, International Journal of Periodontics and Restorative Dentistry and Journal of Implant and Maxillofacial Surgery.*

Eligibility criteria

During the first phase of the systematic review, studies were considered eligible for inclusion if they met the following criteria; randomized controlled trials (RCT) with at least two types of intervention (use of mechanical therapy alone or with the use of some adjuvants - chlorhexidine, for example - and mechanical therapy associated with the use of probiotics); patients diagnosed with peri-implantitis or peri-implant mucositis; trials that reported results according to the variables: plaque index (PI), gingival bleeding index (GBI), Periodontal probing depth (PPD), bleeding on probing (BOP), collection of gingival crevicular fluid and measurement of levels of chemical mediators (interleukins) and microbiological effects (not necessarily all evaluated in the same study); minimum follow-up of 4 (four) weeks.

During the second phase of the review, studies were excluded if they met one or more of the following exclusion criteria; reviews, pilot studies, reports of clinical cases, letters to the editor, clinical trials whose patients presented systemic conditions (diabetes, for example), studies that presented some type of previous surgical intervention (periodontal / implantoplasty or bone regeneration), studies with partial or incomplete results and duplicate studies.

Study selection

In both phases of the study, three reviewers independently selected the eligible research studies and selected titles and abstracts retrieved by electronic searches and manual search. Disagreements regarding the inclusion or exclusion of studies were resolved through discussion and consensus or by consulting a fourth author of the review.

Types of outcome

The primary outcomes of interest were changes in BOP and PPD. The variables PI, microbiological and immunological parameters, were selected as secondary outcomes of interest.

Quality assessment

Two reviewers independently assessed the methodological quality of all included studies. Disagreements were resolved through discussion and consensus. The risk of bias was estimated for each study selected, according to the recommendations of the CONSORT statement (Moher *et al*., 2001) and based by the guidelines recommended in the Cochrane Collaboration group (Higgins and Green, 2011). Thus, evaluation took into account random sequence generation, allocation concealment, adequate blinding of all involved, completeness of outcome data, and selective reporting.

Results

For this review, the initial electronic search, employing the databases listed, resulted in the identification of eleven titles, which were selected as potentially relevant to the study in question. After reading the titles and abstracts of these papers, six were excluded, as they did not represent the type of study of choice for this review (Table 1), leaving just five studies for analysis, for which the complete texts were obtained and assessed for eligibility and their results analyzed (Table 2). These five studies addressed probiotics and peri-implantitis and / or peri-implant mucositis, and complied with the inclusion criteria for the final analysis (Figure 1).The five articles reported the administration of probiotics using *Lactobacillus reuteri*. Four studies were placebo controlled and one did not use placebo when comparing groups. In addition, all four studies were funded by private laboratories, which provided the probiotics and placebos used.

Description of the studies

Among the randomized clinical trials selected, five were placebo controlled; two were double-blind, with a parallel-study design (Hallström *et al*., 2015; Tada *et al*., 2018); and two studies were triple blind and parallel studies (Galofré *et al*., 2018; Peña *et al*., 2018); and one study was a compartative study (Alqahtani *et al*., 2019).

In all studies, prior to administration of the probiotics, all participants underwent mechanical debridement (supra and subgingival scaling) and received oral hygiene instructions. One study (Peña *et al*., 2018) used a systemic antibiotic (Azithromycin, once daily for 3 days) prior to probiotic therapy, in addition to scaling. In two studies (Peña *et al*., 2018; Alqahtani *et al*., 2019), authors prescribed a chlorhexidine mouthwash (0.12%) twice daily for 15 days, prior to the start of probiotic administration. Only two studies used ultrasound to perform mechanical debridement (Galofré *et al*., 2018; Peña *et al*., 2018), while the other two studies used titanium curettes (Hallström *et al*., 2015; Tada *et al*., 2018).

The protocols of the studies selected varied with regard to the probiotic strain used, administration and posology, and brand. All five studies used *L. reuteri* ($1x10^8$ DSM 17938 and $1x10^8$ ATCC PTA 5289). Those studies that standardized the dosage (Galofré *et al*., 2018; Tada *et al*., 2018) employed probiotic administration once daily for 30 days, while the other studies (Tada *et al*., 2018; Alqahtani *et al*., 2019) employed probiotic use for a range of 14 to 60 days. With regard to brands, three studies (Galofré *et al*., 2018; Peña *et al*., 2018, Alqahtai *et al*., 2019) used probiotics sold by the Periobalance laboratory and two used probiotics from ProDentis (Hallström *et al*., 2015; Tada *et al*., 2018).

