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Review Paper

Changes in the Oral Microbiota Induced by Peri-implantitis: A Meta-Analysis

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ABSTRACT

Background: Peri-implantitis is an infectious disease around dental implants characterized by inflammation of the peri-implant connective tissues and progressive loss of supporting bone, with an estimated prevalence of around 22%. Peri-implantitis microbiota is different from that observed in both periodontitis and healthy implants. Knowledge of this microbiota is crucial for the proper treatment of the disease.

Objective: To assess the differences in the oral microbiota in dental implant-bearing patients with and without peri-implantitis.

Methods: A search for studies on microbiota and peri-implantitis up to June 2021 was conducted in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science, Scopus, ProQuest, LILACS, and Google Scholar. For dichotomous outcomes, the effects of the intervention were expressed as odds ratios (OR) using Mantel-Haenszel (M-H) method with 95% confidence intervals.

Results: Twelve studies with 1324 participants were included in this meta-analysis. Peri-implantitis patients were more likely to be carriers of the following microorganisms: *Tannerella forsythia* (OR=3.17, 95% CI: 1.55 to 6.51, P<0.01); *Prevotella intermedia* (OR=2.21, 95% CI: 1.73 to 2.82, P<0.001); *Treponema denticola* (OR=2.18, 95% CI: 1.70 to 2.79, P<0.001); *Porphyromonas gingivalis* (OR=2.04, 95% CI: 1.16 to 3.59, P=0.01); *Fusobacterium nucleatum* (OR=1.81, 95% CI: 1.21 to 2.72, P<0.01), and *Campylobacter rectus* (OR=1.69, 95% CI: 1.32 to 2.17, P<0.001). In contrast, the bacteria *Aggregatibacter actinomycetemcomitans* and *Streptococcus mitis* were more prevalent in peri-implantitis patients but not significantly (P>0.05).

Conclusion: Peri-implantitis modifies the quantitative and qualitative composition of the oral microbiota.

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1. Introduction

Periimplantitis is a polymicrobial infection around dental implants characterized by inflammation of the peri-implant connective tissue and progressive loss of the supporting bone. Its prevalence ranges from 1% to 47%, with a weighted average prevalence of around 22% [1].

Bacterial plaque is the main etiological agent of peri-implantitis. Its control is essential to prevent microbial aggression and minimize peri-implant inflammation. Peri-implantitis is an infectious disease that shares certain similarities with periodontitis, although there are differences in the oral microbiota composition between these diseases [2].

Peri-implantitis is a disease in which several gram-negative anaerobic pathogenic bacteria are implicated, such as *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Staphylococcus aureus*, and *Aggregatibacter actinomycetemcomitans* [3]. Some studies show that certain periodontal pathogens, such as *P. gingivalis*, *T. denticola*, or *T. forsythia*, are prevalent in peri-implantitis compared to healthy implants [4]. This microbiota is associated with the appearance and progression of infection, and its monitoring is a crucial step in evaluating the effectiveness of different therapeutic alternatives [5].

This study assessed the differences in the oral microbiota in dental implant-bearing patients with and without peri-implantitis.

2. Materials and Methods

Search strategy and study selection criteria

A search for studies on microbiota and periimplantitis was conducted up to June 2021 in the following databases: PubMed (MEDLINE, Cochrane Library), Web of Science (WOS), Scopus, ProQuest, Scientific health information from Latin America and the Caribbean countries (LILACS), and Google Scholar. Search strategies were developed for each database using Medical Subjects Headings (MeSH) and free-text terms. The search terms were as the following: "bacteria" [MeSH Terms] and "peri-implantitis" [MeSH Terms]; ("peri-implantitis" and "microbi*" and "control"); TITLE-ABS-KEY (("peri-implantitis" and "microbi*" and "control")); "peri-implantitis" and "microbiota;" "peri-implantitis" and "bacteria;" "periimplantitis" and "microbiology" and "case control." There were no restrictions regarding the year or the language of publication. Articles with the same title and abstract (duplicate articles) were removed. The exclusion criteria were as follows: articles without full-text availability, studies that did not consider subjects without peri-implantitis, articles with a score of fewer than 6 points on the Newcastle-Ottawa methodological quality assessment scale, and studies with non-usable data.

Data extraction

The characteristics of the selected studies comprised the first author, year of publication, study populations (gender distribution, mean age), methods for detecting microorganisms, Newcastle-Ottawa scale score, and the outcome variable (bacteria analyzed).

Assessment of methodological quality

The methodological quality of the studies considered in this manuscript was analyzed with the Newcastle-Ottawa methodological quality assessment scale composed of 8 items that assess 3 dimensions: selection, comparability, and exposure [6]. According to the score obtained, the studies are classified as high quality (≥7 points), moderate quality (4-6 points), and low quality (1-3 points). Two evaluators (A.R.A. and B.P.C.) independently reviewed the studies and agreed on the articles included in this study.

