Microbial Profiles and Detection Techniques in Peri-Implant Diseases: a Systematic Review

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ABSTRACT

Objectives: To describe the microbial profiles of peri-implant diseases and the main detection methods.
Material and Methods: A literature search was performed in MEDLINE via PubMed database to identify studies on microbial composition of peri-implant surfaces in humans published in the last 5 years. Studies had to have clear implant status definition for health, peri-implant mucositis and/or peri-implantitis and specifically study microbial composition of the peri-implant sulcus.
Results: A total of 194 studies were screened and 47 included. Peri-implant sites are reported to be different microbial ecosystems compared to periodontal sites. However, differences between periodontal and peri-implant health and disease are not consistent across all studies, possibly due to the bias introduced by the microbial detection technique. New methods non species-oriented are being used to find 'unexpected' microbiota not previously described in these scenarios.
Conclusions: Microbial profile of peri-implant diseases usually includes classic periodontopathogens. However, correlation between studies is difficult, particularly because of the use of different detection methods. New metagenomic techniques should be promoted for future studies to avoid detection bias.

Keywords: dental implants; diagnosis; microbiology; peri-implantitis.

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INTRODUCTION

Peri-implant diseases are not an emerging group of diseases. Peri-implant diseases are a prevalent reality: 19 to 65% of implants present peri-implant mucositis (weighted mean of 43% [CI = 32 to 54%]) and 1 to 47% develop peri-implantitis (weighted mean of 22% [CI = 14 to 30%]) alongside a positive relationship with function time [1]. Moreover, peri-implant diseases are challenging to treat [2], and, in some cases, with aggressive progression patterns [3]. However, consensus has been reached so far only on few facts associated with increased risk of peri-implant disease development: 1) lack of regular supportive therapy; 2) plaque accumulation; 3) smoking; 4) history of periodontal disease; and 5) excess cement [4]. Fortunately, it has been established that patient-administered mechanical plaque control (with manual or powered toothbrushes) and professional intervention comprising oral hygiene instructions and mechanical debridement are adequate measures to reduce peri-implant mucositis and its progression to peri-implantitis [5]. Several strategies are being investigated to reduce plaque accumulation over implants: surface modifications [6-11], lasers and other physical methods [12-16], locally delivered antibiotics [17-19], and even better seals of the connection implant-abutment to reduce this particular reservoir of microbiota [20-23]. However, these and other adjunctive measures to reduce plaque, including systemic antibiotics, have not been found to reduce clinical signs of inflammation [5,24].

So far, the main diagnostic methods of peri-implant disease are based on clinical and radiographic data. These data are obviously insufficient and they only detect the disease when it has produced some level of destruction. Thus, early diagnosis and identification of risk factors are of extreme importance to prevent the disease in the first place. Probably the more studied risk factor for peri-implant disease is the microbiota associated with the peri-implant sulcus. In fact, the presence of periodontophatic bacteria in the peri-implant sulcus has been proposed as a risk indicator for both peri-implant mucositis and peri-implantitis [4,25]. The characteristics of the sulcus environment favour its colonization by anaerobic Gram-negative bacteria. The ecological succession of the microbes in the sulcus may lead to the development of the disease. The peri-implant disease has been described as poly-microbial anaerobic infection similar to that found in chronic periodontitis [3,26,27]. However, new technologies are finding an increasing number of microorganisms in peri-implant sites not found around teeth [4].

Many studies have evaluated the microbiota around healthy and diseased teeth as well as around healthy and diseased implants by different techniques. Thus, this systematic narrative review is aimed at identifying the microbiological factors that have been associated with the presence of peri-implant disease by describing the findings published and discussing the main detection techniques.

MATERIAL AND METHODS

Protocol and registration

The methods of the analysis and inclusion criteria were specified in advance and documented in a protocol. The review was registered in PROSPERO, Registration number: CRD42016037647.

The reporting of this systematic analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [28].

Focus question

The following focus question was developed according to the population, intervention, comparison, and outcome (PICO) study design: what are the microbial profiles of human patients suffering peri-implantitis in comparison to healthy implants? Additionally, the comparisons with implants suffering mucositis and with healthy or diseased teeth were also explored.

Information sources

A literature search was performed in MEDLINE via PubMed database of the US National Library of Medicine on April 25th, 2016 using Medical Subject Heading search terms and free text terms in different combinations. A hand search was also performed in dental and implant-related journals from April 2011 to April 2016, including "Journal of Dental Research", "Journal of Clinical Periodontology", "Clinical Oral Implants Research", "Journal of Periodontology", "International Journal of Oral and Maxillofacial Implants", "Journal of Oral Implantology", "Implant Dentistry", "Clinical Implant Dentistry and Related Research", "European Journal of Oral Implantology", "International Journal of Oral and Maxillofacial Surgery", "Journal of Oral and Maxillofacial Surgery", "Journal of Prosthetic Dentistry", "International Journal of Prosthodontics", "International Journal of Periodontics & Restorative Dentistry".

The search was limited to English language articles. A hand search of the reference lists in the articles retrieved was also carried out for additional relevant publications.

Search

The electronic search strategy and limits was: ((("Microbiology") OR ("Microbiome") OR ("Microbial")) AND ("Dental Implants" [Mesh])) AND (("English and humans" [Filter]) AND ("published last 5 years" [Filter])) NOT ("review" [Filter]).

Selection of studies

The articles, at any stage (abstract or full-text assessment) were independently reviewed by 2 of the authors. Reviewers compared decisions and resolved differences through discussion and consulting the other authors when consensus could not be reached.

Types of publications

Studies on humans published in the English language were selected. Letters, editorials, case reports, literature reviews, and PhD theses were excluded.

Types of studies

No limitations as to the type of study design were established.

