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

eriimplantitis 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 periimplantitis. 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 gramnegative 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"); TI-TLE-ABS-KEY (("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 (\geq 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 (I²). A random-effects model was applied if the heterogeneity was high (I²>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

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Study	Year	Country	Study Population	Detection Method	Analyzed Bacteria	NOS
Ebadian [7]	2012	Iran	13 peri-impl. (7 M; 6 F; 58.3 γ) 13 control (3 M; 10 F; 42.5 γ)	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 Neth- erlands	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

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

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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.

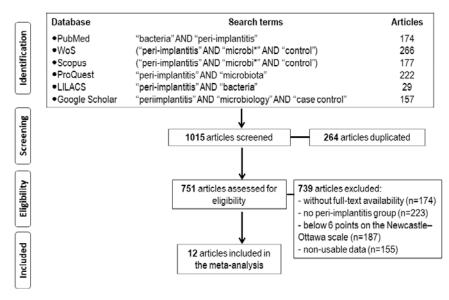


Figure 1. Study flow diagram

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	Peri-impla	Intitis	No peri-impl	antitis		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Al-Ahmad 2018	6	94	4	73	9.0%	1.18 [0.32, 4.33]	
Canullo 2016	126	231	553	1276	16.5%	1.57 [1.18, 2.08]	-
Cortelli 2013	27	50	6	53	11.1%	9.20 [3.33, 25.39]	
Ebadian 2012	9	13	5	13	7.1%	3.60 [0.71, 18.25]	
Gao 2018	1	20	1	24	3.2%	1.21 [0.07, 20.67]	· · · · · · · · · · · · · · · · · · ·
Kato 2017	14	15	4	15	4.4%	38.50 [3.75, 395.41]	
Neilands 2015	6	25	1	25	4.8%	7.58 [0.84, 68.46]	· · · · · · · · · · · · · · · · · · ·
Persson 2014	31	166	4	47	10.5%	2.47 [0.82, 7.39]	│
Verdugo 2015	14	23	15	23	9.7%	0.83 [0.25, 2.75]	
Waal 2017	10	85	13	69	12.1%	0.57 [0.23, 1.40]	
Wang 2016	17	34	16	34	11.6%	1.13 [0.43, 2.91]	
Total (95% CI)		756		1652	100.0%	2.04 [1.16, 3.59]	•
Total events	261		622				
Heterogeneity: Tau ² =	0.48; Chi ² =	29.09, d	f = 10 (P = 0.0	01); l² = (66%		
Test for overall effect:	Z = 2.47 (P =	= 0.01)					0.01 0.1 1 10 10
Porphyromonas g	qingivalis						

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Figure 2. Data from studies and forest plot for the detection of *Porphyromonas gingivalis* in peri-implantitis patients and no periimplantitis 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 nonusable data (n=155). After applying these criteria, 12 studies were included in this meta-analysis (Figure 1). 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

The main descriptive characteristics and the methodological quality analysis of the 12 articles evaluated in

	Peri-impla	ntitis	No peri-imp	lantitis		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Al-Ahmad 2018	18	94	7	73	6.9%	2.23 [0.88, 5.68]	
Canullo 2016	161	231	619	1276	62.7%	2.44 [1.81, 3.30]	
Cortelli 2013	16	50	12	53	8.6%	1.61 [0.67, 3.86]	
Ebadian 2012	7	13	6	13	3.0%	1.36 [0.29, 6.36]	
Gao 2018	2	20	1	12	1.2%	1.22 [0.10, 15.11]	
Neilands 2015	6	25	0	25	0.4%	17.00 [0.90, 320.37]	
Persson 2014	26	166	7	47	10.0%	1.06 [0.43, 2.62]	
Tamura 2013	2	20	0	20	0.5%	5.54 [0.25, 123.08]	· · · ·
Verdugo 2015	10	23	7	23	4.3%	1.76 [0.52, 5.91]	
Waal 2017	5	85	2	69	2.3%	2.09 [0.39, 11.14]	
Total (95% CI)		727		1611	100.0%	2.21 [1.73, 2.82]	•
Total events	253		661				
Heterogeneity: Chi ² = 6	6.37, df = 9 (P = 0.70); I ² = 0%				
Test for overall effect: 2	Z = 6.34 (P <	< 0.0000	1)				0.1 0.2 0.5 1 2 5 10

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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

