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EFFECTIVENESS OF PROBIOTICS AS AN ADJUNCT IN PERIODONTAL CARE

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Keywords: chronic periodontitis, scaling and root planning, adjunct care, probiotics, supplements.

Summary

Relevance of the problem. Periodontitis is a multifactorial inflammatory disease related with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Treatment of periodontitis aims to prevent further disease progression, to minimize symptoms and perception of the disease, possibly to restore lost tissues and to support patients in maintaining a healthy periodontium. Scaling and root planning (SRP) is the gold standard for the treatment of periodontitis. For the reduction in bacterial recolonization probiotics have been suggested as promising agents not only to retard recolonization, but also to increase the number of beneficial bacteria and to modulate immunological parameters in the prevention and treatment of periodontal disease.

Aim of the work. To find out and assess the data of clinical trials that proposes clinical outcomes of the adjunctive use of probiotic for 3 months after SRP in comparison to SRP combined with a placebo.

Tasks: 1) ascertain and assess the recolonization of bacteria after active treatment of periodontitis; 2) clarify and evaluate clinical variables improvement after the usage of local adjunctives; 3) find out and assess the distinction between different probiotics strains.

Material and methods. This literature review has been carried out in accordance with the PRISMA Statement [23]. Electronic literature review was performed using MEDLINE and ELSEVIER databases and the selection of the articles, published in English between 2010 and 2020 year. The search for publications was based on keywords and their combinations: chronic periodontitis, scaling and root planning, adjunct care, probiotics, supplements.

Results. This literature review includes eight suitable studies that met the inclusion criteria.

Conclusions. The qualitative findings of the studies showed that major part of the included trials reported significant improvement in clinical periodontal parameters in periodontitis patients with the adjunctive use of probiotics compared with control group. 75 % of included studies made with L. reuteri found probiotic containing L. reuteri usage as an adjunct therapy to be significant in the improvement of clinical parameters. Probiotic therapy could be used for managing periodontal diseases. This review puts a stress on L. reuteri effectiveness. However, further studies are needed to substantiate its longitudinal effect.

Introduction

Periodontitis is a multifactorial inflammatory disease related with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. (Papapanou et al., 2018). It can be recognized by presence of decreased clinical attachment level, periodontal pocketing and gingival bleeding on probing. Periodontitis case is defined when interdental CAL is detectable at ≥2 non-adjacent teeth, or 2. Buccal or oral CAL ≥3 mm with pocketing ≥3 mm is detectable at ≥2 teeth but the observed CAL cannot be ascribed to non-periodontitis-related causes such as: 1) gingival recession of traumatic origin; 2) dental caries extending in the cervical area of the tooth; 3) the presence of CAL on the distal aspect of a second molar and associated with malposition or extraction of a third molar, 4) an endodontic lesion draining through the marginal periodontium; and 5) the occurrence of a vertical root fracture (Papapanou et al., 2018). Treatment of periodontitis aims to prevent further disease progression, to minimize symptoms and perception of the disease, possibly to restore lost tissues and to support patients in maintaining a healthy periodontium (Graziani, Karapetsa, Alonso and Herrera, 2017). Scaling and root planing (SRP) is the gold standard for the treatment of periodontitis (Berezow and Darveau, 2010). Mechanical debridement substantially reduces the number of periodontal pathogens,

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however recolonization with pathogenic species takes place over a short period of time ((Tekce et al., 2015) (Magnusson et al. 1984)). Re-colonization starts almost immediately after scaling and root planing (SRP) ((Tekce et al., 2015) (Magnusson et al. 1984, (Quirynen et al., 2005)). For the reduction in bacterial re-colonization different therapeutic approaches, such as antimicrobial agents, lasers and photodynamic therapy have been proposed as adjunctive treatments ((Tekce et al., 2015) (Quirynen et al. 2002, Herrera et al. 2008, Yılmaz et al. 2013)). Probiotics have been suggested as promising agents not only to retard re-colonisation, but also to increase the number of beneficial bacteria and to modulate immunological parameters in the prevention and treatment of periodontal diseases (Teughels, Loozen and Quirynen, 2011). Probiotic organisms are thought to act through a variety of mechanisms, including 1) exclusion and competition with potential pathogens for nutrients and epithelial cell adhesion; 2) production of antimicrobial substances against periodontopathogens; 3) local and systemic immunomodulation; and 4) enhancement of the mucosal barrier function. ((İnce et al., 2015) (Teughels W et al 2010)) The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) defined probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" ((Invernici et al., 2018) (Joint FAO/WHO Working Group, 2002)). Probiotics can contain a wide range of microorganisms (Tekce et al., 2015).

