Does subgingival bacterial colonization differ between implants and teeth? 
A systematic review

Abstract: The aim was of this study was to determine the current weight of evidence for the existence of specific differences between the microbiota of healthy teeth and healthy implants, or of teeth with periodontitis and implants with peri-implantitis. A systematic review was conducted according to the PRISMA statement. The MEDLINE, EMBASE and Cochrane databases were searched up to February 2018 for studies comparing microbiological data of biofilm samples collected from healthy teeth and implants or from teeth with periodontitis and implants with peri-implantitis. The weight of evidence was defined in three categories (strong, moderate and mild/some), according to the difference in number of studies showing statistically significantly higher counts and/or proportions and/or abundance and/or prevalence of microorganisms in health or in disease. Of the 132 articles identified, 8 were included. A wide range of microorganisms were present in different conditions but no microorganisms showed strong, moderate or mild/some evidence for a specific association with either teeth or implants. The results of this systematic review indicated that there is insufficient evidence in the literature to support specific differences between microorganisms colonizing teeth and implants, either in health or in disease.

Keywords: Peri-Implantitis; Periodontitis; Microbiota; Systematic Review.

Introduction

Peri-implantitis is a plaque-associated pathological condition characterized by inflammation of the peri-implant connective tissues and progressive loss of supporting bone.1 Peri-implantitis is not a rare event,2,3,4 and if not diagnosed and treated may lead to implant loss.

After some debate around the etiology of peri-implantitis, it has been well established that this is an infectious disease that share some similarities with periodontitis.5,6 Previous Association studies evaluating the microbiota of healthy and diseased implants7,8 and a recent systematic review9 have suggested that established periodontal pathogens, such as Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia are elevated in peri-implantitis in comparison with healthy implants. Despite this evidence, in the literature it is still unclear whether or not there are essential differences between the microbial profile of
teeth and implants, and if there are pathogens or host-compatible species specifically associated with implant surfaces.

Understanding the microbiota associated with the onset and progression of an infection is a crucial step to studying the effectiveness of different treatments. Considering that the treatment of periodontal diseases has been extensively studied for over 50 years, understanding the similarities/differences between the microbiota colonizing teeth and implants may provide important information for the development of preventive and therapeutic strategies for peri-implantitis. Therefore, the aim of this systematic review was to determine the current weight of evidence for the existence of specific microbiological differences between the subgingival biofilms around implants and teeth, in health and disease.

**Methods**

**Protocol and registration**

This systematic review was registered with the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (registration number #CRD42018093317) and conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.11

**Focused question**

Are there specific differences in the composition of the subgingival/submucosal microbiota between teeth and implants, in health and disease?

**Eligibility criteria**

The studies were selected according to the following inclusion criteria:

a. Studies of any design comparing microbiological data obtained from subgingival/submucosal biofilm samples collected from patients with periodontitis and peri-implantitis;

b. Studies of any design that compared microbiological data obtained from subgingival/submucosal biofilm samples collected from patients with periodontal and peri-implant health.

Studies that met the following criteria were excluded:

a. Narrative or systematic reviews, meta-analyses, comments, editorials, letters to the editor, study protocols, case reports or case series;

b. Lack of a direct comparison of baseline microbiological data between periodontitis and peri-implantitis in case of prospective interventional studies;

c. Studies that evaluated only viruses;

d. Studies not presenting statistical analysis of the microbiological findings;

e. Studies evaluating healthy teeth or implants in patients with periodontitis.

**Search strategy, study selection and data collection**

The MEDLINE (through PubMed), EMBASE and Cochrane Library databases were searched up to February 19, 2018, by two independent reviewers (B.R-V. and M.Fe.) using MeSH terms and other keywords described in Table 1. In addition, a manual search was conducted based on the list of References of the selected manuscripts and other Review articles. Titles and abstracts of studies identified in the search were read independently by two researchers (M.L.A. and A.F.) and any disagreement was solved through discussion. If disagreement persisted, another researcher was consulted in order to achieve consensus (M.Fe.). After abstract reading, those studies that fulfilled the inclusion and exclusion criteria were read in full. Data extraction was conducted by four different independent researchers (B.R-V., K.A.F., M.Fo. and M.W.).