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	Peri-impla	ntitis	No peri-imp	lantitis		Odds Ratio		Odd	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fiz	ked, 95% CI		
Al-Ahmad 2018	13	94	7	73	17.8%	1.51 [0.57, 4.01]			-	_	
Canullo 2016	229	231	1193	1276	8.3%	7.97 [1.95, 32.62]					-
Ebadian 2012	5	13	8	13	12.9%	0.39 [0.08, 1.90]	•	-	<u> </u>		
Gao 2018	1	18	1	28	1.9%	1.59 [0.09, 27.11]			· · · ·		
Neilands 2015	8	25	6	25	10.7%	1.49 [0.43, 5.17]					
Persson 2014	52	166	9	47	25.3%	1.93 [0.87, 4.27]			+	_	
Tamura 2013	1	25	0	15	1.5%	1.90 [0.07, 49.60]	←		+ · · ·		
Waal 2017	6	85	8	69	21.5%	0.58 [0.19, 1.76]	-				
Total (95% CI)		657		1546	100.0%	1.81 [1.21, 2.72]			\bullet		
Total events	315		1232								
Heterogeneity: Chi ² =	12.18, df = 7	(P = 0.0	9); l ² = 43%				+ +		+ +	<u> </u>	+
Test for overall effect:		,	.,,				0.1 0.2	0.5	1 2	5	1

a. Fusobacterium nucleatum

	Peri-impla	ntitis	No peri-impla	antitis		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Canullo 2016	133	231	638	1276	22.2%	1.36 [1.02, 1.80]	-
Cortelli 2013	27	50	5	53	15.1%	11.27 [3.84, 33.05]	_
Ebadian 2012	9	13	7	13	10.7%	1.93 [0.39, 9.60]	
Neilands 2015	2	25	0	25	4.4%	5.43 [0.25, 118.96]	
Persson 2014	81	166	7	47	17.3%	5.45 [2.31, 12.85]	
Verdugo 2015	22	23	20	23	6.7%	3.30 [0.32, 34.35]	
Waal 2017	5	85	1	69	7.4%	4.25 [0.48, 37.27]	
Wang 2016	19	34	14	34	16.3%	1.81 [0.69, 4.73]	+
Total (95% CI)		627		1540	100.0%	3.17 [1.55, 6.51]	•
Total events	298		692				
Heterogeneity: Tau ² =	0.59; Chi ² =	22.93, d	f = 7 (P = 0.002	2); ² = 69	9%		
Test for overall effect:							0.01 0.1 1 10 100
. Tannerella fors	sythia						