Table 1: Overview of the excluded studies

Study	Country	Reason for rejection
Lauritano et al., 2019	Italy	Pilot study
Cereda et al., 2018	Italy	Review study
Albaker et al., 2018	Saudi Arabia	Review study
Ahmedbeyli et al., 2019	Russia	Language
Flichy-Fernandez et al., 2015	Spain	Cross-over study
Mongardini et al., 2017	Italy	Cross-over study

Risk of bias

There was complete agreement for the overall risk of bias for all studies evaluated. Quality assessment of the studies (Table 3) revealed that three studies showed a high risk of bias toward one or more domains, as they presented no adequate randomization (Tada *et al*., 2018; Peña *et al*., 2018); or showed no blinding of evaluators/assessors (Alqahtani *et al*., 2019). Two of the studies analyzed presented low risk of bias (Galofré *et al*., 2018; Hallström *et al*., 2015).

Table 2. Characteristics of the included studies

Authors/year	Type of infection	Type of intervention before the treatment	Probiotic and concentration	Groups	Frequency and duration (F and D)	Results
Hallström *et al.*, 2015	Peri-implant mucositis	Initial examination + mechanical debridement + OHG and topical application of oil with *L. reuteri* strain in the mucositis implant	*L. reuteri* DSM 17938 ATCC PTA 5289 (2x 10^7)	Probiotic and placebo	1, 2, 4, 12 and 26 w	PPD with a decrease of between 0.7-1.2 mm from the baseline in both groups (P <0.05); PI and GBI with reduction of more than 50%; persistent improvement in PPD and BoP until after the end of the intervention; GCF volume decreased in both groups during the intervention and during follow up (P <0.05); F. nucleatum, P. micra, P. intermedia, P. nigrescens more prevalent strains. P.gingivalis, A.A and T. denticola were lightly detected; Levels of IL-1R alpha, IL-8, TNF-alpha, CCL5 were lower than at baseline (P <0.05).=
Galofré *et al.*, 2018	Peri-implant mucositis or Peri-implantitis	Subgengival scraping at implants with mucositis and mechanical non-surgical subgingival debridement of implants with peri-implantitis	*L. reuteri* DSM 17938 ATCC PTA 5289 (1x10^8)	Probiotic and control	30 days	PPD reduced 0.25 mm and 0.53 mm in implants with mucositis and peri-implantitis, respectively, 30 days after the start of probiotic treatment. BoP decreased 3-fold for mucositis (P = 0.031); PI: no significant difference between probiotics and placebo; Reduction of P. gingivalis for peri-implant mucositis (P = 0.031)
Tada *et al.*, 2018	Soft or mild peri-implantitis	OHG + SRP + Azithromycin, 500 mg, 1x/ day, 3 days.	*L. reuteri* DSM 17938 ATCC PTA 5289 (1x10^8)	Placebo and probiotic	F:0, 4, 12 and 24 w D: 6 mo	PPD reduction at 4 weeks and 24 weeks in the probiotic group (3.42 and 3.21, respectively) (P <0.05); BoP: between baseline and week 0 reduction of 3.20 to 2.33 sites with positive bleeding (probiotic group) and 3.67 to 2.73 (placebo group), with no significant difference. Decreases in F. nucleatum, P. gingivalis, P. intermedia, T. denticola, T. forsythia after administration of Azithromycin;
Peña *et al*, 2018	Peri-implant mucositis	Mechanical debridement, mouthwash with 0.12% chlorhexidine and subsequent administration of a probiotic agent	*L. reuteri* (no description of dose)	Probiotic and placebo	3 mo	PI and GBI: decreased by 7% until the 135th day in the test group; PPD: reduction of 0.34 mm in the control group and reduction in 0.22 mm in the test group (in 3 months). No significant difference between groups of bacterial load.
Alqahtani *et al.*, 2019	Peri-implant mucositis	Mechanical debridment, OHG, mouthwash with 0.12% chlorhexidine	*L. reuteri* 1 × 108 CFU of ATCC PTA 5289 and 1 × 108 CFU of DSM 17938.	Smokers and non-smokers	3 w/6mo	3-months' follow-up: the mean scores of PI (P < 0.05), BOP (P < 0.05), and PPD (P < 0.05) were significantly higher among individuals non-smokers that underwent MD alone compared with individuals that underwent MD with adjunct PT.