Types of participants/population

Included studies describe findings from human participants with at least one osseointegrated titanium screw-shaped dental implant with signs of peri-implantitis or peri-implant mucositis, with or without healthy implants or teeth.

Disease definition

Peri-implant mucositis or peri-implantitis must have been defined in each article according to the current classification of peri-implant diseases [29].

Inclusion and exclusion criteria

To be included in the study, studies had to have clear implant status definition for the conditions health, mucositis and/or peri-implantitis and analyse the microbiome of those situations, with or without comparisons among them or with or without before and after results.

The applied exclusion criteria for studies were animal or *in vitro* studies, not enough information on the microbial analysis, analysis not performed on peri-implant sulcus of dental implants aimed at supporting restorations and no access to the abstract or full-text.

Sequential search strategy

Following the initial literature search, all article titles were screened to eliminate irrelevant publications, review articles, case reports, *in vitro*, and animal studies. Next, studies were excluded based on data obtained from screening the abstracts. The final stage of screening involved reading the full texts to confirm each study's eligibility, based on the inclusion and exclusion criteria.

Data extraction

The data was independently extracted from studies by two authors. Data extracted was descriptive findings of microbial profiles around dental implants and additional information such as findings around teeth with or without disease.

Data items

Data collected from the included articles were:

- Full reference - identification of study;
- Type of patients/sites - healthy implants, peri-implant mucositis or peri-implantitis, and healthy or diseased teeth;
- Number of patients included in the study for each condition;
- Number of implants/sites included in the study for each condition;
- Outcome - description of the main findings of the study;
- Detection method - how the microbial profile was evaluated (culture, polymerase chain reaction (PCR), checkerboard or metagenomics).

Risk of bias assessment

Risk of bias within articles was assessed independently, and in duplicate by the authors according to the RTI Item Bank guide for bias and confounding assessment in observational studies of interventions or exposures [30].

Possible sources of bias include: inclusion/exclusion criteria, recruitment of participants, selection of the comparison group, variations in the execution of the study from the proposed protocol,

blindness to the outcome, exposure, or intervention, valid and reliable measures, length of follow-up, impact of missing data, missing primary outcomes, harms or adverse events, balance between the groups or match groups, and confounding variables.
Table 1 summarizes the findings for each of the included articles. An overall risk of bias was finally assigned to each report.

Statistical analysis

No meta-analysis was intended as no common microbial detection methodology is used across studies.

RESULTS

Study selection

Figure 1 shows the PRISMA flow diagram of studies identified, screened and included. The initial electronic and hand search retrieved 194 citations after duplicates were removed. These 194 were screened by titles and abstracts, from which 134 were excluded. Thus, 60 articles were assessed in full text. Of these, 14 were excluded: no analysis of peri-implant sulcus = 4 [31-34]; not performed in oral mucosa = 2 [35]; no full-text available = 1 [36]; not enough microbiological data = 3 [37-39]; not in conventional dental implants = 4 [40-44]. Finally, 46 studies were included in the qualitative synthesis and analysis, as described in Tables 1 - 5.

Study characteristics

Studies on peri-implant microbiota using culture techniques are limited in the last 5 years (Table 1). With no doubt, this clearly reflects the incorporation of new technologies in the peri-implant diagnosis field as their used is declining. Only 4 studies have been identified using this methodology. It is concluded that *Streptococcus spp*. and *Peptostreptococcus spp*. are correlated with the increase in BOP 1 to 6 months after loading [45]. Similarly, there is a significantly higher prevalence of *Porphyromonas*, *Prevotella* and anaerobic Gram positive cocci in peri-implantitis vs. peri-implant health [46]. In contrast, a reduction on spirochetes was found from implant placement on periodontal sites to 12 months [47]. Using bacteria culture, similar effectiveness has been described when using placebo or chlorhexidine for the treatment of peri-implantitis sites [48].
A total of 14 studies have been identified using PCR techniques (Table 2). These studies, overall, fail to demonstrate similar patterns in terms of detected species, frequencies of detection as well as bacterial load. As an example, some studies found no differences in the detection frequencies of *Aggregatibacter actinomycetemcomitans (A.a.)*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Treponema denticola* between healthy and diseased implants [49,50]. Others did find differences for *A.a.*, *P. gingivalis*, *Tannerella forsythia*, *T. denticola* [51], *Fusobacterium nucleatum*, *P. intermedia*, *Peptostreptococcus micros*, *Campylobacter rectus*, *Eikenella corrodens*, *Candida albicans*, *Prevotella nigrescens*, *Centruroides gracilis*, *Capnocytophaga ochracea*, *Campylobacter concisus*, *Streptococcus spp.*, *Actinomyces odontolyticus*, *Veillonella parvula* and *Enterococcus faecalis* [52,53].
Compared to teeth, implants are usually reported to have less bacterial species; periodontitis is also reported to be more diverse than peri-implantitis [54]. Other studies did not find these differences [50,55].

Table 1. Studies using culture techniques

Study	Year of publication	Type of patients/sites	Number of patients	Number of implants/sites	Outcome
Asadzadeh et al. [45]	2012	Peri-implant tissues	20 patients	20 implants	Correlation between the increase in peri-implant BOP from 1 to 6 months after loading and an increase in colonies of *Streptococcus spp*. and *Peptostreptococcus spp*.
Neilands et al. [46]	2015	Peri-implantitis vs. peri-implant health	50 patients (25 peri-implantitis; 25 healthy)	1 implant per patient	Highly variable microbial composition. Significantly higher prevalence of *Porphyromonas*/*Prevotella* and anaerobic Gram positive cocci in peri-implantitis.
Tripodakis et al. [47]	2011	Peri-implant tissue vs. periodontal disease	20 patients	20 periodontal sites that became 20 peri-implant sites	Spirochetes in peri-implant samples: 69% vs. 2% at baseline and 12 months, respectively. Higher colony forming units (CFU)/ml in samples from periodontal sites.
de Waal et al. [48]	2013	Peri-implantitis	30 patients (15 placebo; 15 test [chlorhexidine])	79 implants (48 placebo; 31 test)	Sixty of the 79 implants were positive at baseline. A.a. not detected. Both procedures reduced *P. gingivalis*, *P. intermedia*, *T. forsythia*, *F. nucleatum*, *P. micra* and *C. rectus*.

