J Oral Res
oral and craniofacial sciences

Review

Effectiveness of probiotics in the prevention of carious lesions during treatment with fixed orthodontic appliances.

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Receipt: 06/19/2017 **Revised:** 07/13/2017
Acceptance: 07/28/2017 **Online:** 07/28/2017

Conflict of interests: None.

Ethics approval: None.

Funding: None.

Authors' contributions: All authors contributed equality to the complete study.

Acknowledgements: None.

Cite as: Contreras P, Kay J, Burgos C, Contreras C & Huber H. Effectiveness of probiotics in the prevention of carious lesions during treatment with fixed orthodontic appliances. J Oral Res 2017; 6(7):186-192. doi:10.17126/joralres.2017.053

Abstract: The difficulty experienced by patients with fixed orthodontic appliances in maintaining adequate oral hygiene poses a risk for dental caries. The use of probiotics has been proposed as a means of prevention. The following systematic review aims to determine the effectiveness of probiotics in the prevention of dental caries during treatment with fixed orthodontic appliances. This review was carried out according to the PRISMA guidelines. A comprehensive electronic search was conducted in the Cochrane Library, EMBASE, PubMed and Google Scholar Beta databases. The inclusion criteria included randomized controlled clinical trials involving the use of probiotics, caries and patients under fixed orthodontic treatment. The methodological quality of the articles was evaluated according to risk of bias. Of the five included studies, three reported significant differences compared to the control group. Of the others, one article reported significant decrease in the final count of microorganisms compared to the beginning of treatment. Only one study reported no differences of any kind. It was estimated that the eligible studies were of moderate methodological quality and had an unclear risk of bias, without affecting key domains for the research. It is concluded that the daily consumption of probiotics can be effective in the prevention of carious lesions in patients under fixed orthodontic treatment. However, this should be interpreted with caution and corroborated by clinical trials of better methodological quality.

Keywords: probiotics, caries, orthodontics.

INTRODUCTION.

The use of fixed orthodontic appliances plays a key role in the treatment of dentomaxillary abnormalities.[1] However, patients are often unable to maintain effective oral hygiene.[2,3] In addition, self-cleaning routines and habits are negatively affected, favoring the accumulation of soft deposits.[4,5]

There is a significant change in the bacterial flora of the oral cavity after the placement of fixed orthodontic appliances, that is characterized by an increase in the concentrations of acidogenic bacteria, such as *Streptococcus mutans* and *Lactobacillus*.[6] These bacteria can cause demineralization of the clinically visible enamel such as white spot lesions, with small lines around the brackets or as large decalcified areas with or without cavitation.[7] These may appear as early as the fourth week after orthodontic treatment has begun.[6] Recent evidence indicates that the incidence of new carious lesions that develop during orthodontic treatment is 45.8%, with a prevalence rate of 68,4%, which raises the need for more effective measures in caries prevention.[8]

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To date, the most effective way to prevent carious lesions secondary to the use of orthodontic appliances has not been established.[9] In the past the use of fluorine varnish, professional cleanings, argon laser[10] and diet control[11,12] have been proposed. However, it is advisable to find a method whose effectiveness is not so provider-dependent, and that can be easily adopted by the patient. It has been observed that probiotics, live microorganisms that, when administered under adequate conditions and amounts give benefits to the host,[13] may play an important role in preventing caries[14] by decreasing the levels of *Streptococcus mutans* in saliva.[15-17]

Clinical studies on probiotic strains such as *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri, Bifidobacterium* DN-173010 and mixtures of *Lactobacillus* species have been conducted. These have demonstrated an antibacterial effect and stabilization of the microbiota, in addition to the modulation of the host immune system by coaggregation, release of antimicrobial byproducts, toxin degradation or competition for substrates and adhesion sites.[18] Probiotics would be effective in the prevention and treatment of oral diseases such as caries, gingivitis and periodontitis.

Given the above, the objective of this systematic review is to determine the effectiveness of probiotics in the prevention of dental carious lesions during treatment with fixed orthodontic appliances.

MATERIALS AND METHODS.