OHG: Oral Hygiene Guidance; PDT: Photodynamic Therapy; PPD: Periodontal probing depth; MD: Mechanical Debridment; PT: Probiotic Therapy; SRP: Scraping and Root Planing; BoP: Bleeding on Probing; PI: Plaque Index; GBI: Gingival Blood Index; GCV: Gingival Crevicular Fluid; A.A: *Agregatibacter Actinomycetencomitans*.

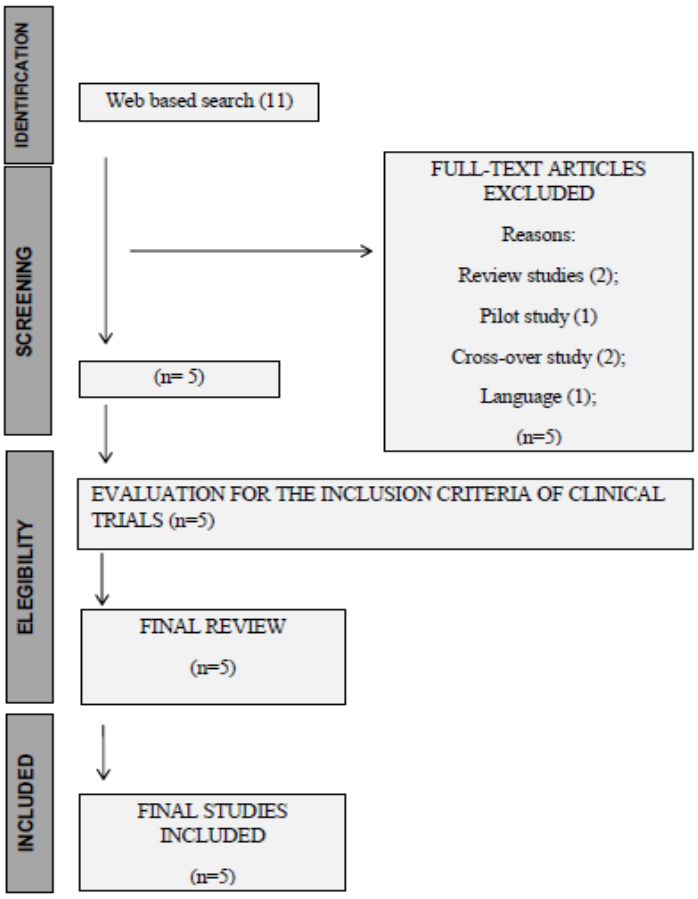

Figure 1: Flow chart of the study selection process

Outcome variables

Due to the clinical heterogeneity of the studies, we considered meta-analysis to be inappropriate as trials that assessed the same outcomes used different follow-up times and / or biases were observed. As such, results were not considered to be comparable.

Plaque Index (PI): Five studies evaluated this outcome (Galofré *et al.*, 2018; Hallström *et al.,* 2015; Tada *et al.*, 2018; Alqahtani *et al.*, 2019). Five studies reported statistically significant differences in plaque index, when comparing probiotics versus placebo. In one study (Galofré *et al.*, 2018), although the decrease in plaque index during the time evaluated was statistically significant in implants with mucositis and peri-implantitis, no significant difference was found between the placebo and probiotic groups for different study times. One study (Alqahtani *et al.*, 2019) evaluated PI between smokers and non-smokers that underwent mechanical debridement associated or not with probiotic therapy. Between cigarette-smokers, no significant difference was found at all time intervals in both groups. PI ($p < 0.05$) was significantly higher in the group that underwent mechanical debridement associated with probiotic therapy than mechanical debridement alone. Among never-smokers that underwent mechanical debridement with or without probiotic therapy the total mean values of PI were significantly higher at baseline compared with their respective scores at 3- and 6-months' follow-up.

