ISRCTN71877931 https://doi.org/10.1186/ISRCTN71877931

Should probiotics be used as adjuvants in the treatment of periodontitis?

Submission date 25/10/2022	**Recruitment status** Recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 11/11/2022	**Overall study status** Ongoing	
Last Edited 11/11/2022	**Condition category** Oral Health	

Plain English summary of protocol

Background and study aims
Imbalance of the oral microbiota, inflammation, colonization by specific pathogenic bacteria and lack of oral hygiene are often associated with oral diseases such as caries, gingivitis and periodontitis. Periodontitis is caused by bacteria accumulated around the tooth and it is responsible for gum inflammation, bone loss, dental loosening and tooth loss. Conventional treatment involves mechanical removal of plaque and local administration of antibiotics or antiseptics, which may have limited effectiveness due to bacterial resistance. It is necessary to look for alternatives to conventional therapeutic and preventive approaches. Probiotics can play an important role in this context, they can help in the formation of a new protective biofilm and reduce inflammation, thus contributing to the prevention, control and treatment of periodontal diseases. Probiotics are non-pathogenic bacteria that are naturally present in multiple foods (e. g. in bioactive yoghurts). Probiotics are regularly used to treat/prevent intestinal diseases but they are still little used in dentistry due to the scarcity of data on their clinical utility. The main aims of this study are to evaluate the effectiveness of probiotics in the treatment of periodontitis in adults, analyze the role of probiotics in the composition of the sub-gingival microbiome, analyze the role of probiotics on inflammation associated with periodontitis, and assess the adherence to therapy and local and systemic adverse effects.

Who can participate?
Adults with and without periodontitis

What does the study involve?
A questionnaire will be completed by the volunteers to determine if they meet the inclusion criteria for participation in the study. The study will involve two interventional study groups and two control groups. The two study groups will consist of subjects with periodontitis in which one group will receive a probiotic tablet (group 1) and the other will receive a placebo or dummy tablet (group 2). The control groups will consist of subjects without periodontitis in which one group will receive a probiotic tablet (group 3) and the other group will receive a placebo tablet (group 4). In subjects with periodontitis, scaling and root planing (SRP) will be performed per arch followed by taking probiotics/placebo for 3 months, twice a day after brushing. Subjects without periodontitis will take only probiotics/placebo (SRP is not performed), which will allow for assessing the magnitude of the effect of probiotics in the absence of mechanical treatment.

The monitoring periods will be as follows: baseline, 3 and 6 months (T0, T3 and T6), when clinical data and biological samples will be collected.

What are the possible benefits and risks of participating?
Probiotics may contribute to improving oral health and be recommended for the prevention, and maintenance of oral health and treatment of periodontal disease. Therapy with probiotics can cause some side effects, namely gastrointestinal changes (e.g. gastric pain, nausea, diarrhea, taste alteration) although these are rare. To assess potential side effects, the subject will need to complete a side effects questionnaire at the 3-month evaluation visit. Minimal discomfort may occur during the collection of biological samples.

Where is the study run from?
The dental clinic of Instituto Universitário Egas Moniz (IUEM) (Portugal)

When is the study starting and how long is it expected to run for?
November 2020 to December 2026

Who is funding the study?
Centro de Investigacao Interdisciplinar Egas Moniz (CiiEM), the Research Center of Egas Moniz – Cooperativa de Ensino Superior (CRL) (Portugal)

Who is the main contact?
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Study information

Scientific Title
Probiotics as adjuvants in non-surgical periodontal treatment: a randomized and placebo-controlled clinical trial