The present study was conducted according to the PRISMA[19] guidelines and aimed to determine: What is the effectiveness of probiotics in the prevention of dental carious lesions during treatment with fixed orthodontic appliances? The formulation of the research question was based on the PICOT[20] strategy. (Table 1)

A comprehensive electronic search of articles in the Cochrane Library, EMBASE, PubMed and Google Scholar Beta databases was conducted. The following MeSH terms were used to properly select the search topic: "probiotics", "oral health", "orthodontics", "caries", "white spot lesions", "orthodontic treatment". The logical operators (OR and AND) were used to combine the descriptors. Researchers have set May 25th, 2017 as the search date. Figure 1 shows the application of the search strategy.

Results were entered into Mendeley® software (Elsevier, USA) to remove duplicate information. Titles and abstracts were read to exclude articles outside the scope of this review. Articles whose abstracts did not provide sufficient information were read completely to apply the inclusion criteria. These evaluations were independently performed by two examiners.

Inclusion criteria included clinical trials that studied the influence of probiotic use and its association with caries in patients under fixed orthodontic treatment compared to a control group. The search was customized to obtain articles published in the last 10 years in any language. Exclusion criteria included *in vitro* or animal studies and those with inadequate methodology.

The articles included in this review were evaluated based on their methodological quality using the Cochrane[21] clinical trial tool for risk assessment of bias. In Figure 2, studies are classified according to five types of bias if they present low, unclear or high risk; this allows for the interpretation of the reliability of the results delivered by each study. The methodological analysis was carried out by three examiners masking the name of the authors of the articles as well as of the journals in which they were published.

Table 1. Research question according to PICOT strategy.

Items	Description
Population	Patients with fixed orthodontic treatment
Intervention	Probiotics intake
Comparison	Orthodontic treatment without probiotics adjuvant
Outcome	Probiotics are effective in preventing carious lesions
Types of studies	Controlled clinical trials

RESULTS.

The search strategy yielded 426 articles, which were reduced to 121 once duplicates were removed. After applying the inclusion and exclusion criteria, five of them were selected as eligible for qualitative synthesis, all of them written in English (Figure 1).

The analysis in context of the studies included in this review concluded that the articles presented an unclear risk of bias,[21] (Figure 2) without involving key domains (generation of the randomized sequence and allocation concealment). Therefore, it is considered as a plausible bias, of low repercussion in the reliability of the results.

Of the five included studies, three of them[22-24] reported significant differences between the treatment and the control groups; another declared significant decreases in the final counts of microorganisms compared to the start of treatment.[25] Only one study[26] reported no differences of any kind. (Table 2)

The probiotic strains used in the selected articles were reported in four of the five studies. In two cases,[22,25] the same bacterial strain, *Bifidobacterium animalis lactis* DN-173010, was used, where as *Lactobacillus paracasei* SD1[24] and *Lactobacillus* reuteri DSM 17938/ATCC PTA 5289[26] were studied in the other two cases. The study that did not specify the probiotic strain used[23] just indicated the name of two commercial products.

Figure 1. Systematic search flowchart and strategy for selecting articles according to PRISMA standards.[19]