Periodontal Probing Depth: All five studies reviewed evaluated this clinical parameter (Galofré *et al.*, 2018; Hallström *et al.*, 2015; Tada *et al.*, 2018; Peña *et al.*, 2018; Alqahtani *et al.*, 2019). All concluded that the use of probiotics led to statistically significant decreases in the depth of probing. Galofré *et al.*, (2018) observed that the mean probing pocket depth at the implant site decreased by 0.25 mm and 0.53 mm in implants with mucositis and peri-implantitis, respectively, after 30 days of starting the probiotic treatment. In implants with mucositis the reduction was similar between probiotic and placebo groups, but in implants with peri-implantitis the decrease was statistically higher in the probiotic group ($p = 0.04$). One study (Alqahtani *et al.*, 2019) did not observed significant differences at any time intervals among the smokers, using mechanical debridement and probiotic therapy versus mechanical debridement alone.

Bleeding on Probing: Five studies evaluated this clinical parameter as an outcome (Galofré *et al.*, 2018; Hallström *et al.*, 2015; Tada *et al.*, 2018; Peña *et al.*, 2018; Alqahtani *et al.*, 2019). Only three studies (Galofré *et al.*, 2018; Hallström *et al.*, 2015; Alqahtani *et al.*, 2019) reported statistical significance in BOP after the use of probiotics. One study (Galofré *et al.*, 2018) found a 3-fold decrease

Table 3. Risk of bias analysis

Study	Entry	Risk of bias	Support for judgment
Hallström *et al.*, 2015	Random sequence generation	Low risk	Randomized.
	Allocation concealment	Low risk	Randomized. "The allocation to the test or placebo group was conducted using the Excel randomizationtool in Microsoft Office".
	Blinding of participants and personnel	Low risk	Double-blind study.
	Blinding of outcome assessment	Unclear	The study did not address this outcome
	Incomplete outcome data addressed	Low risk	Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). "Two patients in the test group were treated with antibiotics before the 6-month follow-up and another received prednisone, so these data were excluded in the final analysis".
	Selective reporting	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
	Overall risk	Low risk	Low risk of bias
Galofré *et al.*, 2018	Random sequence generation	Low risk	Randomized.
	Allocation concealment	Low risk	Randomized. "The selected subjects were randomly assigned to 1 of the 2 treatment groups ("A" or "B") through a randomization program"
	Blinding of participants and personnel	Low risk	Triple-blind study.
	Blinding of outcome assessment	Low risk	Triple-blind study.
	Incomplete outcome data addressed	Low risk	Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). "9 patients withdrew from the study because they were unable to attend the assigned visits (1 patient due to hospitalization)".
	Selective reporting	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
	Overall risk	Low risk	Low risk of bias.
Tada *et al.*, 2018	Random sequence generation	High risk	Non-random. "The study was performed between March 2016 and December 2016 at 7 facilities including Kyushu Dental University Hospital. Out of 46 eligible patients with peri-implantitis, 30 gave their informed consent and were consecutively enrolled in this study".
	Allocation concealment	Low risk	Randomized. "Simple randomization was carried out using a computer software program (Microsoft Excel) that generates random numbers to assign participants".
	Blinding of participants and personnel	Low risk	Double-blind study. "All clinical examiners and patients were blinded until the end of the study".
	Blinding of outcome assessment	Unclear	The study did not address this outcome
	Incomplete outcome data addressed	Unclear	The study did not address this outcome
	Selective reporting	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
	Overall risk	High risk	High risk of bias for one or more key domains

Table 3 continued overleaf....