Statistical analysis

Data were processed using RevMan v. 5.4 meta-analysis software (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the odds ratio (OR) with the Mantel-Haenszel Chi-square formula (M-H) and 95% confidence interval (CI) were used. Heterogeneity was determined according to the Higgins statistics (I^2). A random-effects model was applied if the heterogeneity was high (I^2>50%). The minimum level of significance was set at $P<0.05$.

3. Results

Study selection

In the initial search, 1015 articles were found (174 in PubMed, 266 in WOS, 177 in Scopus, 222 in ProQuest, 29 in LILACS, and 157 in Google Scholar); 264 of them duplicates, leaving 751 articles for eligibility. The exclusion criteria were as follows: articles without full-text availability (n=174), studies not considered subjects

Table 1. Description and methodological quality evaluation of 12 studies included in this meta-analysis

Study	Year	Country	Study Population	Detection Method	Analyzed Bacteria	NOS
Ebadian [7]	2012	Iran	13 peri-impl. (7 M; 6 F; 58.3 y) 13 control (3 M; 10 F; 42.5 y)	PCR	Pg, Pi, Fn, Tf, Cr	6
Cortelli [8]	2013	Brazil	50 peri-impl. (16 M; 34 F; 40.3 y) 53 control (18 M; 35 F; 38.3 y)	PCR	Pg, Pi, Tf, Td, Cr, Aa	7
Tamura [9]	2013	Japan	15 peri-impl. (7 M; 8 F; 56.9 y) 15 control (11 M; 4 F; 63.4 y)	PCR	Pi, Fn, Aa, Sm	6
Persson [10]	2014	Sweden	166 peri-impl. (62 M; 104 F; 67.0 y) 47 control (21 M; 26 F; 53.7 y)	PCR	Pg, Pi, Fn, Tf, Td, Cr, Aa, Sm	8
Neilands [11]	2015	Sweden	25 peri-impl. (na; na; na) 25 control (na; na; na)	FPAK	Pg, Pi, Fn, Tf, Sm	6
Verdugo [12]	2015	Spain	23 peri-impl. (9 M; 14 F; 56.0 y) 23 control (9 M; 14 F; 56.0 y)	PCR	Pg, Pi, Tf, Td,	6
Canullo [13]	2016	Spain	53 peri-impl. (25 M; 28 F; 59.7 y) 481 control (210 M; 281 F; 55.1 y)	PCR	Pg, Pi, Fn, Tf, Td, Cr, Aa	8
Wang [14]	2016	USA	34 peri-impl. (15 M; 19 F; 65.3 y) 34 control (20 M; 14 F; 62.1 y)	PCR	Pg, Tf, Td	7
de Waal [15]	2017	The Netherlands	85 peri-impl. (25 M; 60 F; 60.6 y) 69 control (23 M; 46 F; 67.7 y)	Culture	Pg, Pi, Fn, Tf, Cr	7
Kato [16]	2017	Japan	15 peri-impl. (9 M; 6 F; 63.9 y) 15 control (4 M; 11 F; 60.7 y)	PCR	Pg	6
Al-Ahmad [17]	2018	Germany	10 peri-impl. (5 M; 5 F; 69.4 y) 10 control (5 M; 5 F; 69.4 y)	PCR	Pg, Pi, Fn, Td, Cr, Sm	6
Gao [18]	2018	China	20 peri-impl. (11 M; 9 F; 45.2 y) 20 control (12 M; 8 F; 39.6 y)	PCR	Pg, Pi, Fn, Td, Cr, Aa, Sm	6

USA: United States of America; peri-impl: peri-implantitis; control: no peri-implantitis; M: male; F: female; y: age in years; na: not available; Pg: *Porphyromonas gingivalis*. Pi: *Prevotella intermedia*; Fn: *Fusobacterium nucleatum*; Td: *Treponema denticola*; Cr: *Campylobacter rectus*; Sm: *Streptococcus mitis;* Tf: *Tannerella forsythia*; Aa: *Aggregatibacter actinomycetemcomitans*; PCR: Polymerase Chain Reaction; FPAK: Fluorescent Protease Assay Kit; Culture: Culturing techniques; NOS: Newcastle-Ottawa methodological quality scale.