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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 periimplantitis 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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	Peri-impla	ntitis	No peri-imp	lantitis		Odds Ratio			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		N	1-H, Fixe	ed, 95%	CI	
Al-Ahmad 2018	5	94	3	73	3.8%	1.31 [0.30, 5.67]		-		•		
Canullo 2016	123	231	489	1276	82.5%	1.83 [1.38, 2.43]						
Cortelli 2013	20	50	4	53	2.7%	8.17 [2.55, 26.20]				-		
Gao 2018	1	20	1	38	0.8%	1.95 [0.12, 32.88]				· · ·		
Persson 2014	19	166	3	47	4.9%	1.90 [0.54, 6.71]						
Verdugo 2015	18	23	8	23	2.0%	6.75 [1.82, 25.03]						
Wang 2016	15	34	5	34	3.3%	4.58 [1.43, 14.69]					•	_
Total (95% CI)		618		1544	100.0%	2.18 [1.70, 2.79]				•		
Total events	201		513									
Heterogeneity: Chi ² =	11.31, df = 6	(P = 0.08	3); ² = 47%				0.05	0.2			<u> </u>	
Test for overall effect:	Z = 6.18 (P <	0.00001)				0.05	0.2		I	5	
. Treponema der	nticola											
· ·	Peri-impla		No peri-imp			Odds Ratio				Ratio		
Study or Subgroup		ntitis Total	No peri-imp Events		Weight	M-H, Fixed, 95% CI		N		Ratio ed, 95%	CI	
Study or Subgroup	Peri-impla Events 2	Total 94	Events 3	Total 73	3.4%	M-H, Fixed, 95% CI 0.51 [0.08, 3.12]		N			CI	
Study or Subgroup Al-Ahmad 2018 Canullo 2016	Peri-impla Events 2 143	Total 94 231	Events	Total 73 1276	3.4% 71.3%	M-H, Fixed, 95% Cl 0.51 [0.08, 3.12] 1.85 [1.39, 2.47]		N				
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013	Peri-impla Events 2	Total 94 231 50	Events 3	Total 73	3.4%	M-H, Fixed, 95% CI 0.51 [0.08, 3.12]		M				
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012	Peri-impla Events 2 143	Total 94 231 50 13	Events 3 596	Total 73 1276	3.4% 71.3%	M-H, Fixed, 95% CI 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86] 5.87 [0.25, 135.15]		N				
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012	Peri-impla Events 2 143 35	Total 94 231 50	Events 3 596 23 0 1	Total 73 1276 53	3.4% 71.3% 6.9%	M-H, Fixed, 95% Cl 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86]		N				
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012 Gao 2018	Peri-impla Events 2 143 35 2	Total 94 231 50 13	Events 3 596 23 0	Total 73 1276 53 13	3.4% 71.3% 6.9% 0.4%	M-H, Fixed, 95% CI 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86] 5.87 [0.25, 135.15]		N				
<u>Study or Subgroup</u> Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012 Gao 2018 Persson 2014 Waal 2017	Peri-impla Events 2 143 35 2 1	Total 94 231 50 13 32	Events 3 596 23 0 1	Total 73 1276 53 13 65	3.4% 71.3% 6.9% 0.4% 0.7%	M-H, Fixed, 95% Cl 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86] 5.87 [0.25, 135.15] 2.06 [0.12, 34.11]		N				
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012 Gao 2018 Persson 2014	Peri-impla Events 2 143 35 2 1 5	Total 94 231 50 13 32 47	Events 3 596 23 0 1 35	Total 73 1276 53 13 65 166 69	3.4% 71.3% 6.9% 0.4% 0.7% 14.1%	M-H, Fixed, 95% Cl 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86] 5.87 [0.25, 135.15] 2.06 [0.12, 34.11] 0.45 [0.16, 1.21]		N			<u></u>	
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012 Gao 2018 Persson 2014 Waal 2017	Peri-impla Events 2 143 35 2 1 5	Total 94 231 50 13 32 47 85	Events 3 596 23 0 1 35	Total 73 1276 53 13 65 166 69	3.4% 71.3% 6.9% 0.4% 0.7% 14.1% 3.2%	M-H, Fixed, 95% Cl 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86] 5.87 [0.25, 135.15] 2.06 [0.12, 34.11] 0.45 [0.16, 1.21] 1.38 [0.32, 5.97]		N			<u></u>	
Study or Subgroup Al-Ahmad 2018 Canullo 2016 Cortelli 2013 Ebadian 2012 Gao 2018 Persson 2014 Waal 2017 Total (95% CI)	Peri-impla Events 2 143 35 2 1 5 5 5	Total 94 231 50 13 32 47 85 552	Events 3 596 23 0 1 35 3 661	Total 73 1276 53 13 65 166 69	3.4% 71.3% 6.9% 0.4% 0.7% 14.1% 3.2%	M-H, Fixed, 95% Cl 0.51 [0.08, 3.12] 1.85 [1.39, 2.47] 3.04 [1.35, 6.86] 5.87 [0.25, 135.15] 2.06 [0.12, 34.11] 0.45 [0.16, 1.21] 1.38 [0.32, 5.97]					CI	-+ 10

b. Campylobacter rectus

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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 metaanalysis.