.....Table 3. continued

Study	Entry	Risk of bias	Support for judgment
Peña *et al.*, 2018	Random sequence generation	High risk	Non-random. "Periodontally healthy patients or treated periodontal patients included in the periodontal maintenance program".
	Allocation concealment	Unclear	The study did not address this outcome
	Blinding of participants and personnel	Low risk	Triple-blinded study.
	Blinding of outcome assessment	Low risk	Triple-blinded study. "The patients, the clinical examiner, the laboratory technician, and the statistician were blinded to the contents of the containers and only the study supervisor knew the contents of each container".
	Incomplete outcome data addressed	Unclear	The study did not address this outcome
	Selective reporting	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
	Overall risk	High risk	High risk of bias for one or more key domains
Alqahtani *et al.*, 2019	Random sequence generation	Low risk	Randomized.
	Allocation concealment	Low risk	Randomized. "Selected patients were randomized into two treatment groups using block randomization. Every consecutive patient (designated by a code) after selection were entered in the paper envelopes to confirm that the number of samples matched between the treatment groups".
	Blinding of participants and personnel	High risk	No blinding
	Blinding of outcome assessment	High risk	No blinding
	Incomplete outcome data addressed	Unclear	The study did not address this outcome
	Selective reporting	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
	Overall risk	High risk	High risk of bias for one or more key domains

in BOP after probiotic treatment for 30 days, compared to placebo treatment, in patients with peri-implant mucositis (27% vs 8%) and peri-implantitis (20% vs 7.5%), with statistical significance for mucositis ($p = 0.031$). One study (Alqahtani *et al.*, 2019) at 3-months' follow-up, the differences in BOP ($p< 0.05$) were significantly higher in the group that underwent mechanical debridment (MD) and probiotic therapy than MD alone. One study (Hallström *et al.,* 2015) found that, after probiotics treatment, the gingival condition improved significantly, when compared to baseline ($p <0.05$).

Gingival Crevicular Fluid: Only one study evaluated changes in this parameter (Hallström *et a*l., 2015). It reported that the volume of GCF decreased in both groups (placebo and probiotics) during the intervention and at the follow-up ($p < 0.05$) compared with baseline.

Immunological and microbiological effects: One study (Hallström *et al.*, 2015) evaluated the levels of interleukins before and after the use of probiotics. The authors found statistically significant changes for this parameter. In addition, microbiological examinations were performed in four studies (Galofré *et al.*, 2018; Hallström *et al.,* 2015; Tada *et al.*, 2018; Peña *et al.*, 2018). One study (Galofré *et al.*, 2018) found that *L. reuteri* had a very limited effect on the peri-implant microbiota (i.e: *T. forsythia* and *E. corrodens*); and a significant microbial reduction ($p = 0.031$) was observed only for the *Porphyromonas gingivalis* subgingivally bacterial load in patients with peri-implant mucositis.

Discussion

The aim of this review was to review the current literature to determine whether probiotics may represent a new category of adjuvants for the treatment of peri-implant diseases. Studies using probiotics as adjuvant

therapy during non-surgical treatment of periodontal disease have already been published, as has a systematic review on the subject (Yanine *et al.*, 2013). In this review the authors concluded that the use of probiotics during the treatment of periodontal diseases is of questionable value as no beneficial clinical effect on pocket depth was observed with this new therapy. Furthermore, improvements in plaque index and gingival inflammation with probiotic therapy were very small.

Cross-sectional studies (Rokn *et al.*, 2017) and / or systematic reviews (Derks and Tomasi, 2015) have shown an increase in the prevalence of peri-implant diseases in the population, fueling the search for new therapeutic solutions as alternatives to conventional treatments. In the studies that we analyzed in this systematic review, depending on the time of evaluation, a reduction in bleeding levels was observed for both the placebo and test groups. The use of probiotics, in conjunction with non-surgical mechanical therapy, resulted in a reduction in bleeding on probing, indicating reduced local inflammation at sites with peri-implant mucositis.

Scientific evidence demonstrating that probiotics are beneficial and effective treatments for peri-implantitis and peri-implant mucositis is still scarce in the literature, and further studies are necessary to prove their efficacy and investigate different modes of administration. The use of probiotics has also been investigated as a form of adjunctive treatment for periodontal diseases, when combined with non-surgical mechanical therapy, systemic antibiotic administration, or with photodynamic therapy to reduce the periodontopathogenic bacterial load at periodontal sites (Renvert *et al.*, 2013).