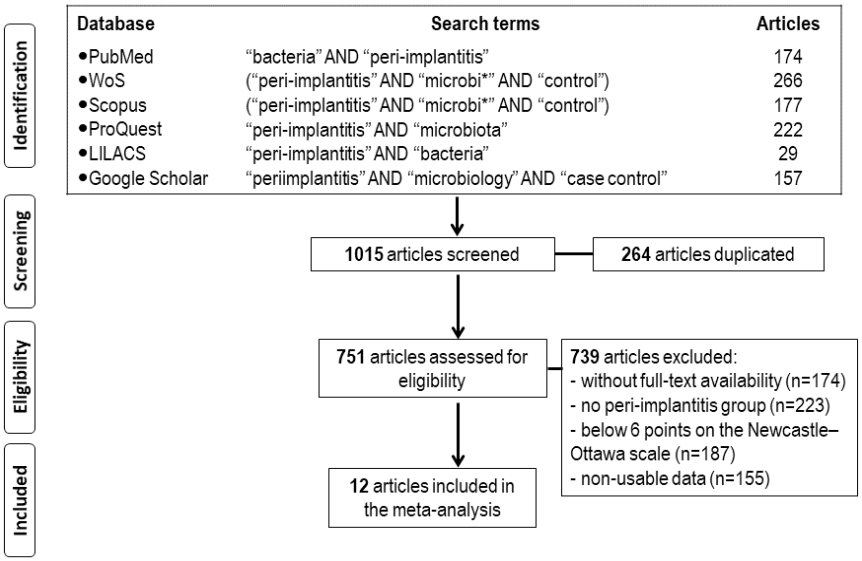

Figure 1. Study flow diagram

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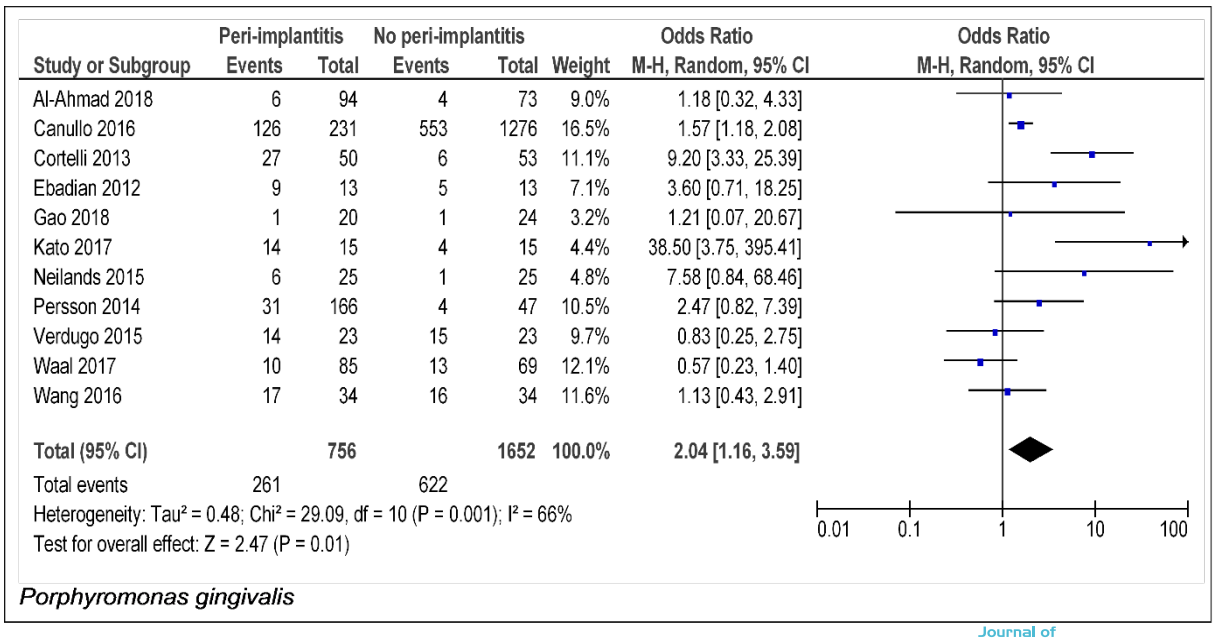

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Figure 2. Data from studies and forest plot for the detection of *Porphyromonas gingivalis* in peri-implantitis patients and no peri-implantitis subjects

without peri-implantitis (n=223), studies with a score lower than 6 on the Newcastle-Ottawa methodological quality assessment scale (n=187), and studies with non-usable data (n=155). After applying these criteria, 12 studies were included in this meta-analysis (Figure 1).