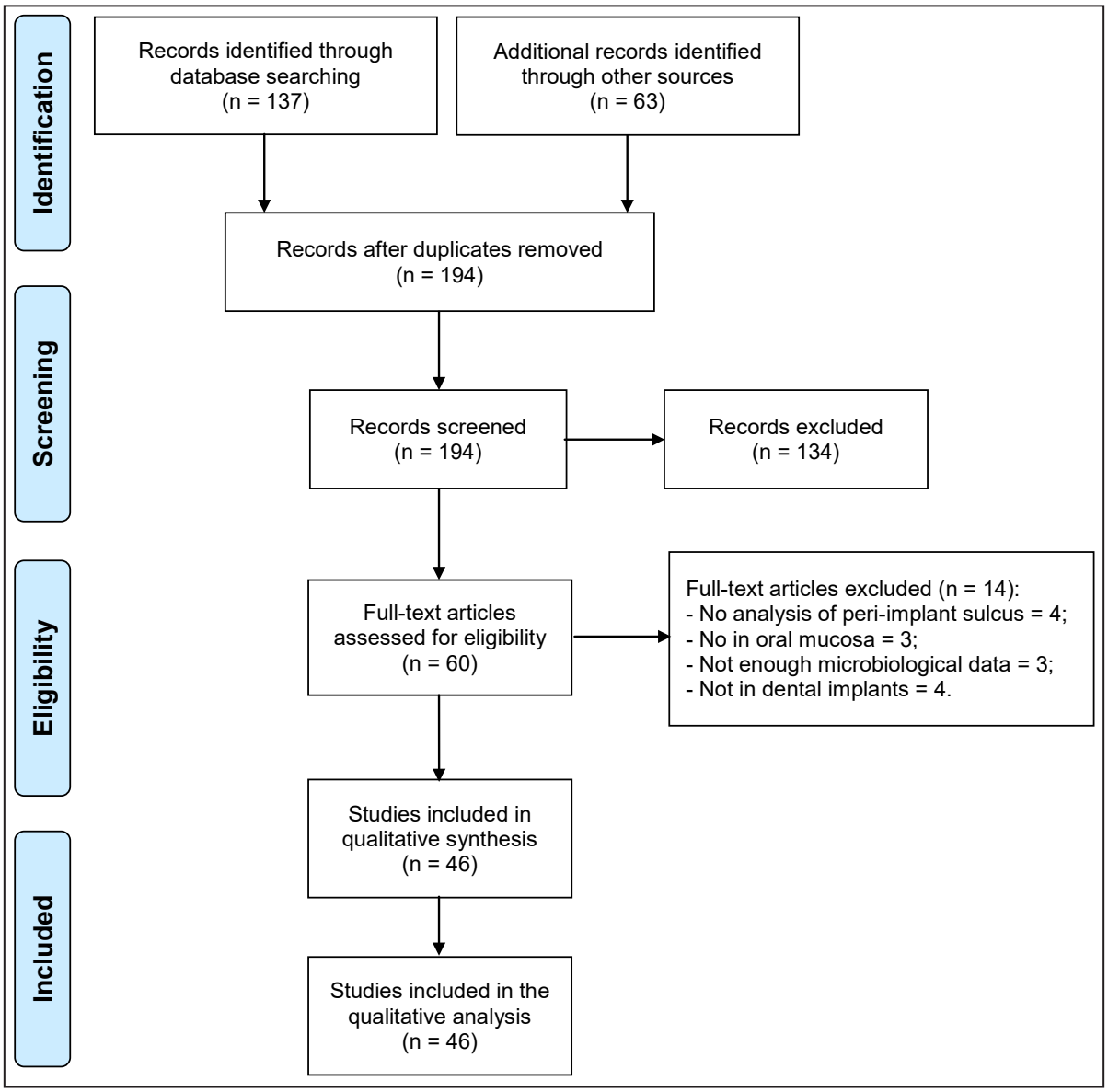


Figure 1. PRISMA flow diagram of included studies.

In any case, it seems that the presence of periodontal disease and implants increase the presence of periodontophatic bacteria in the peri-implant sulcus, which does not necessarily mean that these bacteria are involved in peri-implant disease [56]. Interestingly, Sato et al. found a higher number and detection rate of periodontopathic bacteria as the cumulative interceptive supportive therapy (CIST) level increased [57].

The next technique identified was checkerboard DNA-DNA. Eight studies have been published using this methodology (Table 3). Several differences have been found with this methodology. As expected, plaque and bleeding on probing scores have been significantly correlated with sulcular levels of bacteria [58], although the total DNA count was not significantly different between implants with shallow and deep pockets [59]. However, other studies involving a greater number of patients also found total DNA count to be correlated to interproximal bleeding index (r = 0.409) and interproximal probing depth (r = 0.307) but no correlations were present with plaque index or radiographic bone level up to 22 years after implant placement [60]. When comparing healthy vs. diseased implant sites, only 37.5% of all species showed a higher prevalence, although only 10 species were explored [61]. In contrast, only 14 species out of the 79 studied (17.7%) were more prevalent in peri-implantitis than in healthy sites in a study by Persson and Renvert [62] involving 166 peri-implantitis sites and 47 healthy implants. Interestingly, this study also found a cluster of *T. forsythia*, *P. gingivalis*, *Treponema socranskii*, *Staphylococcus aureus*, *Staphylococcus anaerobius*, *Staphylococcus intermedius*, and *Streptococcus mitis* that comprised 30% of the total microbiota at peri-implantitis sites.