The combination of mechanical therapy and the use of systemic antibiotics is common for the treatment of periodontal diseases. The administration of antibiotics, in cases of peri-implantitis, contributes to the reduction in bleeding on probing and the decreasing of probing depth of pockets. However, the continuous use of systemic antibiotics leads to bacterial resistance in the peri-implant sulcular environment and subsequent re-colonization and is not recommended as a regular treatment approaches (Rams *et al.,* 2014; Heitz-Mayfield *et al.*, 2012). One study in this review (Tada *et al.*, 2018) observed that the bacteria load was reduced after administration of azithromycin in both test and control groups but soon increased again after discontinuation. The bacterial count in both groups studied remains without any significant difference. In contrast, positive results were found for parameters, such as probing of pocket depth and bleeding on probing, in the probiotic group. Authors suggested that probiotic microorganisms might prevent inflammation, inducing a positive host response to this type of treatment.

Microbiological examinations in these types of studies are extremely important to verify the effectiveness of the treatment on the bacteria present in the periodontal and peri-implant sites. Probiotic microorganisms act to form a biofilm that will compete with the microbial biofilm present at sites affected by mucositis or peri-implantitis. One study (Galofré *et al.*, 2018) reported that the probiotic, *L. reuteri,* had a limited effect on the peri-implant microbiota, as the only parameter that was significantly decreased by treatment was the *P. gingivalis* count at implants with peri-implant mucositis. For the treatment of chronic periodontitis, one placebo-controlled study (Teughels *et al.*, 2013) performed microbiological analyzes and observed significant differences in the reduction of *P. gingivalis* counts at subgingival and supragingival sites and in saliva in the group that received mechanical therapy, associated with the use of probiotics for 12 weeks. One of the major characteristics of probiotic microorganisms is their ability to form a biofilm that can compete with the microbial biofilm present in sites affected by mucositis or peri-implantitis (Schincaglia *et al.*, 2017).

One of the reasons for not carrying out a meta-analysis study was due to the differences in the types of studies (case-control, crossover) and due to small differences with respect to the methodologies employed. These limitations were due to the lack of characterization of the dosage of the probiotic administered, the period of administration, and of the best form of administration for achieving high enough concentrations in the oral environment to overcome the bacterial challenge.

Conclusion

This review provides evidence that probiotics can be used during the treatment of peri-implant disease. However, the most appropriate form of the administration of probiotics and their effectiveness against the actions of peri-implant microbiota are still unclear. In order to achieve clinical success in peri-implant disease treatment, practitioners should aim to control the factors reported in this review, including factors that contribute to the limitations of the studies discussed.

Acknowledgements and conflict of interest

Conflict of Interest and funding

None of the authors of this review declares a conflict of interest or obtained any kind of financing or support from any company related to the production of probiotics. This investigation did not receive any private financial support.

References

Alqahtani F, Alqahtani M, Shafqat SS, Akram Z, Al-Kheraif AA and Javed F. Efficacy of mechanical debridement with adjunctive probiotic therapy in the treatment of peri-implant mucositis in cigarette-smokers and never-smokers. *Clinical Implant Dentistry and Related Research* 2019; **21**:734–740.

Boyle RJ, Ismail IH, Kivivuori S, *et al*. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy* 2011; **66**:509–516.

Derks J and Tomasi C. Peri-implant health and disease: a systematic review of current epidemiology. *Journal of Clinical Periodontology* 2015; **42**(Suppl 16):S158–S171.

Galofré M, Palao D, Vicario M, Nart J and Violant D. Clinical and microbiological evaluation of the effect of Lactobacillus reuteri in the treatment of mucositis and periimplantitis: a triple-blind randomized clinical trial. *Journal of Periodontal Research* 2018; **53**:378–390.

Hallström H, Lindgren S, Widén C, Renvert S and Twetman S. Probiotic supplements and debridement of peri-implant mucositis: a randomized controlled trial. *Acta Odontologica Scandinavica* 2016; **74**:60–66.

Heitz-Mayfield LJA and Lang NP. Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis. *Periodontology 2000* 2010; **53**:167-181.

Heitz-Mayfield LJA, Salvi GE, Mombelli A, Faddy M and Lang NP. On behalf of the Implant Complication Research Group. Antiinfective surgical therapy of peri-implantitis. A 12-month prospective clinical study. *Clinical Oral Implants Research* 2012; **23**:205-210.

Higgins J and Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. England: *The Cochrane Collaboration* 2011, Oxford.