The main descriptive characteristics and the methodological quality analysis of the 12 articles evaluated in the meta-analysis are shown in Table 1 [7-18]. These studies included 509 patients (191 males, 293 females) with peri-implantitis and 815 dental implant carriers (336 males, 454 females) without peri-implantitis. In 10 studies (83.3%), the detection method was a polymerase chain reaction (PCR); in one (8.3%), a fluorescent protease assay kit (FPAK), and in another one (8.3%), microbiological culturing techniques. The

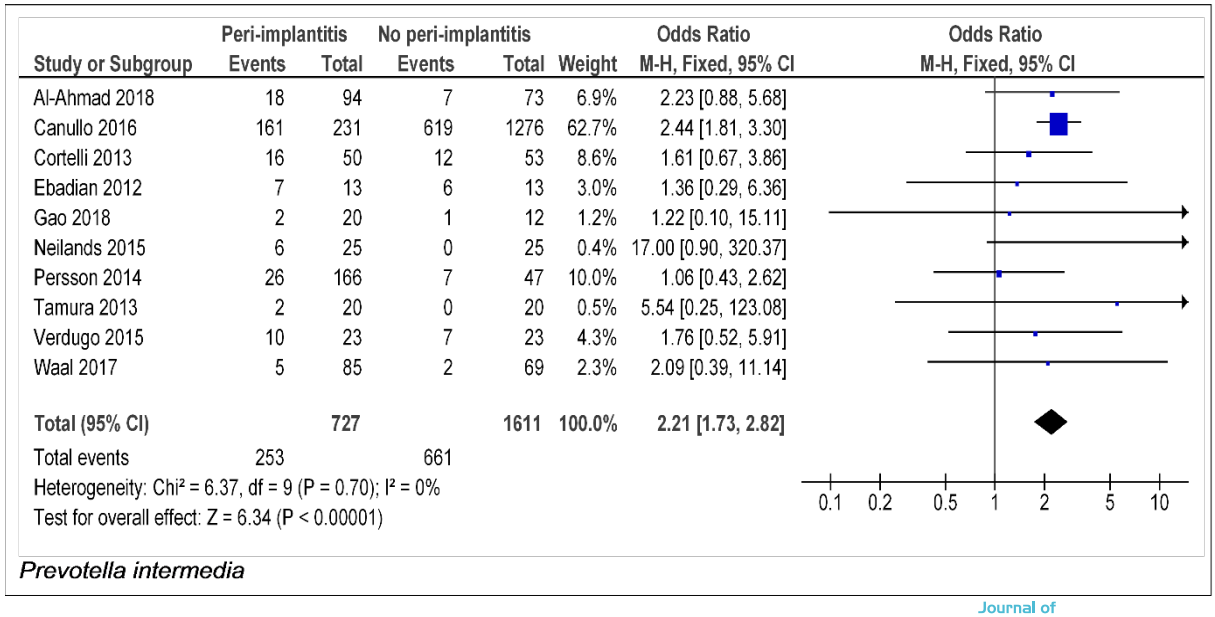

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Figure 3. Data from studies and forest plot for the detection of *Prevotella intermedia* in peri-implantitis patients and no peri-implantitis subjects