**Risk of bias in individual studies**

Two reviewers (M.Fo. and M.L.A.) appraised the risk of bias on the selected studies using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Cases of disagreement were solved by a third reviewer (M.Fe.).

**Additional analyses: weight of evidence**

To estimate the weight of evidence for microorganisms associated with periodontitis and peri-implantitis and/or periodontal and peri-implant health, the following categories were defined, according to differences in...
number of studies showing specific microorganisms in statistically significantly higher counts/proportions/abundance/prevalence in each condition: a) Strong evidence: difference shown by > 5 studies, b) Moderate evidence: difference shown by 3–5 studies, and c) Mild/Some evidence: difference shown by 2 studies.12

Summary measures

The following information was collected from each study and registered in predefined forms: microbiological outcomes (e.g., microorganisms appraised, taxa in higher counts and/or proportions and/or abundance and/or prevalence in teeth or in implants [primary outcome of interest]), study design, characteristics of participants (e.g., age, proportion of men and smokers, case definition of periodontitis/peri-implantitis and periodontal/peri-implant health, mean plaque index, probing depth [PD], clinical attachment level, and number of sites with PD ≥ 5mm, PD ≥ 6mm and PD ≥ 7mm), as well as number of samples collected, sampling strategy, diagnostic method used and data expression. For longitudinal observational/interventional studies, only baseline data were collected.

Results

Studies included

The flow chart of the study is represented in Figure 1. The electronic search (Table 1) detected a total of 107 articles. After title and abstract screening, 91 articles were excluded and 16 were selected for full-text reading. During the manual search, no additional articles were selected. Eight articles were excluded after full-text reading: six articles did not directly compare microbiological data from healthy teeth with healthy implants, or periodontitis and peri-implantitis5,7,9,13,14,15,16 and two studies did not present statistical analysis comparing periodontal and peri-implant health or disease (Table 2).17,18 Therefore, 8 articles were included in the current systematic review.19,20,21,22,23,24,25,26

Figure 1. Flow chart of paper selection.
Methodological features of the studies included and demographic characteristics of the population evaluated

Table 3 presents the methodological features of the studies included and demographic characteristics of the populations evaluated. Seven studies were cross-sectional and one was a longitudinal cohort. The mean age of the studied volunteers ranged between 35.5–60.1 years old. Two studies included smokers.25,26 Different clinical criteria were used to define periodontal and peri-implant health, periodontitis and peri-implantitis. Two articles did not describe the inclusion criteria of the volunteers.21,24 A total of 102 individuals with periodontal and peri-implant health and 68 subjects with periodontitis and peri-implantitis were assessed (data not shown). The clinical characteristics of the studies volunteers are presented in Table 4.

Methodological features related to sampling and microbiological analysis are presented in Table 5. A total of 553 subgingival/submucosal biofilm samples were evaluated (periodontal health = 137, peri-implant health = 158, periodontitis = 131, peri-implantitis = 127). In six studies19,20,21,24,25,26 the samples were collected and processed individually, and in two studies22,23 they were pooled. One study used culture,24 one used Checkerboard DNA-DNA Hybridization,21 one used real time PCR,19 and five studies used sequencing/pyrosequencing20,22,23,25,26 for microbial identification.

Microbiological data

The microorganisms found in statistically significantly higher counts/proportions/abundance/prevalence in the different periodontal and peri-implant conditions are presented in Table 6. Fifty taxa (25 bacterial species, 23 bacterial genera and 2 unclassified) differed significantly between periodontal and peri-implant health in at least one study, and 52 taxa (27 bacterial species, 22 bacterial genera, 1 fungus, 1 virus and 1 unclassified) differed significantly between periodontitis and peri-implantitis in at least one study. Three studies found no statistically significant differences for any taxa between health implants/teeth or diseased implants/teeth.23,24,26

No taxa presented Strong, Moderate or Mild/Some evidence for a specific association with peri-implantitis in comparison with periodontitis, or for peri-implant health in comparison with periodontal health, based on the criteria defined by Perez-Chaparro et al.12

Risk of bias within studies

Table 7 shows the risk of bias analysis of the studies included in this systematic review, according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. All articles explicitly defined a research question (Item #1), the population from which the study participants were selected (Item #2), recruited more than 50% of the target population (Item #3), defined - in detail - the exposure measures and assessments (Item #9), elucidated the
| Reference | Study design | Mean age (years) | Male (%) | Smokers (%) | Inclusion criteria | Periodontitis | Peri-implantitis |
|-----------|--------------|-----------------|----------|-------------|-------------------|--------------|-----------------|
| Schierano et al. (2010) | Cross-sectional | Unclear | 22.22 | 0 | ND | Periodontal health | Peri-implant health | ND | ND |
| do Nascimento et al. (2011) | Cross-sectional | 44.00 | 40.00 | ND | PD ≤ 3 mm CAL ≤ 1 mm | No BOP or suppuration and no radiographic evidence of marginal bone loss | > 30% of sites with CAL ≥ 4 mm (chronic periodontitis) | Clinical signs of inflammation along with radiographic evidence of bone loss after 1 year in function |
| Kumar et al. (2012) | Cross-sectional | PH: 35.50 PI: 41.00 PIH: 65.00 Pt: 60.00 P: 75.00 | ND | PD ≤ 3 mm CAL ≤ 1 mm | BOP = 0 SUP = 0 M = 0 | Bone loss ≤ 2 mm after coronal restoration | Mucosal inflammation with or without ≥ 2 mm bone loss following restoration |
| Dabdoub et al. (2013) | Cross-sectional | Unclear | Unclear | BOP = 0 PD < 3 mm CAL ≤ 1 mm No redness and swelling | BOP = 0 PD > 3 mm CAL > 1 mm Redness and swelling | Bone loss radiologically | Bone loss |
| Schumann et al. (2014) | Cross-sectional | 60.10 | 28.57 | 0 | No cited | No cited | BOP ≠ 0 PD ≥ 4 mm | BOP ≠ 0 PD ≥ 4 mm |
| Yu et al. (2016) | Cross-sectional | 54.80 | 50.00 | 11.1 | PD < 3 mm PD < 3 mm | BOP = 0 PD ≥ 4 mm | BOP = 0 PD ≥ 5 mm |
| Canullo et al. (2017) | Cross-sectional | PIH: 48.40 PIH: 53.19 Pt: 54.10 Pt: 58.14 | 0 | ND | BOP = 0 | BOP positive | Bone loss ≥ 2 mm |
| Sousa et al. (2017) | Longitudinal cohort | PH: 41.30 PI: 48.00 Pt: 47.00 PIH: 46.50 PIM: 39.00 | 41.18 | 13.04 | ND | Patients treated for AgP and without signs of PIM and PI | CAL ≥ 5 mm AgP: bone loss ≥ 30% of root length affecting at least 3 teeth order than first molars and incisors | BOP ≠ 0 SUP ≠ 0 PD ≥ 5 mm |

PH: Periodontal Health; PIH: Peri-implant Health; PI: Peri-implantitis; P: Periodontitis; ND: Not described; PD: Probing Depth; CAL: Clinical Attachment Level; BOP: Bleeding on Probing; SUP: Suppuration; M: Mobility; AgP: Aggressive Periodontitis; PIM: Peri-implant Mucositis.
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follow-up rate (Item #13) and conducted the statistical analyses (Item #14). Only 7 studies used previously determined eligibility criteria (Item #4), and only one presented sample size justification (Item #5). No study complied with the following Items: #6 (Exposure assessed prior to outcome measurement), #7 (Sufficient timeframe to see an effect), #10 (Repeated exposure assessment) and #12 (Blinding of outcome assessors) of the NIH Quality Assessment Tool. Three studies showed different levels of the exposure of interest (Item #8), and six studies defined the outcomes in details (Item #11).