Jain P and Sharma P. Probiotics and Their Efficacy in Improving Oral Health: A Review. *Journal of Applied Pharmaceutical Science* 2012; **2**:151-163.

Jepsen S, Berglundh T, Genco R, et al. Primary prevention of peri-implantitis: managing peri-implant mucositis. *Journal of Clinical Periodontology* 2015; **42**(Suppl 16): S152–S157.

Krasse P, Carlsson B, Dahl C, Paulsson A, Nilsson A and Sinkiewicz G. Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri. *Swedish Dental Journal* 2006; **30**:55–60.

Moher D, Schulz KF and Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Annals of Internal Medicine* 2001; **134**:657–662

Mongardini C, Pilloni A, Farina R, Di Tanna G and Zeza B. Adjunctive efficacy of probiotics in the treatment of experimental peri-implant mucositis with mechanical and photodynamic therapy: a randomized, cross-over clinical trial. *Journal of Clinical Periodontology* 2017; **44**:410–417.

Peña M, Barallat L, Vilarrasa J, Vicario M, Violant D and Nart J. Evaluation of the effect of probiotics in the treatment of peri-implant mucositis: a triple-blind randomized clinical trial. *Clinical Oral Investigations* 2018; **23**:1673-1683.

Rams TE, Degener JE and Van Winkelhoff AJ. Antibiotic resistance in human chronic periodontitis microbiota. *Journal of Periodontology* 2014; **85**:160–169.

Reid G, Jass J, Sebulsky MT and McCormick JK. Potential Uses of Probiotics in Clinical Practice. *Clinical Microbiology Reviews* 2003; **16**:658-672.

Renvert S, Polyzois I and Persson GR. Treatment modalities for peri-implant mucositis and peri-implantitis, *American Journal of Dentistry* 2013; **26**:313-8.

Rokn A, Aslroosta H, Akbari S, Najafi H, Zayeri F and Hashemi K. Prevalence of peri-implantitis in patients not participating in well-designed supportive periodontal treatments: a cross-sectional study. *Clinical Oral Implants Research* 2017; **28**:314-319.

Schincaglia GP, Hong B, Rosania A et al. Clinical, immune and microbiome traits of gingivitis and peri-implant mucositis. *Journal of Dental Research* 2017; **96**:47–55.

Schwarz F, Schmucker A and Becker J. Efficacy of alternative or adjunctive measures to conventional treatment of peri-implant mucositis and peri-implantitis: a systematic review and meta-analysis. *International Journal of Implant Dentistry* 2015; **1:**1-22.

Szkaradkiewicz AK, Stopa J and Karpiński TM. Effect of oral administration involving a probiotic strain of Lactobacillus reuteri on pro-infl ammatory cytokine response in patient with chronic periodontitis. *Archivum immunologiae et therapiae experimentalis* 2014; **62**:495-500.

Tada H, Masaki C, Tsuka S, Mukaibo T, Kondo Y and Hosokawa R. The effects of Lactobacillus reuteri probiotics combined with azithromycin on peri-implantitis: A randomized placebo-controlled study. *Journal of Prosthodontic Research* 2018; **62**:89-96.

Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M and Haytac MC. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. *Journal of Clinical Periodontology* 2013; **40**:1025–1035.

Twetman S, Derawi B, Keller M, Ekstrand K, Yucel-Lindberg T and Stecksen-Blicks C. Short-term effect of chewing gums containing probiotic Lactobacillus reuteri on the levels of inflammatory mediators in gingival crevicular fluid. *Acta Odontologica Scandinavica* 2009; **67**:19–24.

Vicario M, Santos A, Violant D, Nart J and Giner L. Clinical changes in periodontal subjects with the probi-otic Lactobacillus reuteri Prodentis: a preliminary randomized clinical trial. *Acta Odontologica Scandinavica* 2013; **71**:813-819.

Vivekananda MR, Vandana KL and Bhat KG. Effect of the probiotic Lactobacilli reuteri (Prodentis) in the management of periodontal disease: a preliminar randomized clinical trial. *Journal of Oral Microbiology* 2010; **2**:2.

Yanine N, Araya I, Brignardello-Petersen R, et al. Effects of probiotics in periodontal diseases: a systematic review. *Clinical Oral Investigations* 2013; **17**:1627-1634.