Acronym
PROPERIO

Study objectives
1. In patients with periodontitis, probiotics better reduce the following clinical parameter scores of insoluble polysaccharide (IP) plaque index (PI), gingival index (GI), probing pocket depth (PPD), probing on bleeding (BoP), suppuration, clinical attachment loss (CAL), and gingival recession (REC), when associated with scaling and root planing (SRP)
2. Probiotics improve the composition of the sub-gingival microbiome and colonization of sub-gingival sites
3. Probiotics reduce the levels of periodontitis inflammatory markers (IL1-ß, IL-6, TNF-α, MMP-8, PGE2)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/04/2022, Egas Moniz Ethics Committee (Egas Moniz, Cooperativa de Ensino Superior, C.R.L. Quinta da Granja, Monte da Caparica, 2829-511 Caparica, Portugal; +351 212 946 700; no email available), ref: process 1097

Study design
Single-center interventional single-blind randomized placebo-controlled study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Periodontitis

Interventions
The study is randomized into four groups, using the IBM SPSS Statistics 21.0 software or equivalent program (eg https://www.random.org/lists/), including probiotics/placebo groups in patients with periodontitis and probiotics/placebo groups in patients without periodontitis.

After performing scaling and root planing in patients with periodontitis, the probiotics group will take a tablet containing two probiotic strains (L. reuteri DSM 17938 and ATCC PTA 5289) twice daily after brushing for 3 months. The placebo group will take a placebo tablet in the same way as the probiotic group. Clinical, microbiological, and immunological parameter data will be collected and adherence rate and adverse effects will be examined at baseline, 3 and 6 months.

Patients with Periodontitis:
Experimental group (probiotic group): (n=39) Scaling and root planning (SRP) + probiotic implementation: SRP per arcade followed by probiotic implementation:
- Strains used: L. reuteri DSM 17938 and L. reuteri ATCC PTA 5289
- Frequency of administration: twice a day (in the morning and evening after brushing) for 3 months
- Vehicle of administration: tablets containing at least 2x108 CFUs (L. reuteriProdentis, BioGaia)
- Follow-up appointment: baseline, 3 and 6 months (we will collect clinical, microbiological, immunological parameters, but also, examine adherence rate and appearance of adverse effects*)
Placebo group: (n=39) SRP + placebo intake:
SRP per arcade followed by placebo intake:
- Frequency of administration: twice a day (in the morning and evening after brushing) for 3 months
- Vehicle of administration: tablets

Patients Without periodontitis
Experimental group (probiotic group): (n=39) Probiotic implementation, SRP not performed: Probiotic implementation
- Strains used: L. reuteri DSM 17938 and L. reuteri ATCC PTA 5289

- Frequency of administration: twice a day (in the morning and evening after brushing) for 3 months
- Vehicle of administration: tablets containing at least 2x108 CFUs (L. reuteriProdentis, BioGaia)
- Follow-up appointment: baseline, 3 and 6 months (*)
Placebo group: (n=39) Placebo intake, SRP not performed
Placebo implementation
- Frequency of administration: twice a day (in the morning and evening after brushing) for 3 months
- Vehicle of administration: tablets
- Follow-up appointment: baseline, 3 and 6 months (*)

Intervention Type
Supplement

Primary outcome(s)
The following outcomes will be measured at baseline, 3 and 6 months:
1. Clinical outcomes: IP, IG, PPD, BoP/suppuration (%); PPD, REC, CAL (mm) measured using a CP12 Hu-Friedy periodontal probe (0.06 mm diameter - 0.25N force) and a periodontal chart
2. Microbiological outcomes: subgingival microbiome, samples of subgingival plaque will be collected with Gracey curettes at an affected site (with PPD=/>6mm with or without BoP), placed in tubes containing DNA/RNA stabilizers and stored at -80°C until shipment to a Canadian company Microbiome Insight. Microbiome Insight will perform DNA extraction and sequencing of the V4 region of the 16S rRNA coding gene to identify and quantify the microbial communities present in the samples and to compare the microbial profile changes between the study groups before and after the probiotic/placebo implementation
3. Immunological outcomes: cytokines (IL1-ß, IL-6 and TNF-α [pg/ml]) and other markers (MMP-8 and PGE2 [pg/ml]) in gingival crevicular fluid. Samples of gingival crevicular fluid will be collected with sterile absorbent paper strips, and placed for 30 sec in contact with an affected site (bag with PPD=/>6mm with or without BoP). Then, they will be inserted into the Periotron 8000 (Periotron Ide-interstate, NY, USA) to quantify the volume collected. Afterwards, they will be placed in an Eppendorf tube with a filter and stored at -80°C until they are sent to the Complutense University of Madrid, Spain, which will analyze the concentration of mediators by enzyme immunoassay ELISA