Table 2. Studies using PCR techniques

Study	Year of publication	Type of patients/sites	Number of patients	Number of implants/sites	Outcome
Casado et al. [49]	2011	Peri-implant health vs. mucositis vs. peri-implantitis	30 subjects	30 implants (10 healthy; 10 peri-implant mucositis; 10 peri-implantitis)	No differences in *A.a.*, *P. gingivalis*, *P. intermedia*, and *T. denticola*.
Canullo et al. [50]	2016	Peri-implant health vs. peri-implantitis vs. neighboring teeth	534 patients (53 peri-implantitis; 481 non-peri-implantitis)	1507 implants (231 peri-implantitis; 1276 non-peri-implantitis)	No relevant differences between the healthy and disease implants in the same patient. Similar in the neighboring teeth with a lower *P. gingivalis*, *T. forsythia*, *P. intermedia*, *P. micros*, and *E. corrodens*.
Wang et al. [51]	2015	Peri-implant health vs. peri-implantitis	68 patients (34 healthy; 34 peri-implantitis)	1 per patient	*A.a.*, *P. intermedia*, *P. gingivalis*, *T. forsythia* and *T. denticola* associated with peri-implantitis although no statistically significant.
Canullo et al. [52]	2015	Peri-implant health vs. peri-implantitis vs. neighboring teeth	110 patients (53 peri-implantitis; 57 non-peri-implantitis)	235 implants (113 peri-implantitis; 122 non-peri-implantitis)	> 20% differences between healthy and disease implants for *T. denticola* and *E. corrodens*. Marked differences between health and peri-implantitis for the red complex bacteria and *P. intermedia*.
Canullo et al. [53]	2016	Peri-implant health vs. peri-implantitis	47 patients (25 peri-implantitis; 22 non-peri-implantitis)	90 implants (113 peri-implantitis; 122 non-peri-implantitis)	Significantly higher *T. forsythia*, *T. denticola*, *F. nucleatum*, *P. intermedia*, *P. micros*, *C. rectus*, *E. corrodens*, *C. albicans*, *P. nigrescens*, *C. gracilis*, *C. ochracea*, *C. concisus*, *Streptococcus spp*., *A. odontolyticus*, *V. parvula*, and *E. faecalis* in peri-implantitis.
Zhuang et al. [54]	2016	Peri-implant health and disease vs. periodontal health and disease	22 patients with at least 1 diseased implant, 1 diseased tooth, 1 healthy implant and 1 healthy tooth	1 per patient and condition	*S. aureus* and *F. nucleatum* were the most commonly detected species. Only *F. nucleatum* was more abundant in periodontitis. Only *P. gingivalis* and *F. nucleatum* were more prevalent in periodontitis than peri-implantitis.
Aoki et al. [55]	2012	Implants vs. adjacent, occluding and contralateral teeth	21 patients	NS	No significant differences in *A.a.*, *P. intermedia*, *P. gingivalis*, *T. forsythia*, *T. denticola* or *F. nucleatum*.
Cosgarea et al. [56]	2012	Implants in chronic periodontitis patients vs. healthy	24 patients (11 periodontitis; 13 no periodontitis)	NS	Higher *P. gingivalis* and *A.a.* at implants and teeth in the chronic periodontitis group. More *A.a.*, *T. forsythia* and *F. nucleatum* at teeth than at implants. PD and CAL correlated with counts of *P. gingivalis* at teeth and implants.
Sato et al. [57]	2011	Peri-implantitis vs. teeth	105 patients with residual natural teeth and implants with peri-implantitis	1 per patient and condition	The number and detection rate of periodontopathic bacteria increased with CIST level. No difference in P. gingivalis and T. denticola between CIST-B and CIST-C. Higher detection rate of all periodontopathic bacteria for CIST-D.
Canullo et al. [82]	2015	Implant-diseased individuals	38 patients	180 sites	3 sites showed presence of *E. faecalis* and 1 showed presence of *Pseudomonas aeruginosa*.
Jankovic et al. [83]	2011	Peri-implant health vs. mucositis vs. peri-implantitis	80 patients (25 healthy; 25 mucositis; 30 peri-implantitis)	1 implant per patient	HCMV-2 detected in 53.3% and EBV-1 in 46.6% of the peri-implantitis sites. HCMV-2 not detected in healthy sites and EBV-1 in only one healthy site. Statistically significant correlation between the presence of HCMV-2 and EBV-1 genotypes and clinical parameters of peri-implantitis.
Swierkot et al. [84]	2013	Healthy implants	83 patients (42 with sonic toothbrush; 41 with manual toothbrush)	1 per patient and condition	No significant changes in the microbiological parameters. Both groups exhibited a small increase in total bacterial load at implants and teeth.
van Brakel et al. [85]	2011	Peri-implant tissues at zirconia and titanium implants	22 patients	1 per patient and type of abutment	Similar *A.a.*, *P. gingivalis*, *P. intermedia*, *T. forsythia*, *P. micros*, *F. nucleatum* and *T. denticola* at 2 weeks and 3 months.

NS = not specified; CIST = cumulative interceptive supportive therapy; PD = probing depth; CAL = clinical attachment level; HCMV = human cytomegalovirus; EBV = Epstein-Barr virus.