This literature review aims to compare different strains of probiotics and its effect on periodontal health in maintenance patients. The objective of this literature review was to evaluate the data of clinical trials what proposes clinical outcomes of the adjunctive use of probiotic for 3 months after SRP in comparison to SRP combined with a placebo.

Methods and materials

The systematic review of scientific literature followed the methodological guidelines of the PRISMA Statement [23]. The electronic databases search accomplished in PubMed (MEDLINE) database. Data collection protocol was prepared before two investigators (J.V. and U.M.S.) started collecting the data and analyzing the literature. The search for publications was based on keywords and their combinations: chronic periodontitis, scaling and root planning, adjunct care, probiotics, supplements. To obviate a disagreement, two authors resolved it during the discussion. The search results are presented in Figure 1. In the electronic search MEDLINE (by PubMed) database were found 116 articles published between 2010 and 2020. 91 articles were excluded because of duplication or the reason that their abstracts failed to conform to the aims of the study. Therefore, 25 full-text articles were evaluated and 17 articles were excluded. The following inclusion and exclusion criteria are presented in Table 1. Eight suitable studies were included in the study.

Table 1. Inclusion and exclusion criteria

No	Inclusion criteria	Exclusion criteria
1	Published earlier than 2010	Published 2010 or later
2	Placebo control study	No placebo group
3	Randomised	Not randomised
4	Free full text	No free full text
5	Articles in English	Articles written in other languages than English
6	Probiotics used as an adjunct periodontal care	Probiotics used as the only periodontal care

Results

8 articles met the inclusion criteria and were selected to be analyzed [1-8]. All data about studies are shown in Table 2. No significant differences in demographic characteristics were found between groups (P >0.05). The mean of sample size was 40.375 ± 10.81 (min 28 [5], max 59 [7]). The shortest period of monitoring time was 12 weeks, whereas the longest 360 days (mean 234 ± 119.18). Losenges usage time mean 56 ± 33.36 days, (min 3 weeks [3, 4], max 3 months [2, 5]). It was used once per day in two clinical trials [2, 5]

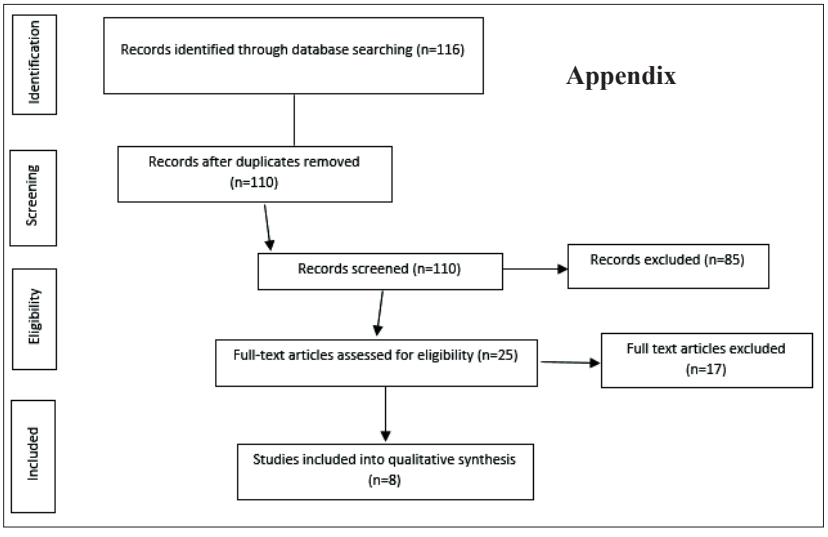

Figure 1. Prisma flow chart

and twice per day in the rest [1, 3, 4, 6-8]. Mostly used probiotic strain was L.reuteri [3, 4, 6, 7], L. rhamnosus SP1 [2, 5]. One study also used B. Lactis [1] and one with S. oralis KJ3, S. uberis KJ2 and S. rattus JH145 [8].

Table 3 shows the BOP, PPD and CAL values for the control and test groups at baseline and 3 months after probiotics or placebo intake. There were no significant intergroup differences in the clinical profile of participants in any study at the baseline. Both test and control groups showed improvements in clinical parameters at evaluation time.

Differences in intergroup comparisons of PPD, CAL and BOP were found to be significant (P <0.05) in favor of the test group at 3 months point in 5 clinical trials [1, 3, 4, 5, 6]. SRP + P group showed a significantly lower percentage of teeth with a PPD ≥5 mm, bleeding on probing and lower loss of clinical attachment ($p < 0.05$). However, no significant inter-group differences were detected in 3 trials [2, 7, 8].

Three studies, what found probiotic usage as an adjunct therapy to be significant are studies made with L. reuteri [3, 4, 6]. However here were no statistically significant inter-

Table 2. Selected clinical trials data

No	Study	Sample (N/age)	Monitoring time	Lozenges usage	Probiotic strain
1	Marcos M. Invernici et al., 2018, Brazil	41/ over 30	At baseline and on days 30, 90	Twice a day for 30 days	B. lactis HN019
2	Alicia Morales et al., 2017, Chile	47/ over 35	At baseline and on days 90, 180, 270	Once a day for 3 months	L. rhamnosus SP1
3	Merve Tekce et al., 2015, Turkey	40/ from 35 to 50	At baseline and on days 21, 90, 180, 360	Twice a day for 3 weeks	L. reuteri
4	Gizem Ince et.al., 2015, Turkey	30/ from 35 to 50	At baseline and on days 21, 90, 180, 360	Twice a day for 3 weeks	L.reuteri
5	Alicia Morales et al., 2016, Chile	28 / from 35 to 68	At baseline and on days 90, 180, 270, 360	Once a day for 3 months	L.rhamnosus SP1
6	Wim Teughels et al., 2013, Turkey	30/ over 30	At baseline and on weeks 3, 6, 9, 12	Twice a day for 12 weeks	L. reuteri
7	George Pelekos et al. 2019, India	59/ over 18	At baseline and on days 90, 180	Twice daily for 28 days	L. reuteri
8	Isabelle Laleman et al. 2015, Turkey	48/ over 36	At baseline and on weeks 4, 8, 12, 24	Twice a day for 12 weeks	S. oralis KJ3, S. uberis KJ2 and S. rattus JH145

Table 3. Results of test group and control group probing pocket depth, clinical attachment level and bleeding on probing

Test group							Control group						
No	PPD (probing pocket depth)		CAL (Clinical attachment level)		BOP (bleeding on probing) %		No	PPD (probing pocket depth)		CAL (Clinical attachment level)		BOP (bleeding on probing) %	
	Baseline ± SD	After 3 months ± SD	Baseline ± SD	After 3 months ± SD	Baseline ± SD	After 3 months ± SD		Baseline ± SD	After 3 months ± SD	Baseline ± SD	After 3 months ± SD	Baseline ± SD	After 3 months ± SD
1	3.01 ± 0.27	2.49 ± 0.27	3.26 ±0.39	2.77 ± 0.38	30.8 ± 22.07	18.8 ± 16.14	1	3.1 ± 0.43	2.85 ± 0.34	3.42 ± 0.54	3.24 ± 0.51	35.00 ± 25.84	30.71 ± 27.86
2	3.8 ± 0.7	3.4 ± 0.6	3.8 ± 0.7	3.4 ± 0.6	49.3 ± 18.1	38.2 ± 14.8	2	3.1 ± 0.9	2.4 ± 0.5	4.7 ± 1.5	4.1 ± 1.4	52.5 ± 12.6	40.7 ± 13.3
3	5.23 ± 0.68	3.80 ± 0.75	–	–	88.9 ± 7.66	16.45 ± 4.21	3	5.36 ±0.72	4.51 ± 0.71	–	–	88.65 ±4.11	21.85 ± 3.98
4	5.85 ± 0.54,	4.25 ± 0.41	–	–	88.90 ± 7.66	17.47 ± 4.37	4	5.57 ± 0.39	4.75 ± 0.48	–	–	88.65 ± 4.11	22.40 ± 4.36
5	2.7 ± 0.6	2.2 ± 0.6	4.2 ± 0.9	3.8 ± 0.9	41.1 ± 16.3	28.2 ± 10.2	5	2.5 ± 0.3	2.1 ± 0.2	4.9 ± 1.3	4.2 ± 1.4	33.8 ± 16.1	23.6 ± 14.8
6	4.15 ±0.71	2.73 ± 0.57	4.97 ± 1.01	3.97 ± 0.97	70.70 ± 14.53	15.51 ± 11.92	6	4.32 ± 0.50	2.93 ± 0.40	4.97 ± 0.61	4.21 ± 0.67	67.53 ± 11.37	16.58 ± 10.54
7	3.1 ± 0.6	2.7 ±0.5	4.2 ± 1.3	4.0 ± 1.3	59.5 ± 21.3	37.4 ± 20.1	7	3.5 ± 1.0	3.0 ± 0.6	4.9 ± 1.7	4.6 ± 1.6	69.1 ± 27.8	42.2 ± 17.6
8	4.5 ± 0.51	3.15 ± 0.52	5.22 ± 0.41	4.47 ± 0.39	87.44 ± 6.03	27.74 ± 10.34	8	4.59 ± 0.52	3.26 ± 0.49	5.36 ± 0.45	4.66 ± 0.45	85.55 ±7.29	28.31 ± 7.71