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

	Peri-impla		No peri-impla			Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H, Random, 98	5% CI	
Canullo 2016	3	231	13	1276	23.9%	1.28 [0.36, 4.52]				
Cortelli 2013	21	50	4	53	24.8%	8.87 [2.77, 28.40]		-	-	
Gao 2018	1	50	1	60	12.4%	1.20 [0.07, 19.75]				
Persson 2014	8	166	4	47	24.0%	0.54 [0.16, 1.89]				
Tamura 2013	1	15	3	20	14.9%	0.40 [0.04, 4.33]				
Total (95% CI)		512		1456	100.0%	1.41 [0.40, 5.00]		-		
Total events	34		25							
Heterogeneity: Tau ² =	1.34; Chi ² = '	12.79, df	= 4 (P = 0.01)	; I ² = 69%	0		0.005		10	200
Test for overall effect: 2	Z = 0.53 (P =	0.60)					0.005	0.1 1	10	200
. Aggregatibacte	r actinom	yceter	ncomitans							
. Aggregatibacte	r actinom Peri-impla		ncomitans No peri-imp			Odds Ratio		Odds Ratio		
					l Weight			Odds Ratio M-H, Fixed, 95%	6 CI	
Study or Subgroup	Peri-impla	antitis	No peri-imp	lantitis					6 CI	
Study or Subgroup	Peri-impla Events	antitis Total	No peri-imp Events	lantitis Total	46.9%	M-H, Fixed, 95% CI			6 CI	
Study or Subgroup Al-Ahmad 2018 Gao 2018	Peri-impla Events 15	antitis Total 94	No peri-imp Events 18	lantitis Total 73	46.9% 4.9%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25]			6 CI	
Study or Subgroup Al-Ahmad 2018 Gao 2018 Neilands 2015	Peri-impla Events 15 2	ntitis Total 94 25	No peri-imp Events 18 2	lantitis Total 73 27	46.9% 4.9% 19.4%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25] 1.09 [0.14, 8.36]			6 CI	
Study or Subgroup Al-Ahmad 2018 Gao 2018 Neilands 2015 Persson 2014	Peri-impla Events 15 2 9	antitis Total 94 25 25	No peri-imp Events 18 2 11	lantitis Total 73 27 25	46.9% 4.9% 19.4% 15.9%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25] 1.09 [0.14, 8.36] 0.72 [0.23, 2.23]			6 CI	
Study or Subgroup Al-Ahmad 2018 Gao 2018 Neilands 2015 Persson 2014 Tamura 2013	Peri-impla Events 15 2 9 12	antitis Total 94 25 25 166	No peri-imp Events 18 2 11 4	lantitis Total 73 27 25 47	46.9% 4.9% 19.4% 15.9% 12.9%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25] 1.09 [0.14, 8.36] 0.72 [0.23, 2.23] 0.84 [0.26, 2.73]			6 CI	
Study or Subgroup Al-Ahmad 2018 Gao 2018 Neilands 2015 Persson 2014 Tamura 2013 Total (95% CI)	Peri-impla Events 15 2 9 12	antitis Total 94 25 25 166 15	No peri-imp Events 18 2 11 4	lantitis Total 73 27 25 47 15	46.9% 4.9% 19.4% 15.9% 12.9%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25] 1.09 [0.14, 8.36] 0.72 [0.23, 2.23] 0.84 [0.26, 2.73] 0.57 [0.13, 2.50]			6 CI	
Study or Subgroup Al-Ahmad 2018 Gao 2018 Neilands 2015 Persson 2014 Tamura 2013 Total (95% CI) Total events	Peri-impla Events 15 2 9 12 5 43	antitis Total 94 25 25 166 15 325	No peri-imp Events 18 2 11 4 7 42	lantitis Total 73 27 25 47 15	46.9% 4.9% 19.4% 15.9% 12.9%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25] 1.09 [0.14, 8.36] 0.72 [0.23, 2.23] 0.84 [0.26, 2.73] 0.57 [0.13, 2.50]		M-H, Fixed, 95%		
Aggregatibacte Study or Subgroup Al-Ahmad 2018 Gao 2018 Neilands 2015 Persson 2014 Tamura 2013 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	Peri-impla Events 15 2 9 12 5 43 0.55, df = 4 (antitis Total 94 25 25 166 15 325 325 P = 0.97	No peri-imp Events 18 2 11 4 7 42	lantitis Total 73 27 25 47 15	46.9% 4.9% 19.4% 15.9% 12.9%	M-H, Fixed, 95% CI 0.58 [0.27, 1.25] 1.09 [0.14, 8.36] 0.72 [0.23, 2.23] 0.84 [0.26, 2.73] 0.57 [0.13, 2.50]	+ + 0.02 0.	M-H, Fixed, 95%	6 CI	5

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 periimplantitis 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 bacte-

ria, which showed high detection frequencies in periimplantitis and low frequencies in healthy implants. Therefore, these two species could be predictive markers of peri-implantitis [15].

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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*, *Parvimo-nas 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-

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 periimplantitis. 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 periimplantitis patients [11]. Oral streptococci are one of the predominant genera in all groups (peri-implantitis, healthy implants). However, a long-term study on periimplant 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. forsythia* (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.

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Ethical Considerations

Compliance with ethical guidelines

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

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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.