Table 3. Studies using checkerboard DNA-DNA hybridization

Study	Year of publication	Type of patients/sites	Number of patients	Number of implants/sites	Outcome
Cosyn et al. [58]	2011	Peri-implant sulcus	8 healthy patients	NS	Plaque and BOP correlated with sulcular levels of 30/40 species. For 25 species, the detection frequency was at least 75%.
De Bruyn et al. [59]	2013	Peri-implant bone level	12 patients	71 implants	25/40 species in more than 80% of the implants. Large variation in bacterial levels between implants. *Fusobacteria*, *Leptotrichia buccalis*, *P. micra*, *V. parvula*, and *T. forsythia* showed the highest levels. Implants with shallow pockets showed significantly lower counts of: *A. odontolyticus*, *C. gracilis*, *F. nucleatum naviforme*, and *Leptotrichia buccalis*. No significantly different total DNA count between implants with shallow and deep pockets.
Dierens et al. [60]	2013	Peri-implant vs. periodontal health	46 patients	NS	*T. forsythia* and *V. parvula* showed the highest concentrations around implants and teeth, respectively. Significantly more *P. gingivalis*, *P. intermedia*, *T. forsythia*, *P. micra* and *T. denticola* around implants. Total DNA count correlated to interproximal bleeding index (r = 0.409) and interproximal probing depth (r = 0.307). No correlations with plaque index or radiographic bone level.
Ebadian et al. [61]	2012	Peri-implant health and disease vs. periodontal health and disease	69 patients (21 non-periodontitis; 22 chronic periodontitis; 13 non-peri-implantitis; 13 peri-implantitis)	1 per patient	Statistical difference between prevalence of *P. intermedia*, *P. gingivalis*, *T. forsythia*, *C. rectus*, *Prevotella tannerae*, *T. denticola* and *P. endonticula* in all groups. Higher incidence of all species in periodontitis sites; only 37.5% of species showed higher prevalence in peri-implantitis. Significant difference for *T. forsythia*, *P. intermedia* and *C. rectus* in PI vs. CP; no significant difference between HI and HP.
Persson et al. [62]	2014	Peri-implantitis vs. peri-implant health	213 patients (166 peri-implantitis; 47 healthy)	1 implant per patient	Higher counts of *A.a.*, *C. gracilis*, *C. rectus*, *Campylobacter showae*, *Helicobacter pylori*, *Haemphilus influenzae*, *P. gingivalis*, *S. aureus*, *S. anaerobius*, *S. intermedius*, *S. mitis*, *T. forsythia*, *T. denticola* and *T. socranskii* in peri-implantitis. A cluster including *T. forsythia* and *S. aureus* are associated with peri-implantitis.
Salvi et al. [63]	2012	Peri-implant mucositis vs. periodontal gingivitis	15 patients	1 per patient and condition	No differences in total DNA counts or detection frequency for putative periodontal pathogens between implant and tooth sites. *P. gingivalis* detected occasionally after 3 weeks of abolished oral hygiene.
Hallström et al. [86]	2012	Peri-implant mucositis	43 patients (21 control; 22 test [systemic antibiotics])	1 per patient	No differences between groups.
Tsoukaki et al. [87]	2013	Flapped vs. flapless implants	20 patients (10 flapped; 10 flapless)	30 implants (15 flapped; 15 flapless)	Significantly higher levels of *P. gingivalis* and *T. forsythia* and higher but not significant *T. denticola* in flapless vs. flapped implants.

NS = not specified; BOP = bleeding on probing; PI = peri-implantitis; CP = chronic periodontitis; HI = healthy implant; HP = healthy periodontium.

Table 4. Studies using 16S rRNA gene sequencing techniques

Study	Year of publication	Type of patients/sites	Number of patients	Number of implants/sites	Outcome
Tamura et al. [64]	2013	Peri-implant health vs. disease	30 patients (15 healthy; 15 peri-implantitis)	1 per patient	Healthy sites: *Streptococcus*, *Pseudoramibacter alactolyticus*, *Actinomyces israelii*, *Propionibacterium acnes*, and *P. micra*. Peri-implantitis: *Eubacterium nodatum*, *Eubacterium brachy*, *Eubacterium saphenum*, *Filifactor alocis*, *Spodoptera exigua*, *Parascardovia denticolens*, *P. intermedia*, *F. nucleatum*, *P. gingivalis*, *Centipeda periodontii*, and *P. micra*. Peri-implantitis sites had approximately 10-fold higher CFU/ml than healthy sites.
Cortelli et al. [65]	2013	Peri-implant health and disease vs. periodontal health and disease	306 patients (53 peri-implant health; 50 peri-implant mucositis; 50 peri-implantitis; 50 gingivitis; 50 periodontitis)	NS	Higher bacterial frequency in peri-implantitis than health; similar frequencies in peri-implantitis and mucositis; higher bacterial frequency at teeth. *P. gingivalis* and red complex: more common in peri-implantitis than mucositis. *C. rectus* and *T. forsythia*: more frequent in healthy teeth/gingivitis than healthy implants/mucositis. *P. gingivalis* and *A.a.*: similar in periodontitis and peri-implantitis. Other species: higher in periodontitis than peri-implantitis.
Zheng et al. [66]	2015	Peri-implant health vs. disease	24 patients (10 healthy; 8 peri-implant mucositis; 6 peri-implantitis)	1 per patient	Higher diversity in ailing implants, vs. healthy implants. *P. gingivalis*, *T. forsythia* and *P. intermedia* clustered in peri-implant mucositis. Peri-implantitis pathogens were present in peri-implant mucositis. Microbiome of mucositis were intermediate in nature between healthy and peri-implantitis.
Tsigarida et al. [67]	2015	Peri-implant health vs. disease	80 patients (40 peri-implant health [20 smokers and 20 non-smokers]; 20 peri-implant mucositis [10 smokers and 10 non-smokers]; 20 peri-implantitis [10 smokers and 10 non-smokers])	1 per patient and condition	Lower diversity with higher disease-associated species in healthy sites of smokers. Shifts from health to mucositis accompanied by loss of several health-associated species. Peri-implantitis did not differ from mucositis. In non-smokers, the shift from health to mucositis increased diversity. Few differences were detected between peri-implantitis and mucositis.
Koyanagi et al. [68]	2013	Peri-implant disease vs. periodontal disease	6 patients	12 sites (6 implants; 6 teeth)	More diverse microbial composition of peri-implantitis than periodontitis. *P. micra* only in peri-implantitis.
da Silva et al. [69]	2014	Peri-implantitis vs. healthy implants vs. healthy teeth	20 patients (10 with healthy implants; 10 with at least 1 healthy implant, 1 peri-implantitis and periodontally healthy teeth)	NS	Higher *Actinomyces*, *Atopobium*, *Gemella*, *Kingella* and *Rothia* and lower *Campylobacter*, *Desulfobulbus*, *Dialister*, *Eubacterium*, *Filifactor*, *Mitsukella*, *Porphyromonas* and *Pseudoramibacter* in healthy implants. Higher *F. nucleatum*, *Dialister invisus*, *Streptococcus sp*. human oral taxon (HOT) 064, *Fillifactor alocis* and *Mitsuokella sp*. HOT 131 and lower *Veillonella dispar*, *Actinomyces meyeri*, *Granulicatella adiacens* in peri-implantitis.
Maruyama et al. [70]	2014	Peri-implant disease vs. periodontal disease	20 patients	1 implant per patient	Higher *Olsenella*, *Sphingomonas*, *Peptostreptococcus*, and unclassified *Neisseriaceae* and lower *Desulfomicrobium* in peri-implantitis vs. periodontitis. *P. gingivalis*, *T. denticola*, and *T. forsythia* were abundant and prevalent in both diseases.
Kumar et al. [71]	2012	Peri-implant health and disease vs. periodontal health and disease	40 patients (10 peri-implantitis; 10 peri-implant health; 10 chronic periodontitis; 10 periodontal health)	1 per patient	Significantly lower diversity of peri-implant biofilms than subgingival biofilms in both health and disease.
Heuer et al. [72]	2012	Peri-implant mucositis vs. periodontal gingivitis	9 patients	1 per patient and condition	Higher diversity in gingival than peri-implant sulci.
Dabdoub et al. [73]	2013	Peri-implant health and disease vs. periodontal health and disease	81 subjects (33 healthy tooth/healthy implant; 23 healthy tooth/diseased implant; 8 diseased tooth/healthy implant; 17 diseased tooth/diseased implant)	162 sites (56 healthy teeth; 13 gingivitis; 12 periodontitis; 41 peri-implant health; 20 peri-implant mucositis; 20 peri-implantitis)	Sixty percent of individuals share < 50% of all species between their periodontal and peri-implant biofilms; 85% of individuals share < 8%. Distinct bacterial lineages associated with health and disease in teeth and implants. The periodontal microbiome demonstrated significantly higher diversity than the implant. *Staphylococcus* and *Treponema* were significantly associated with diseased implants, but not teeth.
Zhang et al. [74]	2015	Peri-implant disease vs. periodontal disease	20 patients (10 healthy; 10 chronic periodontitis)	1 per patient	Lower *A.a.*, *P. gingivalis*, *T. forsythia* and *T. denticola* and higher *Pseudomonas* in peri-implant sites vs. chronic periodontitis. Different SR1 genus, *Brevundimonas*, *Catonella*, *Desulfovibrio*, *Mogibacterium*, *Peptostreptococcus*, *Propionibacterium* and *Pseudomonas* between the two groups. Higher bacterial diversity in teeth vs. implants.
Schaumann et al. [88]	2014	Peri-implant disease vs. periodontal disease	7 patients with bleeding periodontal and peri-implant tissues and bone loss	1 per patient and condition	*Streptococcacea*, *Rothia* and *Porphyromonas* were the most abundant taxa in supramucosal or supragingival plaques on implants and teeth. In submucosal plaques at implants, the most abundant taxa were *Rothia*, *Streptococcaceae* and *Porphyromonas*. The most abundant subgingival bacteria on teeth were *Prevotella*, *Streptococcaceae* and TG5.
Faveri et al. [89]	2011	Peri-implantitis vs. healthy implants vs. healthy teeth	50 patients (25 healthy; 25 with at least 1 healthy implant, 1 peri-implantitis and periodontally healthy teeth)	NS	Higher positive sites for *Archaea* in peri-implantitis than healthy implants or healthy teeth. No significant differences in healthy teeth vs. healthy implants.
Heuer et al. [90]	2013	Peri-implant tissue at implant-supported bar attachments vs. implant-fixed telescopic double crown attachments vs. teeth	16 patients (8 healthy implant-supported bar-attached supraconstruction; 8 healthy implant-anchored telescopic double crown attachments)	1 implant per patient	No statistically significant differences.

NS = not specified.

Table 5. Studies using other techniques or a variety of them

Study	Year of publication	Type of patients/sites	Detection method	Number of patients	Number of implants/sites	Outcome
Ata-Ali et al. [91]	2011	Peri-implant mucositis vs. healthy implants	Hybridization with specific P32 arrays directed against the sRNA ribosomal subunit	34 patients	90 patients	Significantly greater *P. gingivalis*, *A.a.*, *T. forsythia* and *T. denticola* in mucositis.
Ata-Ali et al. [92]	2015	Peri-implantitis vs. healthy implants	Hybridization with specific P32 arrays directed against the sRNA ribosomal subunit	35 patients (22 healthy; 13 with peri-implantitis)	78 implants (54 healthy; 24 with peri-implantitis)	Significantly greater periodontal pathogens in peri-implantitis.
Ata-Ali et al. [93]	2013	Peri-implant mucositis vs. healthy implants	Hybridization with specific P32 arrays directed against the sRNA ribosomal subunit	34 patients (22 healthy; 12 with peri-implant mucositis)	77 implants (54 healthy; 23 with peri-implant mucositis)	No differences in *T. forsythia*, *P. gingivalis*, and *T. denticola*.
Albertini et al. [94]	2015	Peri-implantitis vs. periodontitis	PCR and Culture	33 patients	48 implants + 48 teeth	No significant differences of *P. gingivalis*, *T. forsythia*, *P. intermedia*, or *T. denticola*. *S. aureus*, *P. aeruginosa* and *C. albicans* present in 15% of the patients.
Charalampakis et al. [95]	2012	Peri-implantitis	Culture	NS	139 implants	*P. intermedia*/*P. nigrescens*: the most representative in magnitude; *S. epidermidis* more prevalent than *S. aureus*. *A.a.*: not identified in 10 of 161 cases. Fungi and enterococci: seldom found.
			Checkerboard DNA-DNA hybridization	NS	120 implants	*T. forsythia*: the most prevalent followed by *T. denticola*. *P. gingivalis*: less prevalent than *P. intermedia*, *P. nigrescens* and *P. endodontalis*. *S. noxia* and *A.a.*: the least representative.
			Both	NS	22 implants	Culture was unable to detect any of the targeted species in 18.6% of the cases, whereas checkerboard only in 0.7%.
Charalampakis et al. [96]	2011	Peri-implantitis	Culture	274 patients pre-treatment	NS	Detection frequencies: *P. intermedia*/*P. nigrescens* (27.3%), AGNB (18.6%), *A.a.* (6%)
			Checkerboard DNA-DNA hybridization			Detection frequencies: *T. forsythia* (37.3%), *T. denticola* (31%), *P. nigrescens* (28.9%), *P. endodontalis* (28.6%), *P. intermedia* (25.4%), *A.a.* (4.2%)
			Culture	27 patients post-treatment	NS	Detection frequencies: AGNB (25.9%), *P. gingivalis* (25.9%), *P. intermedia*/*P. nigrescens* (22.2%), *Enterococci* (7.4%), *A.a.* (4%), *S. aureus* (0%), *S. epidermidis* (0%), Fungi (0%)
Van Assche et al. [97]	2011	Peri-implant vs. periodontal health	Culture, qPCR and checkerboard DNA-DNA hybridization analysis of 40 species	18 patients	66 implants (34 rough surface; 32 machined surface)	No statistically significant differences between the two implant designs or level of bone loss. Similar subgingival composition around implants and teeth.

NS = not specified.

In terms of differences between teeth and implants, inconsistent results have been reported. Although Ebadian and co-workers [61] found no significant differences between healthy implants and teeth, other studies have identified some particular species, such as *T. forsythia*, *P. gingivalis*, *P. intermedia*, *Parvimonas micra*, and *T. denticola*, in higher concentration around implants [60]. In the presence of periodontal disease, differences between periodontitis and peri-implantitis sites, specifically in the concentrations of *T. forsythia*, *P. intermedia* and *C. rectus*, are clear [61]. The difference between periodontal gingivitis and peri-implant mucositis, however, was not significant in an experimentally induced gingivitis – mucositis study by Salvi and co-workers [63].

Finally, 14 studies have been identified that used the 16S rRNA gene sequencing technique (Table 4). When comparing peri-implant healthy sites with diseased, 10-fold higher mean colony-forming units have been identified in peri-implantitis sites compared to healthy implant sites, with periodontopathic bacteria not being the only periodontal pathogens active in peri-implantitis [64]. In this sense, the microbiome of mucositis can be described as intermediate in nature between healthy and peri-implantitis sites. In fact, the pathogens found in peri-implantitis sites can already be seen at a moderate abundance in mucositis sites [65-67]. In this transition from health to mucositis, loss of several health-associated species occurs, which interestingly in non-smokers, is based on an increase in diversity [67].

The comparison between implants and teeth in several studies agrees that peri-implantitis sites present higher diversity than periodontitis sites [68-70]. In contrast, other studies have found significantly lower diversity of peri-implant biofilms than subgingival biofilms in both health and disease [71-74]. In this sense, Dabdoub and co-workers [73] found that less 50% of all species were shared between periodontal and peri-implant biofilms in the majority of the patients (60%). These numbers are more evident as less than 8% of species are found in both teeth and implants in more than 85% of patients [73]. This is, in the vast majority of patients, microbes at each site are different; therefore, the ecosystem can also be referred to be different.

Risk of bias within studies

As a summary of the risk of bias within studies, we must highlight the fact that most of the studies included were observational cross-sectional studies. Most of them made a sound selection of the comparison group (if present) and used valid and reliable measures. However, in most cases when a comparison group was present it was difficult to identify the method of balancing the groups by important potential confounding variables that in some cases were not even taken into account, including age, gender, presence of periodontal disease, concomitant intake of antibiotics or anti-inflammatory drugs, type of implant-abutment connection, or last periodontal therapy, among others. Because of this, it can be said that most of the studies in this topic contain a moderate risk of bias.

Risk of bias across studies

There were several limitations present in the current review. The main difficulty in the topic under study is the difference in the microbial detection technique. In addition, the latter consensus in disease classification, diagnosis and reporting is not always followed in the included studies, although they do report the conditions properly. Also, few studies analyse simultaneously the microbiome and the host, which indicate limited information on this important interactions. Thus, the lack of comparable studies in terms of design, patient selection, defect and systemic conditions and microbial analysis make it difficult to draw solid conclusions.