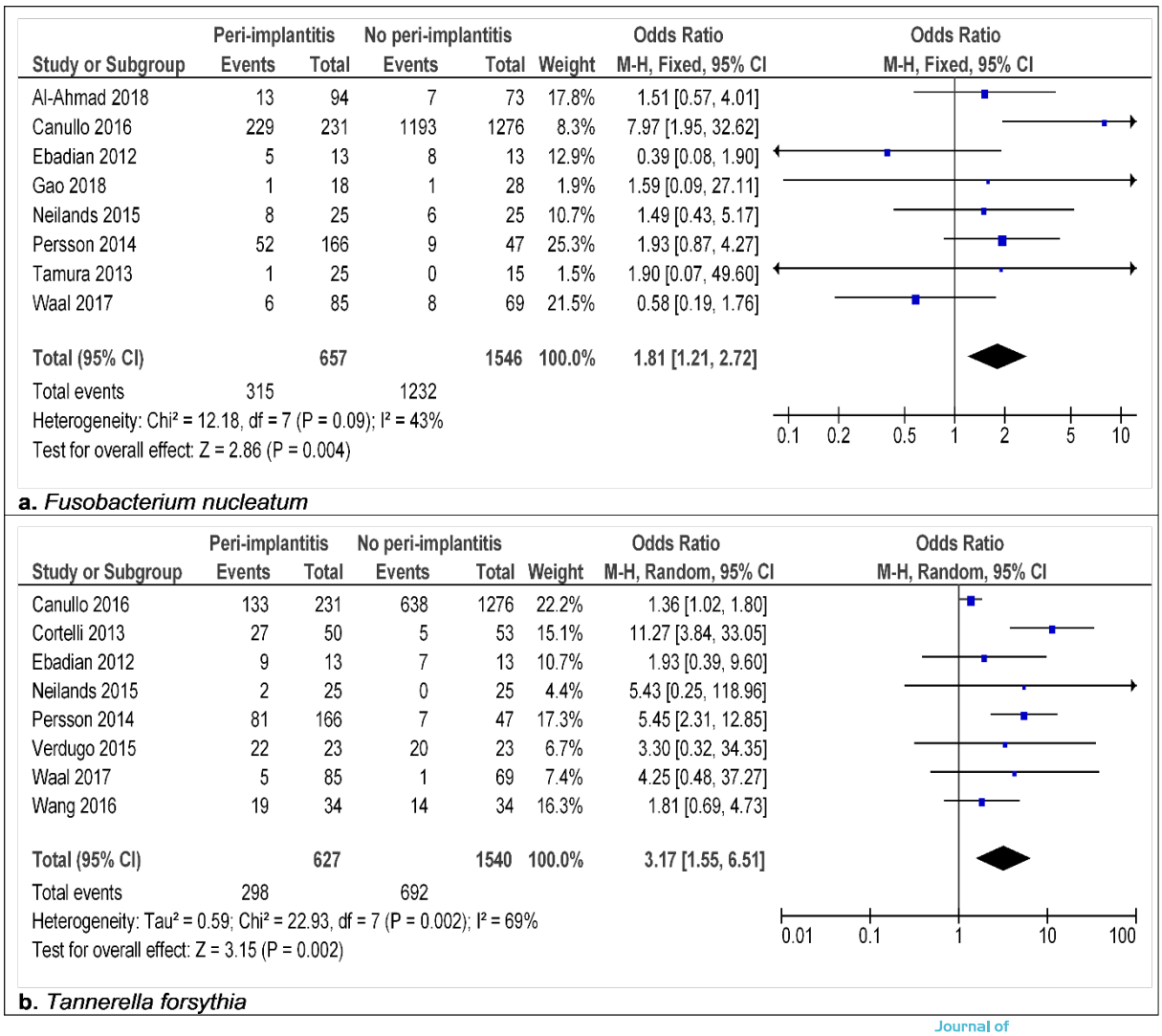

Figure 4. Data from studies and forest plots for the detection of *Fusobacterium nucleatum* (a) or *Tannerella forsythia* (b) in peri-implantitis patients and no peri-implantitis subjects

bacteria studied were *P. gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *T. denticola*, *Campylobacter rectus*, *Streptococcus mitis*, *T. forsythia*, and *A.actinomycetemcomitans.*

Bacteria detected in peri-implantitis

Eleven studies [7, 8, 10-18] examined the presence of *P. gingivalis* (Figure 2), showing that patients with peri-implantitis were twice as likely to have this bacterium with a statistically significant relationship (OR=2.04; 95% CI: 1.16-3.59; P=0.01). Ten studies [7-13, 15, 17, 18] analyzed the presence of *P. intermedia* (Figure 3), finding 2.21 times more probability of this bacterium in patients with peri-implantitis than in subjects without peri-implantitis, with a highly significant statistical association (OR=2.21; 95% CI: 1.73-2.82; P<0.001).

Eight studies [7, 9-11, 13, 15, 17, 18] investigated the presence of *F. nucleatum* (Figure 4a). They observed an increase of 1.81 times in the probability of this microorganism with a statistically significant difference (OR=1.81; 95% CI: 1.21-2.72; P<0.01) in patients with peri-implantitis. Eight other studies [7, 8, 10-15] investigated the bacterium *T. forsythia* (Figure 4b). They found that it was 3.17 times more likely in the microbiota of patients with peri-implantitis, a statistically significant relationship (OR=3.17; 95% CI: 1.55 -6.51; P<0.01).

Seven studies [8, 10, 12-14, 17, 18] analyzed the identification of *T. denticola* (Figure 5a). They observed that patients with peri-implantitis were 2.18 times more likely to have this bacterium. In the statistical analysis, a highly significant statistical association was