group differences in any outcomes at any time points (all, p > .05) nor in the changes in outcomes (Δ) with time (all, p > .05) in one trial made with L. reuteri [7]. There was only a trend of a greater magnitude of statistical change occurring among the test group compared to the control group [7].

There were two studies made with L. rhamnosus and one of it found clinical intergroup changes to be significant [5]. Statistically significant intragroup differences were observed in the amount of full-mouth CAL (P <0.05). There was also a significant PD reduction in the test group (P <0.05). However, multiple comparisons of intragroup measures showed that there were no differences (P>0.005). In another L. rhamnosus study although the SRP + P group consistently resulted in better outcomes when compared to SRP in both studies, there were no significant differences between groups.

There were also one study what used B. Lactis. The Test group presented a decrease in probing pocket depth and a clinical attachment level significantly higher than those of the Control group at 3 months [1].

In trial what used S. oralis KJ3, S. uberis KJ2 and S. rattus JH145 no differences were detected when comparing the adjunctive use of a placebo or the investigated streptococci containing probiotic tablet after SRP.

Discussion

Current literature review aimed to assess different strains of probiotics and its effect on periodontal health in maintenance patients. The qualitative findings of the study showed that 62.5 % of the included trials [1, 3, 4-6] reported significant improvement in clinical periodontal parameters in periodontitis patients with the adjunctive use of probiotics compared with control group. Most frequently evaluated parameters were PPD, CAL and BOP. Differences in intergroup comparisons were found to be significant (P <0.05) in favor of the test group. At 3 months follow up point in the test group there were significantly lower percentage of teeth with a PPD ≥5 mm, bleeding on probing and lower loss of clinical attachment (p < 0.05). However, no significant intergroup differences were detected in 37.5 % of the included studies [2, 7, 8].

75 % of included studies found probiotic containing *L. reuteri* usage as an adjunct therapy to be significant [3, 4, 6]. Only one study which was made with *L. reuteri* did not show any statistically significant inter-group differences in any outcomes after 3 months from baseline. However, there was a tendency of a greater magnitude of statistical change occurring among the test group compared to the control group [7]. These results were consistent with Sana Ikram *et al.* systematic review and meta-analysis which declares adjunctive probiotics could result in additional benefits in CAL gain in periodontitis [9]. M. Vivekananda *et al.* states *L.reuteri* losenges to be effective not only as adjunct therapy but also as alternative to periodontal treatment when SRP might be contraindicated [10].

50 % of analised trials made with *L. rhamnosus* found clinical intergroup changes to be significant. It is confirmed by A. Mendi et al. study which provides evidence that *L. rhamnosus* can modulate the inflammatory signals and present pathogen *P. gingivalis* to immune systems. As a result, chemokine secretion is induced and in this way recolonization is eased down, whereas clinical outcomes of periodontitis are improved [11].

To our knowledge, this is the first study assessing and comparing the microbiological impact of the use of *B. lactis* probiotics on the treatment of periodontitis with a 3-months follow-up. This is the first research to demonstrate the potential effect of a probiotic bacterium of the genus *Bifidobacterium* on the non- surgical treatment of periodontitis [1]. It coincides Larry E. Miller *et al.* systematic review and meta-analysis of the effect of *Bifidobacterium animalis ssp. lactis HN019* on cellular immune function in healthy elderly subjects that claims *B. lactis HN019* supplementation to be highly efficacious in increasing PMN phagocytic capacity and moderately efficacious in increasing NK cell tumoricidal activity [12].