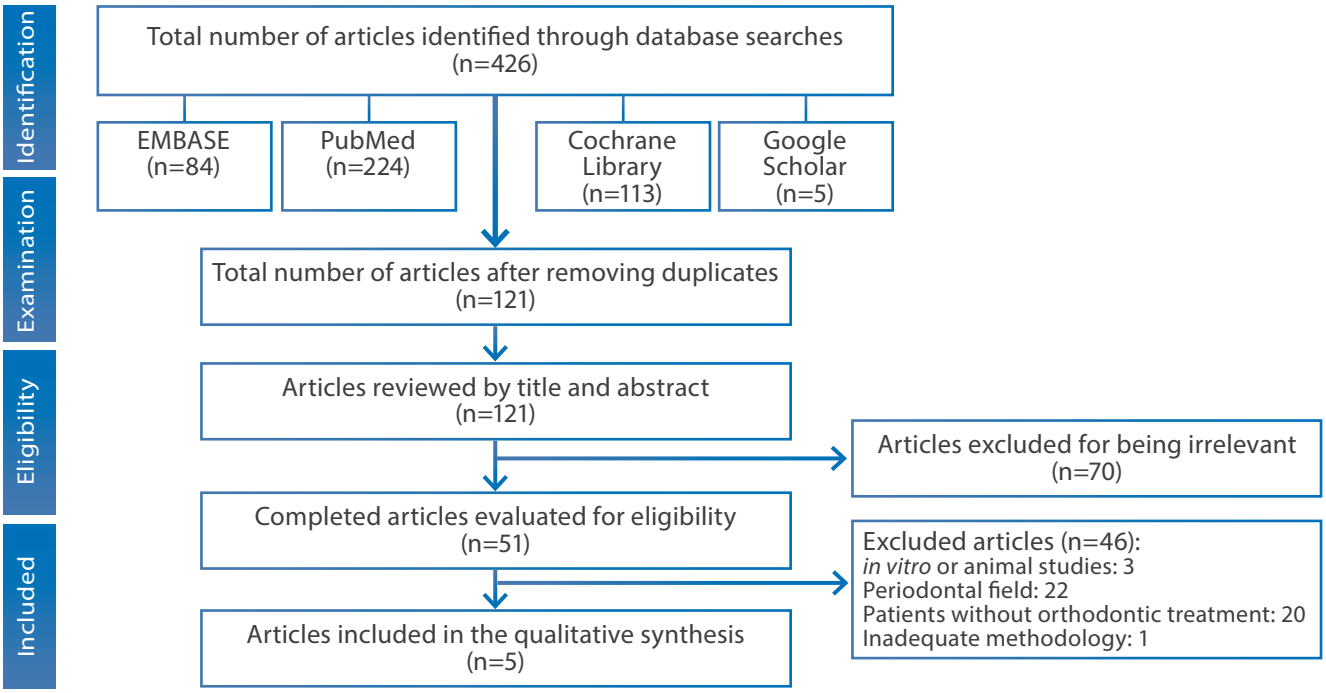

Figure 2. Risk assessment tool for Cochrane Collaboration clinical trials.[22]

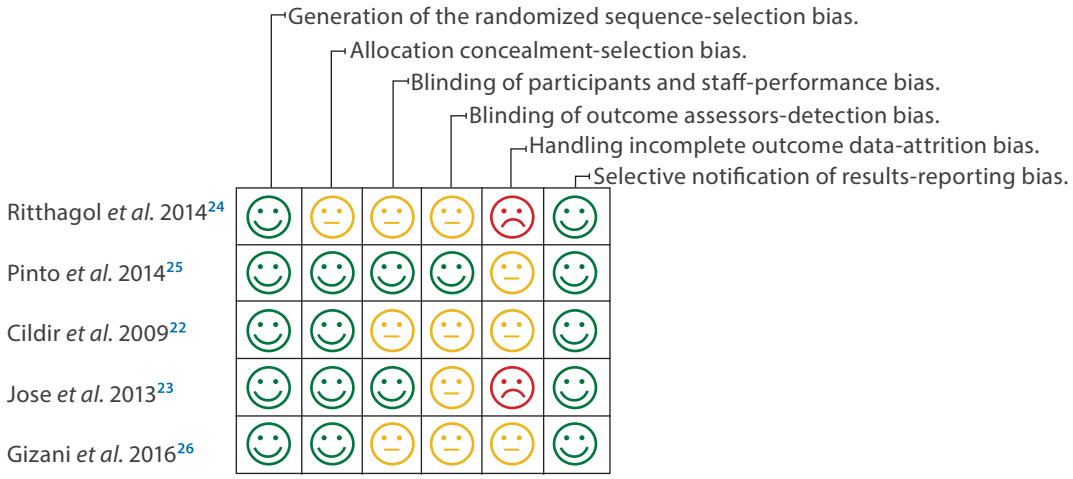

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Table 2. Description of the main data provided by the eligible articles.