References

- Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. J Clin Periodontol. 2015; 42(S 16):S158-71. [DOI:10.1111/jcpe.12334] [PMID]
- [2] Fu JH, Wang HL. Breaking the wave of peri-implantitis. Periodontol 2000. 2020; 84(1):145-60. [DOI:10.1111/ prd.12335] [PMID]
- [3] Eick S, Ramseier CA, Rothenberger K, Brägger U, Buser D, Salvi GE. Microbiota at teeth and implants in partially edentulous patients. A 10-year retrospective study. Clin Oral Implants Res. 2016; 27(2):218-25. [DOI:10.1111/ clr.12588] [PMID]
- [4] Retamal-Valdes B, Formiga MC, Almeida ML, Fritoli A, Figueiredo KA, Westphal M, et al. Does subgingival bacterial colonization differ between implants and teeth? A systematic review. Braz Oral Res. 2019; 33(S 1):e064. [DOI:10.1590/1807-3107bor-2019.vol33.0064] [PMID]
- [5] Pérez-Chaparro PJ, Duarte PM, Shibli JA, Montenegro S, Lacerda Heluy S, Figueiredo LC, et al. the current weight of evidence of the microbiologic profile associated with peri-implantitis: A systematic review. J Periodontol. 2016; 87(11):1295-304. [DOI:10.1902/jop.2016.160184] [PMID]
- [6] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. [Link]

- [7] Ebadian AR, Kadkhodazadeh M, Zarnegarnia P, Dahlén G. Bacterial analysis of peri-implantitis and chronic periodontitis in Iranian subjects. Acta Med Iran. 2012; 50(7):486-92. [PMID].
- [8] Cortelli SC, Cortelli JR, Romeiro RL, Costa FO, Aquino DR, Orzechowski PR, et al. Frequency of periodontal pathogens in equivalent peri-implant and periodontal clinical statuses. Arch Oral Biol. 2013; 58(1):67-74. [DOI:10.1016/j. archoralbio.2012.09.004] [PMID]
- [9] Tamura N, Ochi M, Miyakawa H, Nakazawa F. Analysis of bacterial flora associated with peri-implantitis using obligate anaerobic culture technique and 16S rDNA gene sequence. Int J Oral Maxillofac Implants. 2013; 28(6):1521-9. [DOI:10.11607/jomi.2570] [PMID]
- [10] Persson GR, Renvert S. Cluster of bacteria associated with peri-implantitis. Clin Implant Dent Relat Res. 2014; 16(6):783-93. [DOI:10.1111/cid.12052] [PMID]
- [11] Neilands J, Wickström C, Kinnby B, Davies JR, Hall J, Friberg B, et al. Bacterial profiles and proteolytic activity in peri-implantitis versus healthy sites. Anaerobe. 2015; 35(Pt A):28-34. [DOI:10.1016/j.anaerobe.2015.04.004] [PMID]
- [12] Verdugo F, Castillo A, Castillo F, Uribarri A. Epstein-Barr virus associated peri-implantitis: A split-mouth study. Clin Oral Investig. 2015; 19(2):535-43. [DOI:10.1007/s00784-014-1250-1] [PMID]
- [13] Canullo L, Peñarrocha-Oltra D, Covani U, Botticelli D, Serino G, Penarrocha M. Clinical and microbiological findings in patients with peri-implantitis: A cross-sectional study. Clin Oral Implants Res. 2016; 27(3):376-82. [DOI:10.1111/clr.12557] [PMID]
- [14] Wang HL, Garaicoa-Pazmino C, Collins A, Ong HS, Chudri R, Giannobile WV. Protein biomarkers and microbial profiles in peri-implantitis. Clin Oral Implants Res. 2016; 27(9):1129-36. [DOI:10.1111/clr.12708] [PMID]
- [15] de Waal YC, Eijsbouts HV, Winkel EG, van Winkelhoff AJ. Microbial characteristics of peri-implantitis: A case-control study. J Periodontol. 2017; 88(2):209-217. [DOI:10.1902/ jop.2016.160231] [PMID]
- [16] Kato A, Imai K, Sato H, Ogata Y. Prevalence of Epstein-Barr virus DNA and Porphyromonas gingivalis in Japanese peri-implantitis patients. BMC Oral Health. 2017; 17(1):148. [DOI:10.1186/s12903-017-0438-6] [PMID] [PMCID]
- [17] Al-Ahmad A, Muzafferiy F, Anderson AC, Wölber JP, Ratka-Krüger P, Fretwurst T, et al. Shift of microbial composition of peri-implantitis-associated oral biofilm as revealed by 16S rRNA gene cloning. J Med Microbiol. 2018; 67(3):332-340. [DOI:10.1099/jmm.0.000682] [PMID]
- [18] Gao X, Zhou J, Sun X, Li X, Zhou Y. Diversity analysis of subgingival microbial bacteria in peri-implantitis in Uygur population. Medicine (Baltimore). 2018; 97(5):e9774. [DOI:10.1097/MD.00000000009774] [PMID] [PMCID]

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