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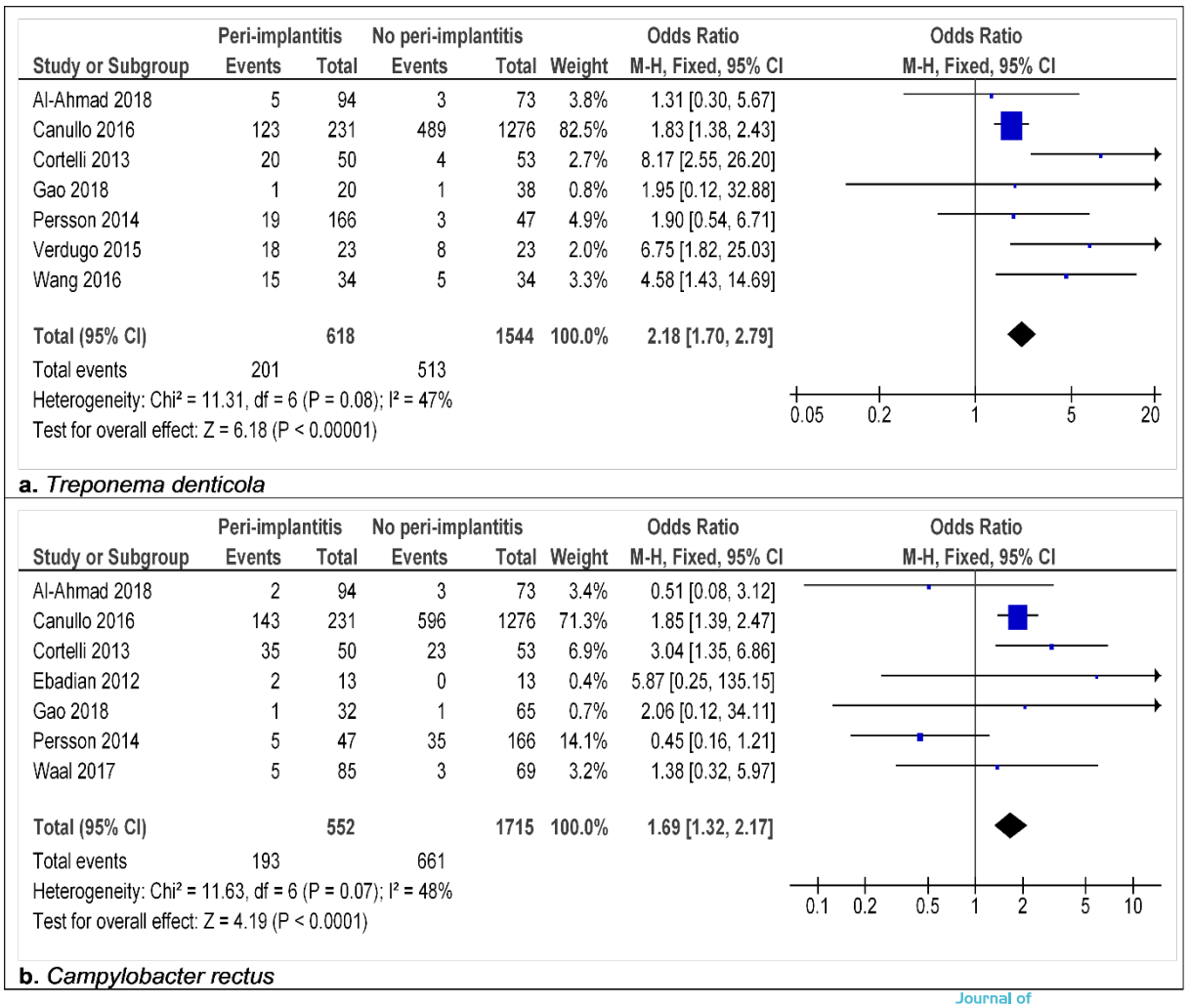

Figure 5. Data from studies and forest plots for the detection of *Treponema denticola* (a) or *Campylobacter rectus* (b) in peri-implantitis patients and no peri-implantitis subjects

found (OR=2.18; 95% CI: 1.70-2.79; P<0.001). Seven other studies [7, 8, 10, 13, 15, 17, 18] considered the *C. rectus* bacterium (Figure 5b). They found a 1.69-fold increase in the probability of detection of this bacterium, with highly significant statistical differences (OR=1.69; 95% CI: 1.32-2.17; P<0.001) in patients with peri-implantitis.

Five studies [8-10, 13, 18] evaluated the presence of Agregatibacter actinomycetemcomitans (Figure 6a). They reported a higher frequency of this bacterium in patients with peri-implantitis, although statistical significance was not reached (OR=1.41; 95% CI: 0.40-5.00; P=0.60). Five other studies [9-11, 17, 18] inspected the presence of *S. mitis* (Figure 6b), proving a lower frequency of this bacterium in patients with peri-implantitis, although no statistically significant relationship was observed (OR=0.67; 95% CI: 0.41-1.11; P=0.12).

4. Discussion

Data from 12 studies on changes in the oral microbiota in peri-implantitis were included in this meta-analysis.

In this study, patients with peri-implantitis were twice as likely (OR=2.04) to present *P. gingivalis* in their oral microbiota than patients without peri-implantitis, with a statistically significant relationship (P=0.01). Of 11 studies that considered the presence of *P. gingivalis* in patients with and without peri-implantitis, 9 of them [7, 8, 10, 11, 13, 15-18], agreed to specify this higher prevalence of the bacterium in cases of peri-implantitis. The analysis of microbial samples from healthy implants, peri-implant mucositis, and peri-implantitis showed that periodontal pathogens *(P. gingivalis, T. forsythia*) were detected more in cases of mucositis and peri-implantitis, suggesting an important role for