None of the included articles fulfilled all items of the NIH Quality Assessment Tool. Three articles complied with 9 items; another 3, with 8 items, and 2 articles with 7 items. Thus, all articles included in this review accomplished at least 50% of the items assessed.

Table 4. Clinical characteristics of the study volunteers.

| Reference | Mean plaque index | Mean PD | Mean CAL | Number of sites |
|-----------|-------------------|---------|----------|----------------|
|           |                   |         |          | PD ≥ 5mm | PD ≥ 6 mm | PD ≥ 7 mm |
| Schierano et al. [2010] | Not cited | Not cited | Not cited | Not cited | Not cited | Not cited |
| do Nascimento et al. [2011] | Not cited | Not cited | Not cited | Not cited | Not cited | Not cited |
| Kumar et al. [2012] | Not cited | PH: 2.4 ± 1.9 | Not cited | Not cited | Not cited | Not cited |
| Dabdoub et al. [2013] | Not cited | P: 7.5 ± 3.5 | Not cited | Not cited | Not cited | Not cited |
| Schumann et al [2014] | Not cited | P: 4.1 ± 1.3 | Not cited | Not cited | Not cited | Not cited |
| Yu et al. [2016] | Not cited | PH: 2.22 ± 0.73 | Not cited | Not cited | Not cited | Not cited |
| Canullo et al. [2017] | PIH: 0.87 ± 0.55 | PIH: 1.83 ± 1.62 | Not cited | Not cited | Not cited | Not cited |
| Sousa et al. [2017] | Not cited | PI: 3.00 ± 0.77 | Not cited | Not cited | Not cited | Not cited |

Table 5. Methodological features of sample collection and analysis.

| Reference | n samples | Sampling strategy | Diagnostic method | Data expression |
|-----------|-----------|-------------------|--------------------|-----------------|
| Schierano et al. [2010] | 9 | - | - | 9 | Individual | Culture | CFU and frequency |
| do Nascimento et al. [2011] | 20 | - | - | 29 | Individual | Checkerboard DNA-DNA Hybridization | Count and proportion |
| Kumar et al. [2012] | 10 | 10 | 10 | 10 | Pool | Pyrosequencing | Abundance and diversity |
| Dabdoub et al. [2013] | 56 | 25 | 40 | 41 | Individual | Pyrosequencing | Abundance and diversity |
| Schumann et al [2014] | - | 7* | 7* | - | Individual | Sequencing | Abundance and diversity |
| Yu et al. [2016] | 18 | 18 | 18 | 18 | Individual | Pyrosequencing | Abundance and diversity |
| Canullo et al. [2017] | 18 | 47 | 47 | 43 | Individual | RT-PCR | Count |
| Sousa et al. [2017] | 24 | 24 | 5 | 8 | Individual | Pyrosequencing | Abundance and diversity |

Total samples: 137, 131, 127, 158

PD: Probing Depth; CAL: Clinical Attachment Level; PH: Periodontal Health; PIH: Peri-implant Health; PI: Peri-implantitis; P: Periodontitis.
Table 6. Microorganisms found in statistically significantly higher counts/proportions/abundance/prevalence in the different periodontal and peri-implant conditions.