Despite a negative correlation between viridans streptococci and certain periodontopathogens found by Hillman *et al. (1985)* study made with *S. oralis KJ3, S. uberis KJ2 and S. rattus JH145* showed almost no effect of the usage of a probiotic tablet as a supplement to SRP on clinical parameters [8].

The following limitations should be taken into account when considering the conclusions of the present literature review. The main limitations of this research were the small number of included studies. The present systematic review only considered studies published in the English language. This could have resulted in publication bias, with potentially relevant studies published in other language being missed. 3 months follow- up period was common for all included studies and that is the reason this period was chosen nevertheless longer follow- up periods could have yielded different outcomes. Assessment of 4 probiotic strains could also be considered as a constraint.

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. The study products were not financial sponsorship provided by the company nor was any contractual agreement signed. Nevertheless, more studies are required with larger cohorts on dose, route of administration, follow up period as well as

strains of probiotics used. All in all, probiotic therapy can be used for managing periodontal diseases. This review puts a stress on *L. reuteri* effectiveness. However further studies are needed to substantiate its longitudinal effect.

Conclusion

Within the limitations of this study, we estimated that the adjunctive probiotic therapy could be used for managing periodontal diseases. This review puts a stress on L. reuteri effectiveness. However, further studies are needed to substantiate its longitudinal effect.

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PROBIOTIKŲ, KAIP PAPILDOMOS PERIODONTITO GYDYMO PRIEMONĖS, EFEKTYVUMAS

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Raktažodžiai: lėtinis periodontitas, skeilingas, papildoma terapija, probiotikai, papildai.

Santrauka

Problemos aktualumas. Periodontitas yra daugiafaktorinė uždegiminė liga, susijusi su disbiotinių apnašų biofilmu ir charakterizuojama progresuojančia dantis supančių audinių destrukcija. Gydant periodontitą, siekiama užkirsti kelią ligos progresavimui, sumažinti simptomus, galimai atkurti prarastus audinius ir padėti pacientams palaikyti sveiką periodontą. Skeilingas yra periodontito gydymo auksinis standartas. Probiotikai buvo pasiūlyti kaip perspektyvi periodontito gydymo priemonė, galinti ne tik stabdyti rekolonizaciją, bet ir padidinti naudingų bakterijų skaičių bei moduliuoti imunologinius parametrus periodonto ligų prevencijoje ir gydyme.

Darbo tikslas – išsiaiškinti ir įvertinti klinikinių tyrimų, pateikiančių probiotikų vartojimo, kaip pridėtinės terapijos po nechirurginio periodontologinio gydymo, klinikinius rezultatus po trijų mėnesių, lyginant su nechirurginio gydymo ir placebo procedūros rezultatais.

Uždaviniai: 1) įvertinti bakterijų rekolonizaciją po aktyvaus periodontito gydymo; 2) paaiškinti ir įvertinti klinikinių parametrų pagerėjimą po probiotikų vartojimo; 3) išsiaiškinti ir įvertinti skirtumus tarp skirtingų probiotikų padermių.

Medžiaga ir metodai. Literatūros apžvalga buvo atlikta pagal PRISMA pareiškimą [23]. Elektroninė literatūros apžvalga atlikta naudojant PubMed (Medline) ir ScienceDirect (Elsevier) duomenų bazes. Atrinkti straipsniai anglų kalba nuo 2010 iki 2020 metų. Publikacijų paieška buvo paremta raktažodžiais ir jų deriniais: *chronic periodontitis, scaling and root planning, adjunct care, probiotics, supplements.*

Rezultatai. Apžvelgti aštuoni įtraukimo kriterijus atitikę tyrimai. Išvados. Kokybiniai duomenys parodė, kad didžiojoje dalyje įtrauktų tyrimų papildomas probiotikų vartojimas turėjo reikšmingą poveikį klinikinių periodonto parametrų pagerėjimui, lyginant su kontroline grupe. 75 proc. įtrauktų tyrimų, atliktų su *L. reuteri,* nustatyta, kad šių probiotikų vartojimas reikšmingai pagerina klinikinius parametrus, todėl papildomas probiotikų vartojimas gali būti veiksmingas periodontito gydymo būdas. Ši apžvalga pabrėžia *L. reuteri* veiksmingumą. Norint patvirtinti šių probiotikų ilgalaikį poveikį, reikalingi tolesni tyrimai.

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