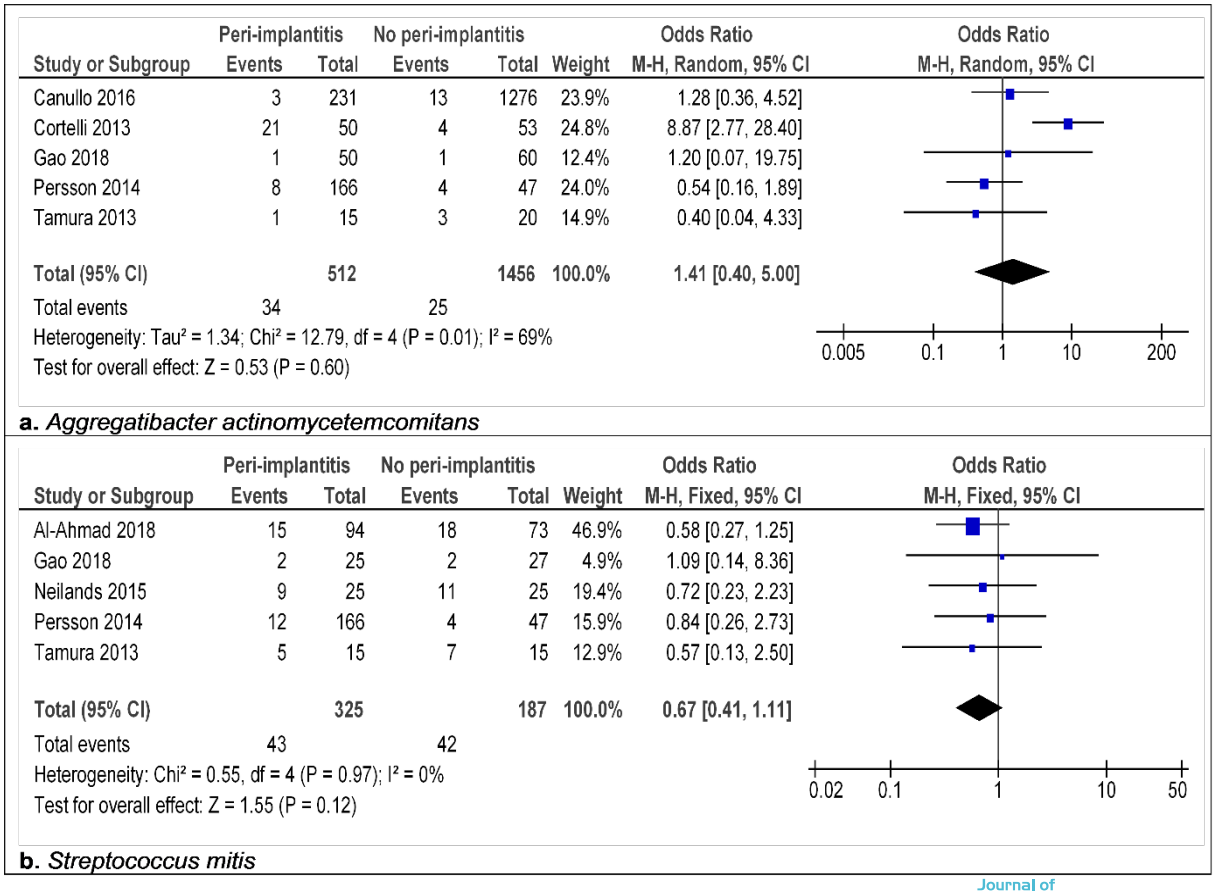

Figure 6. Data from studies and forest plots for the detection of *Aggregatibacter actinomycetemcomitans* (a) or *Streptococcus mitis* (b) in peri-implantitis patients and no peri-implantitis subjects.

them in the pathogenesis of peri-implant diseases (mucositis and peri-implantitis). Specifically, *P. gingivalis* is strongly associated with peri-implantitis cases [17]. On the other hand, the concentrations of the main periodontopathogenic bacteria (*P. gingivalis*, *T. forsythia*, *P. intermedia*, *T. denticola*, *F. nucleatum*) in peri-implantitis are approximately four times higher than those in healthy implants, confirming the polymicrobial etiology of these disorders [10].

In this study, patients with peri-implantitis were 2.21 times more likely to have *P. intermedia* in their microbiota compared to patients with healthy implants, a highly significant statistical association (P<0.001). Also, 10 studies [7-13, 15, 17, 18] that analyzed this bacterium confirmed this higher prevalence in patients with peri-implantitis. Peri-implant disease is significantly associated with the submucosal presence of *P. intermedia* and *T. forsythia*. Significantly higher detection frequencies of these pathogens were observed around implants with peri-implantitis compared to healthy implants. The association with peri-implant disease status was more obvious for these two bacteria, which showed high detection frequencies in peri-implantitis and low frequencies in healthy implants. Therefore, these two species could be predictive markers of peri-implantitis [15].

In this study, patients with peri-implantitis vs patients without peri-implantitis had 1.81 times more probability of detecting *F. nucleatum*, a statistically significant difference (P<0.01). Six [9-11, 13, 17, 18] of the 8 studies that examined this bacterium agreed with this result. The biofilms associated with peri-implantitis contain more periodontopathogens of the so-called "orange complex," such as *F. nucleatum*, *Parvimonas micra*, or *P. intermedia*, compared to the biofilms found in healthy implants [15].