DISCUSSION

Most of the studies on microbiology around implants and teeth use paper points to collect the samples. A recent study concluded that paper points used for sampling can contain contaminating bacterial DNA [75]. Therefore, the use of paper points as sampling tool for microbial profiling should be substituted by other methods such as sterile curettes.

Efforts are being made on generating a complete analysis of the human microbiome, the most important of them being the Human Microbiome Project (HMP). It should not be surprising that approximately 26% of all bacteria in the human body are located in the oral cavity [76]. It has been calculated that the microbiota on a human body outnumbers our somatic cells by 10-fold. Therefore, understanding the human microbiome, its distribution and evolution is key in the understanding of the human physiology, as have been highlighted in several reviews [77].

The studies developed under the HMP project try to answer the question on what are the synergistic activities between humans and microbes. Other questions come from an ecological point of view

such as how stable and resilient is the microbiota over the course of a day within one individual, and during the course of his or her lifespan, how similar they are between members of a family, a human community, and between communities living in different environments, etc. [77]. These studies were proposed to use the deep analysis tools that were developed under the Human Genome Project: random shotgun sequencing procedures, targeted large-insert clone sequencing, and assessments of intra- and inter-individual variation by using high-density microarrays [78].

Much of the current understanding of microbiomes comes from culture-based approaches. However, as much as 20% to 60% of the human-associated microbiome has been estimated to be uncultivable [76]. This obviously results in an underestimation of the diversity of the human microbiome. Therefore, new technologies were needed. Then, genomic analysis by checkerboard or PCR was introduced. PCR as the first technique of a group identified as "molecular techniques", was introduced in the 80s. It uses an enzymatic replication process of the DNA that will be later observed in a gel or quantified after a number of replication cycles [3]. These techniques overcame the limitations of culturing techniques and also allowed great time-saving. They also offer great sensitivity. Then, the DNA-DNA hybridization ('checkerboard') technique was applied in periodontal studies by Socransky et al. [79]. It allows the evaluation of large amounts of plaque samples for multitude of species on a single support membrane by hybridizing the DNA samples against whole genomic DNA probes, detecting up to 78 species at once [3]. The use of DNA-DNA hybridization highly improved the studies performed before using traditional culture techniques. The vast majority of the studies on peri-implantitis, obviously, focused on the species identified before on periodontitis sites, as a high similarity was suspected at the time. However, the main disadvantage of the PCR and DNA-DNA hybridization methods is the need to preselect probes for the bacteria to be investigated [3]. Therefore, there is a certain bias as the observer selects which and which not should be looked for and does not allow finding 'unexpected' microbiota. Thus, studies are really difficult to be compared. In addition, the quality of the results depends highly on the quality of the probe and the hybridization conditions. Consequently, although useful for exploratory studies, these techniques should be discarded in the future.

New studies are sequencing genomic libraries made from DNA extracted directly from the sample without "looking for" a specific organism, a method called "metagenomics" [80]. The several limitations mentioned above for the previous techniques can be overcome by this new technology. It mainly refers to the gene sequencing of the 16S rRNA gene. This technique is able to identify universal and conserved targets with important and distinctive phylogenetic information in complex microbial communities. Within the specific field of Dentistry, the analysis of the 16S ribosomal gene sequence is probably the tool providing the more comprehensive examination of the taxonomically heterogeneous community associated with periodontal health and disease, as well as peri-implant diseases [69]. However, the technique presents limitations in identifying differences at the strain level, which may actually be the level that distinguishes between health and disease [3]. This can be overcome by shotgun sequencing of the whole genome. To date, no studies on peri-implant disease have been identified using this methodology.

Summary of evidence

It has been reported that the microbial profile in the peri-implant sulcus and adjacent periodontal pockets is specific for peri-implantitis and have high predictive value [53]. However, periodontal pathogens have been identified in healthy, peri-implant mucositis, and peri-implantitis sites. Thus, it could be argued that these microorganisms are not strictly associated with peri-implantitis [49,81] and other species not analysed in some of those studies may be involved in the pathogenesis of peri-implant diseases [65]. Furthermore, in some cases, microorganisms not associated with periodontal disease have been a common finding at implants with peri-implantitis [62]. Therefore, conventional pathogens in periodontal disease may not be the only microorganisms active in peri-implantitis [64].

In any case, based on this review and according to others, the microbiota around implants is complex [4]. Nonetheless, in general, higher amounts of microorganisms have been found in sites diagnosed with peri-implantitis than in healthy sites. Despite the geographic proximity and some common microorganisms, the microbiota of periodontal tissues is different than the one found around implants [64,68,70,73]. Also, as properly discussed by Charalampakis and Belibasakis [3], with whom we agree, it may sound logical to think that if the microbiota at teeth and implants share a limited space they should be similar. However, the differences in topography and immunological characteristics of periodontal and peri-implant tissues must also drive to the logical conclusion that the biofilms associated with these surfaces have to be different.

Limitations

Most of the studies published so far used techniques such as culture, PCR and checkerboard DNA-DNA hybridization that limit the possibility to detect species not considered in the analysis. Metagenomics techniques must be used in future studies and findings correlated with specific host characteristics (site, defect, region and systemic conditions and background). In most cases comparison groups were not balanced by important potential confounding variables, including age, gender, presence of periodontal disease, concomitant intake of antibiotics or anti-inflammatory drugs, type of implant-abutment connection, or last periodontal therapy, among others.

CONCLUSIONS

Microbial profile of peri-implant diseases usually includes classic periodontopathogens. However, correlation between studies is difficult, particularly because of the use of different detection methods. New metagenomic techniques to avoid detection bias and careful balance and description of the included patients and implants should be promoted for future studies.

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