| Reference                  | Periodontal health | Peri-implant health | Periodontitis | Peri-implantitis |
|----------------------------|--------------------|---------------------|--------------|-----------------|
| Schierano et al. (2010)24  | N/D                | N/D                 | N/E          | N/E             |
| do Nascimento et al. (2011)21 | Prevotella intermedia | Prevotella nigrescens |              |                 |
|                            | Streptococcus oralis | Tannerella forsythia |              |                 |
|                            | Synergistes ssp.    | Prevotella ssp.     |              |                 |
|                            | Corynbacterium ssp. | Leptotrichia ssp.   |              |                 |
|                            | Neisseria ssp.      | Treponema ssp.      |              |                 |
|                            | Veillonella ssp.    | Butyribrio ssp.     |              |                 |
|                            | Dialister ssp.      | Streptococcus mutans|              |                 |
|                            | Granulicatella ssp. | Cantonella ssp.     |              |                 |
|                            | Actinomyces ssp.    | Propionibacter ssp. |              |                 |
|                            | Fusobacterium ssp.  | Lactococcus ssp.    |              |                 |
| Kumar et al. (2012)22      |                    |                     |              |                 |
|                            | Desulfovibulbous ssp. | Actinomyces bovis   |              | Streptococcus agalactiae |
|                            | Caulobacter ssp.    | Streptococcus infantis |            | Neisseria elongate  |
|                            | Peptostreptococcus anaerobius | Desulfovibulbous ssp. |            | Prevotella oralis  |
|                            | Unclassified Rs-045 | Veillonella dispar |            | Megasphaera elsdii |
|                            | Butleidia ssp.      | Haemophilus influenza|            | Prevotella loeschei|
|                            |                      | Streptococcus minor |            | Campylobacter spitorium |
|                            |                      | Mycoplasma fauicium |            | Staphylococcus pettenkoferi |
|                            |                      | Streptococcus macedonicus |        | Staphylococcus hominis |
|                            |                      | Streptococcus pseudoporcinus |  | Prevotella baronii |
|                            |                      | Unclassified Bacillales |          | Atopobium rimae |
|                            |                      | Actinomyces radicidentis |        | Aggregatibacter aphrophilus |
|                            |                      | Streptococcus ursoris |            | Arthrobacter sp. |
|                            |                      | Actinomyces meyeri |              | Streptococcus parasanguinis |
| Dabdoub et al. (2013)20     |                    |                     |              | Unclassified Methylobacteriaceae |
| Schaumann et al. (2014)23   | N/D                | N/D                 | N/D          | N/D             |
| Yu et al. (2016)26         | N/D                | N/D                 | N/D          | N/D             |
| Canullo et al. (2017)19    | N/E                | N/D                 | N/D          |                 |
| Sousa et al. (2017)25      | Rothia             | N/D                 | Actinomyces | N/D             |

N/E: Not Evaluated; N/D: No Differences
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Discussion

The results of this systematic review indicated that there is insufficient evidence in the literature to support specific differences between the composition of the subgingival biofilm colonizing teeth and implants, either in disease (periodontitis versus peri-implantitis) or in health (healthy teeth versus healthy implants).

Although no previous studies have weighed the evidence for the existence of specific differences between the microbiota colonizing teeth and implants, the studies comparing healthy and diseased implants had previously shed light on the lack of striking differences between pathogens associated with peri-implantitis and periodontitis. A previous systematic review gathering data of all Association studies evaluating the composition of the biofilm surrounding healthy and diseased implants showed that the microbiota associated with peri-implantitis was predominantly dominated by recognized periodontal pathogens, such as P. gingivalis, T. denticola and T. forsythia.

The rationale for the existence of specific microorganisms colonizing different surfaces in the mouth is based on the concept established by Ron Gibbons and co-workers in the 1970’s that oral bacteria adhere selectively to different surfaces in the oral cavity. Gibbons also showed that this specific adhesion was an ecological determinant for the establishment and distribution of bacteria on oral surfaces.