The *T. forsythia* bacterium was 3.17 times more likely in the oral microbiota of peri-implantitis patients, with a statistically significant relationship (P<0.01). Six studies [10, 12, 13, 15, 17, 18] that examined this organism showed this higher prevalence in peri-implantitis cases. The evolution of the peri-implant disease is significantly correlated with the submuco-

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sal presence of *P. gingivalis*, *F. nucleatum, P. intermedia*, and *T. forsythia*. These periodontal pathogens are much more prevalent in the tissues surrounding implants in peri-implantitis compared to the surrounding implant tissue in healthy conditions. This association with disease status was more obvious for *P. intermedia* and *T.forsythia*, two bacteria with high detection rates in peri-implantitis and low detection frequencies in healthy implants. Therefore, these two species could be predictive markers of peri-implantitis [15].

In this study, patients with peri-implantitis had a 2.18 times higher risk of presenting *T. denticola* than patients without peri-implantitis, with a highly significant statistical association (P<0.001). All the studies [7, 8, 10, 13, 15, 17, 18] that considered this bacterium confirmed this positive relationship between the bacterium and peri-implantitis. In patients with peri-implantitis, high concentrations of *T. denticola* are detected in the gingival sulcus and saliva. In general, the concentrations of these and other periodontal pathogens are higher than those in healthy implants. The analysis of salivary concentrations of *T. denticola* is a good predictor of infection status and the probability of granulation tissue formation throughout the inflammatory process [12].

In this study, patients with peri-implantitis were also 2.18 times more likely to have *C. rectus* than patients without peri-implantitis, showing highly significant statistical differences (P<0.001). Of the 7 studies that examined this bacterium, some found a higher frequency of *C. rectus* in patients with peri-implantitis [5, 7, 8, 13, 15, 18]. Red complex bacteria and other anaerobic bacteria, including *C. rectus*, are much more prevalent in significantly higher numbers in deep periodontal pockets and peri-implant lesions [7].

When Agregatibacter actinomycetemcomitans was investigated in the oral microbiota, no significant predilection for this bacterium was observed in any group studied without reaching statistical significance (P=0.60). Among the five studies that investigated this bacterium, 3 studies [8, 13, 18] found a greater presence in the cases of peri-implantitis, and 2 others [9, 10] did not report a higher prevalence of the bacteria. Although Agregatibacter actinomycetemcomitans does not appear to play a relevant etiological role in peri-implantitis, this disease results from an imbalance between host response and bacterial load, especially anaerobic gram-negative bacteria in susceptible patients. Apart from these infectious agents, other risk factors include genetic factors, poor oral hygiene, smoking, a history of periodontitis, excessive alcohol consumption, and local implant-dependent factors that may favor the development of peri-implant disease [13].

In this study, *S. mitis* was uncommon in patients with peri-implantitis, although no statistically significant relationship was observed (P=0.12). Four [9-11, 17] of the 5 studies on this bacterium confirmed this lower detection in the oral microbiota of patients with peri-implantitis. Oral streptococci (*S. mitis*, *Streptococcus salivarius,* and *Streptococcus sanguinis*) were more frequently isolated in the group with healthy implants than in the group with peri-implantitis. In contrast, other pathogens, such as *S. anginosus* and particularly *S. constellatus*, are especially prevalent in peri-implantitis patients [11]. Oral streptococci are one of the predominant genera in all groups (peri-implantitis, healthy implants). However, a long-term study on peri-implant area colonization showed a decrease in the proportion of facultative anaerobic cocci (Streptococcus) and an increase in the percentage of strict anaerobic bacilli (Fusobacterium and Prevotella) [9].

One of the main limitations of this study is the difficulty in assessing the severity of peri-implantitis and the lack of quantification of microbial concentrations in some studies considered.

The comparisons of this meta-analysis should be interpreted with caution because of the high heterogeneity among the studies. Individual differences between studies could be due to the type of design, the methods used to collect samples, or the microorganism detection techniques used.

5. Conclusions

In this meta-analysis, patients with peri-implantitis were significantly more likely to be carriers of the following microorganisms: Cytomegalovirus (OR=19.07), *T. forsythi*a (OR=3.17), *P. intermedia* (OR=2.21), *T. denticola* (OR=2.18), *P. gingivalis* (OR=2.04), *F. nucleatum* (OR=1.81), and *C. rectus* (OR=1.69). In contrast, *A. actinomycetemcomitans* and *S. mitis* were not significantly (P>0.05) more prevalent in patients with peri-implantitis.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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This study was self-funded.

Authors' contributions

The authors equally participated in conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, original draft preparation, review, editing, visualization, supervision, and project administration. Both authors read and approved the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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