Authors, year of publication and country of origin	Size of the sample and sex	Age	Research design	Type of Intervention	Frequency of Application	Evaluation of results	Clinical Work Outcome
Ritthagol *et al.* 2014[24] Thailand.	30 (sex not specified).	19.2 +/- 3.6 years.	Randomized, double-blind, controlled clinical trial.	Milk reconstituted with *L. paracasei* SD1.	10g with 7.5 x 10^8 CFU*/g daily for 4 weeks.	SM** count in saliva evaluated by chair-side test.	Significant reduction in number of SM,** significant increase in LB*** count.
Pinto *et al.* 2014[25] Brazil.	26 (16 females and 10 males).	15 years (between 10 and 30 years).	Randomized, double-blind, controlled clinical trial.	Yogurt with *Bifidobacterium animalis* subsp. *lactis* DN-173010.	200g daily yogurt, does not concentration for 2 weeks.	SM** count in saliva and plaque by chair-side test.	Significant reduction of the total count of microorganisms in plaque for study and control groups, there were no differences in saliva.
Cildir *et al.* 2009[22] Turkey.	24 (16 females and 8 males).	14 +/- 1.2 years.	Randomized, double-blind, controlled clinical trial.	Yogurt with *Bifidobacterium animalis* subsp. *lactis* DN-173010.	200g yogurt daily with 2x10^8 CFU*/g, for 1 week.	SM** and LB*** count in saliva evaluated by chair-side test.	Significant reduction in the number of SM**, there was no difference in the LB*** count.
Jose *et al.* 2013[23] India.	60 (42 females and 18 males).	20 years (between 14 and 29 years).	Randomized, double-blind, controlled clinical trial.	Probiotic curd/Probiotic toothpaste. No strain specified.	200mg of curd daily/toothpaste 2 times a day, both for 30 days. Does not specify concentration.	SM** count in plate evaluated by RT-PCR.****	Significant reduction in SM** count.**
Gizani *et al.* 2016[26] Greece.	85 (56 female and 29 males).	15.9 +/- 3.9 years.	Randomized, double-blind, controlled clinical trial.	Tablets with two strains of *Lactobacillus reuteri* (DSM 17938 and ATCC PTA 5289).	10^8 CFU/g live bacteria of each strain per tablet daily for 17 months.	SM** and LB*** salivary and plaque counts by chair-side test/ Photo study of enamel demineralization.	Significant reduction in LB*** count. No significant differences in SM** count.**

* Colony Forming Units, ** *Streptococcus mutans,* *** *Lactobacillus,* **** Real time-polymerase chain reaction

DISCUSSION.

This review evaluated the effect of probiotic therapy through counting of colony forming units of *Streptococcus mutans* and *Lactobacillus*. This methodology is likely to be chosen because caries is a slow process[27] and probiotics are often used for short periods as they do not permanently colonize the oral cavity or intestines and should therefore be ingested in sufficient quantities on a daily basis.[28]

The enamel demineralization is mainly caused by *Streptococcus mutans,*[29] which along with *Streptococcus sobrinus* and *Streptococcus salivarius* are among the first organisms that colonize the initial carious lesion.[30,31] They are also the most cariogenic due to their adhesive and organic acid release properties.[32,33] In turn, *Lactobacillus* have been associated with the progression of caries in the dentin and not with the initiation of caries in the enamel.Despite their cariogenic potential, some species of *Lactobacillus* have been introduced as potential dental enamel protective agents, mainly due to their inhibitory activity against cariogenic *Streptococcus* spp.[34,35]

Lactobacillus and *Bifidobacteria* are the bacterial strains most widely used in the exploration of the potentialities of probiotic properties.[36] The focus on these species is due to their production in the dairy industry, showing a sym-

biotic relationship with humans.[37] With the development of evidence-based knowledge on the usefulness and safety of probiotics, these bacteria are replacing traditional prophylactic and treatment regimens.[38,39]

This review showed that when comparing probiotic groups with controls, in the majority of the studies, patients in the probiotic group had lower levels of *Streptococcus mutans* than those in the control group, this difference being significant in three of the studies.[22-24] This reduction can be attributed to the formation of a biofilm that prevents the adhesion of pathogens and competitively inhibits *Streptococcus mutans.* This may explain the increase in *Lactobacillus* reported by Ritthagol *et al.*[24] and although they do not specify the type of strains, several studies have agreed on the presence of a strong inhibitory activity of *Lactobacillus paracasei, Lactobacillus lanthus plantarum, Lactobacillus rhamnosus* and *Lactobacillus salivarius.*[40,41]

In addition, Pinto *et al.*[25] reported that there was a significant decrease in the total number of microorganisms evaluated in bacterial plaque, with no differences in the saliva count. The only study in which no decrease in Streptococcus mutans was reported was in the one published by Gizani *et al.*[26] which had important methodological differences with respect to the studies previously published in the area. The probiotic concentration used (10^8 bacteria per strain used daily) is well below the recommended concentration used to evaluate its effect on the oral cavity.[42] The administration vehicle, a tablet, has previously been used in studies that have not reported results favorable to the use of probiotics.[43] This method has been questioned as a technique of administration because of the poor contact with the oral cavity, which does not allow the colonization of probiotic bacteria.

It is thought that the use of different combined probiotic strains may be useful in potentially selective inhibition of cariogenic bacteria in the oral cavity,[44,45] showing a comparatively strong inhibition of the growth of caries-related pathogens.[18] An increase in salivary pH provides a suitable condition for the remineralization of the mineral structure of the tooth.[37,46] In this review it was observed that the inhibition capacity in the studies varied as did the strains employed, which could be related to the different pH and buffering effects achieved. The findings indicate that the outcome of probiotic therapy may vary between individuals and depend on the specific strain used.[47]

Daily intake of probiotics by means of a vehicle derived from milk versus control groups, which only received the vehicle derived from the milk, showed similar results. Milk derivatives may influence the cariogenic potential and colonization of the cavity.[48] The production of acid is attenuated by the buffering ability of these foods, as they increase the pH (buffer) by producing ammonia, prevent bacterial adhesion to the surfaces of teeth and delay the formation of biofilms.[49] The presence of calcium, calcium lactate and other organic and inorganic components of milk are considered to be anticariogenic and may reduce the colonization of pathogens regardless of the addition of probiotics.[50] Therefore, it is critical that experiments examining the effects of probiotics are conducted using on a non-dairy vehicle.[25]

The age of participants may also be important to consider, since studies have shown that adherence of probiotic species to the mature biofilm of the elderly is more difficult than in very young subjects.[51] The studies analyzed included people between 12 and 29 years old, which would imply a very variable representation of the bacterial colonization and the immune response of the host.[52]

Other aspects to take into account are the methodology used by the studies to quantify bacterial colonization, which is done by sampling the salivary microbiota and plaque. In the case of saliva, the microbiota is more similar to that of the tongue than to that of a tooth on its surface, so that its measurement would not be as representative[53] as would be the evaluations carried out in plaque samples. The quantification of colony forming units was evaluated in four of the five studies using chairside tests and conventional methods of culture in selective agar plates. Although a significant correlation has been demonstrated regarding bacterial counts for these methods,[54] experience with these tests shows that they should be improved, since the steps are complicated and have several sources of error. To date, there are more sensitive and specific techniques available, such as the real-time polymerase chain reaction (RT-PCR), which was only used in one of the studies.[23]

Finally, within the limitations of this review we can consider that currently there are no controlled clinical

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trials of high methodological quality that study the relationship between the prevention of caries through the use of probiotics and patients under fixed orthodontic treatment.

Therefore, it is necessary to conduct research with less risk of bias to evaluate more reliably the results obtained and to be able to establish more effective ways of administering probiotics, choosing the most suitable strain and its use in optimal concentration.

CONCLUSION.

Daily consumption of probiotics may be effective in preventing carious lesions during treatment with fixed orthodontic appliances. However, this should be interpreted with caution and corroborated by clinical trials of better methodological quality.

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