Table 7. Quality assessment of the included studies according to the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

| Question                              | Schierano et al. (2010)24 | do Nascimento et al. (2011)21 | Kumar et al. (2012)22 | Dabdoub et al. (2013)20 | Schaumann et al. (2014)23 | Yu et al. (2016)26 | Canullo et al. (2017)19 | Sousa et al. (2017)25 | Total |
|---------------------------------------|---------------------------|-------------------------------|-----------------------|-------------------------|-------------------------|----------------------|------------------------|-----------------------|-------|
| 1. Research question                  | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 8     |
| 2. Study population                   | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 8     |
| 3. Participant rate of eligible persons | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 8     |
| 4. Eligibility criteria               | CD                        | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 7     |
| 5. Sample size                        | No                        | No                            | No                    | No                      | No                      | No                   | No                     | Yes                   | 1     |
| 6. Exposure assessment                | No                        | No                            | No                    | No                      | No                      | No                   | No                     | No                    | 0     |
| 7. Timeframe                          | No                        | No                            | No                    | No                      | No                      | No                   | No                     | Yes                   | 0     |
| 8. Exposure levels                    | Yes                       | Yes                           | Yes                   | NA                      | NA                      | NA                   | No                     | NA                    | 3     |
| 9. Exposure measures                  | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 8     |
| 10. Repeated exposure assessment      | No                        | No                            | No                    | No                      | No                      | No                   | No                     | No                    | 0     |
| 11. Outcomes measures                 | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | No                   | No                     | Yes                   | 6     |
| 12. Assessors blinding                | No                        | No                            | No                    | No                      | No                      | No                   | No                     | No                    | 0     |
| 13. Follow-up rate                    | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 8     |
| 14. Statistical analyses              | Yes                       | Yes                           | Yes                   | Yes                     | Yes                     | Yes                  | Yes                    | Yes                   | 8     |
| Total                                 | 8                         | 9                             | 9                     | 8                       | 8                       | 7                    | 7                      | 9                     |       |

CD: cannot determine; NA: not applicable.
lack of differences between the microbiota colonizing implants and teeth in the present study suggest that the initial colonizers of these two structures probably do not differ substantially. In addition, the fact that they are sheltered in a very similar environment (periodontal or peri-implant sulcus/pocket); are exposed to the same fluids (crevicular fluid and saliva), similar nutritional conditions and redox potential, may also contribute to the establishment of similar biofilms. Thus, although there are important structural differences between periodontal and peri-implant surfaces that translate into some differences in host response30, these differences may not be sufficient to generate distinct microbial profiles. Based on the widely recognized concept that peri-implantitis and periodontitis are associated with a microbial challenge31 and the data of the present study that there are no recognized differences between the microbiota of diseased teeth and implants, it could be hypothesized that the anti-infective treatments of peri-implantitis and periodontitis would also be similar. Nonetheless, points of consideration in this line of thought are the difficulties associated with the disinfection of irregular implant surfaces.32.

An interesting information provided by this systematic review was the high number of studies using sequencing/pyrosequencing (5 of the 8 articles included), which provided comprehensive data for several bacterial taxonomic levels (e.g., species, genus, phylum), viruses, fungi and parasites.33 In addition, this type of analysis may detect unclassified microorganisms or uncultured bacterial species that could be associated with periodontal/peri-implant health or disease. Another important point of discussion refers to the different inclusion criteria used to define the clinical conditions evaluated: periodontal and peri-implant health, periodontitis and peri-implantitis (Table 3). This lack of standardization probably occurred due to some difficulties associated with the use of the 1999 Classification System for Periodontal Disease and Conditions34 and the lack of consensus about the definition of peri-implant diseases. It is expected that the recently published Classification of Periodontal and Peri-implant Diseases and Conditions1,31 will help to standardize future studies evaluating these clinical conditions.

The main limitation of this systematic review was the inclusion of studies using different microbiological diagnostic tests, data expression (counts/proportions/abundance/prevalence) and inclusion/exclusion criteria. The main strength is that it is the first study to assess the current weight of evidence concerning specific differences in the composition of the subgingival/submucosal microbiota colonizing teeth and implants surfaces, respectively.

In conclusion, the results of this systematic review indicated that there is insufficient evidence in the literature to support specific differences between microorganisms colonizing teeth and implants, either in health or in disease.

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