Key secondary outcome(s))
The following outcomes will be measured at baseline, 3 and 6 months:
1. Adverse effects measured using a questionnaire (nature/severity/duration)
2. Adherence rate measured using a questionnaire and by calculating the remaining tablet numbers

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Adults aged 18-65 years old diagnosed with untreated periodontitis
2. Adults aged 18-65 years old without periodontitis (health periodontal)

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Key exclusion criteria
1. Unsigned informed consent
2. Pregnant and lactating women
3. Systemic diseases (eg inflammatory bowel diseases, diabetes, infectious diseases, transplant recipients, etc.)
4. Use of certain medications (eg corticoids, cyclosporine, xerostomy medications, NSAIDs, etc.)
5. Taking antibiotics and/or probiotics in the last 3 months
6. Use of antiseptics
7. Drug and/or alcohol abuse, smoking
8. Chemotherapy, radiotherapy for less than 1 year
9. Periodontal treatment for less than 6 months
10. Mental illness
11. Intolerance to lactose, gluten or tablet component
12. Participants with incomplete data or not using ¼ of the pills

Date of first enrolment
30/01/2023

Date of final enrolment
30/06/2026

Locations

Countries of recruitment
Portugal

Study participating centre
IUEM, Egas Moniz Cooperativa de Ensino Superior CRL
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Sponsor information

Organisation
Instituto Superior de Ciências da Saúde Egas Moniz

ROR
https://ror.org/01prbq409

Funder(s)

Funder type
Research organisation

Funder Name
Centro de Investigacao Interdisciplinar Egas Moniz (CiiEM)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the team responsible for the Study. The results of the Study will be disseminated through doctoral reports, presentations at conferences, and submission for publication in scientific journals and academic thesis. The information collected will be handled by the person(s) responsible for the study.

The results will be available at the end of the study and the participant has the right to access their data after analysis of the results. The participant must request it from the team responsible for the Study. The participant will not be identified in any report or publication of the Study.

Participants' data will be treated confidentially and are protected in accordance with the provisions of the General Data Protection Regulation (RGPD), Law 58 of 2019, and in accordance with the ethical standards approved by the Egas Moniz Ethics Commission (CEEM).
To guarantee the confidentiality and protection of the data collected, the anonymization procedure of your data will be carried out immediately after signing the Informed Consent, which will be valid for the entire duration of the study. This process consists of assigning a code made up of numbers and letters to each participant, so that they are not identifiable by their name, but only by the code. Decoding can only be carried out by those responsible for the study, who will be responsible for the database, in accordance with the legal provisions in force.
The biological samples collected within the scope of this study, duly anonymized, will be transferred for laboratory analysis to be carried out in foreign laboratories (Canada and Spain), with the consent of the participant, expressed in the informed consent statement.
By signing this Informed Consent, you allow leftover samples to be retained for the duration of

the project.
The study team will maintain confidentiality about the medical records of your participation in this Study, which will not be made available to the public. The participant has the right to obtain access to his/her personal data and to receive a copy of the Study results. The biological samples collected will not be used for commercial purposes.
The samples will be kept for a period of 4 years at the IUEM Dental Clinic under the responsibility of the team linked to the project. The samples will be destroyed after this period. An extension of the conservation of the samples may be requested, which will imply contacting the donors again to obtain their authorization.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			26/10/2022	No	Yes
Participant information sheet			26/10/2022	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes