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Review article

Periodontitis as a risk factor for peri-implantitis: Systematic review and meta-analysis of observational studies

Ferreira Sérgio Diniz[a], Martins Carolina Castro[b], Sergio Antonucci Amaral[a], Vieira Thais Ribeiral[a], Albuquerque Bárbara Nascimento[a], Cota Luís Otávio Miranda[a], Esteves Lima Rafael Paschoal[a,*], Costa Fernando Oliveira[a]

[a] Department of Dental Clinical, Oral Pathology and Oral Surgery, Federal University of Minas Gerais, Antônio Carlos Avenue, 6627, 31270-901, Pampulha, Belo Horizonte, Brazil
[b] Department of Pediatric Dentistry and Orthodontics, Federal University of Minas Gerais, Antônio Carlos Avenue, 6627, 31270-901, Pampulha, Belo Horizonte, Brazil

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ABSTRACT

Objectives: To evaluate the scientific evidence from observational studies concerning the risk of peri-implantitis development in periodontally-compromised patients.
Source: The search was carried out in Medline, via PubMed, and the Cochrane Library up to March 2018.
Study selection: Clinical studies reporting data on periodontitis and peri-implantitis, with confirmed diagnosis of peri-implantitis based on specific parameters (peri-implant probing depth and peri-implant bleeding on probing) and with evaluations of implants with at least 1 year of function were selected.
Data: Nineteen articles were included; only two did not show any association between periodontitis and peri-implantitis. Quality analysis of the articles revealed a low risk of bias in most of the studies. Meta-analyses by study design on patient data showed that patients with periodontitis had a 2.29 higher risk of peri-implantitis than patients without periodontitis (95%CI: 1.34–3.24). However, the effect estimate was OR 5.15 (95%CI: -3.35; 13.65; I2: 0%, p = 0.887) for cohort studies. A subgroup analysis showed a significant association between peri-implantitis and chronic periodontitis (patient based data: OR = 2.89, 95% CI: 1.79–4.00). Meta-analysis by study design on implant data showed that implants in individuals with periodontitis had 2.15 higher chances of having peri-implantitis (95%CI: 1.10; 3.21). However, the effect estimate was OR 3.24 (95%CI: -0.05; 6.53) for cohort studies.
Conclusions: This systematic review showed that diagnosis or history of periodontitis was associated with the occurrence of peri-implantitis. However, this association was not observed when only the cohort studies were analyzed. Results should be evaluated with caution due to heterogeneity among the included primary studies. Registration number CRD42015009518.
Clinical significance: Peri-implantitis is a prevalent condition and and present an uncertain prognosis. Determining the potential factors associated with peri-implantitis is fundamental for preventive strategies.

1. Introduction

In recent decades, oral rehabilitation of edentulous patients using dental implants has become a routine in dentistry. However, the number of those affected by peri-implant diseases has considerably increased [1].

The literature indicates that the presence or history of periodontitis (PE) is one of the most studied risk factors for peri-implantitis (PI). However, findings on this association are inconsistent [2,3]. Some studies showed an association between PI and history of PE [4–6] and others showed increased risk for PI [7] and implant loss in periodontally compromised patients (PCP) [8–10]. Patients with a history of chronic PE may also show changes in peri-implant probing depth (PPDi) and a greater marginal bone loss (BL) [2].

Similarities between the microbiota of dental implants and that of teeth support the concept that periodontal pathogens may be involved in peri-implant infections [11]. These data strengthen the hypothesis that PCP have an increased susceptibility to PI.

* Corresponding author at: Federal University of Minas Gerais, School of Dentistry, Department of Periodontology, Antônio Carlos Avenue, 6627 PO Box 359, Pampulha, 31270-901, Brazil.
E-mail address: rafaelpaschoalesteves@yahoo.com.br (R.P. Esteves Lima).

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Previous systematic reviews have assessed different studies in which the presence of PI was estimated using one of the following parameters: marginal BL [12,13]; implant loss [14]; success rate [15,16]; inflammation signs [16]; or isolated clinical parameters, including changes in PPDi or peri-implant bleeding on probing (BOPi) [2,15]. However, several systematic reviews [2,13,14,16–20] on the topic reached no consensus regarding the potential association between PE and PI. It is important to notice that, to the best of our knowledge, this is the first systematic review of observational studies on the association between PI and PE using rigid study selection criteria, that is, only studies that reported PI diagnosis through BL and PPDi were included).

2. Methods

The aim of the present study was to evaluate the scientific evidence on whether implants installed in patients with a diagnosis or history of PE (chronic and aggressive periodontitis) have a higher chance of developing PI. The PECO question was: "Do patients with a diagnosis or history of PE **(E)** that were rehabilitated with dental implants **(P)** have a higher risk of developing PI **(O)** than periodontally healthy patients (PHP) **(C)** with no history of PE?"

This systematic review was registered at PROSPERO (# CRD42015009518) and conducted according to the Guidelines on Transparent Communication of Systematic Reviews and Meta-analysis - PRISMA [21].

2.1. Search strategy

The present study searched for articles published until March 2018 without date restrictions. The databases Medline via PubMed, and Cochrane Library were searched as follows: ((peri-implant disease OR periimplant disease OR peri-implantitis [Mesh] OR periimplantitis [Mesh] OR peri-implant mucositis OR periimplant mucositis) AND (periodontal disease [Mesh] OR periodontitis [Mesh] OR chronic periodontitis [Mesh] OR aggressive periodontitis [Mesh] OR risk factors [Mesh])). The Web of Science was searched as follows: ((peri-implant disease OR periimplant disease OR peri-implantitis OR periimplantitis OR peri-implant mucositis OR periimplant mucositis) AND (periodontal disease OR periodontitis OR chronic periodontitis OR aggressive periodontitis OR risk factors)). A manual search was also performed in the list of references of the included studies in attempt to find items not found in the electronic search (Fig. 1). Grey literature was searched on the U.S National Institute for Health (U.S. Clinical Trials) using combined uniterms of “peri-implantitis” and “periodontitis” or “periodontal disease”. The references were organized using the Reference Manager® software version 12.0.3 (Reference Manager, version 12.0.3, Thomson Reuters, Philadelphia, USA).

Titles and abstracts were analyzed using the following inclusion criteria: 1) studies of patients rehabilitated with dental implants, 2) studies reporting specific PI clinical diagnostic parameters (PPDi and BOPi) in association or not with radiographic BL, 3) studies including evaluations of implants with at least 1 year of function, 4) studies

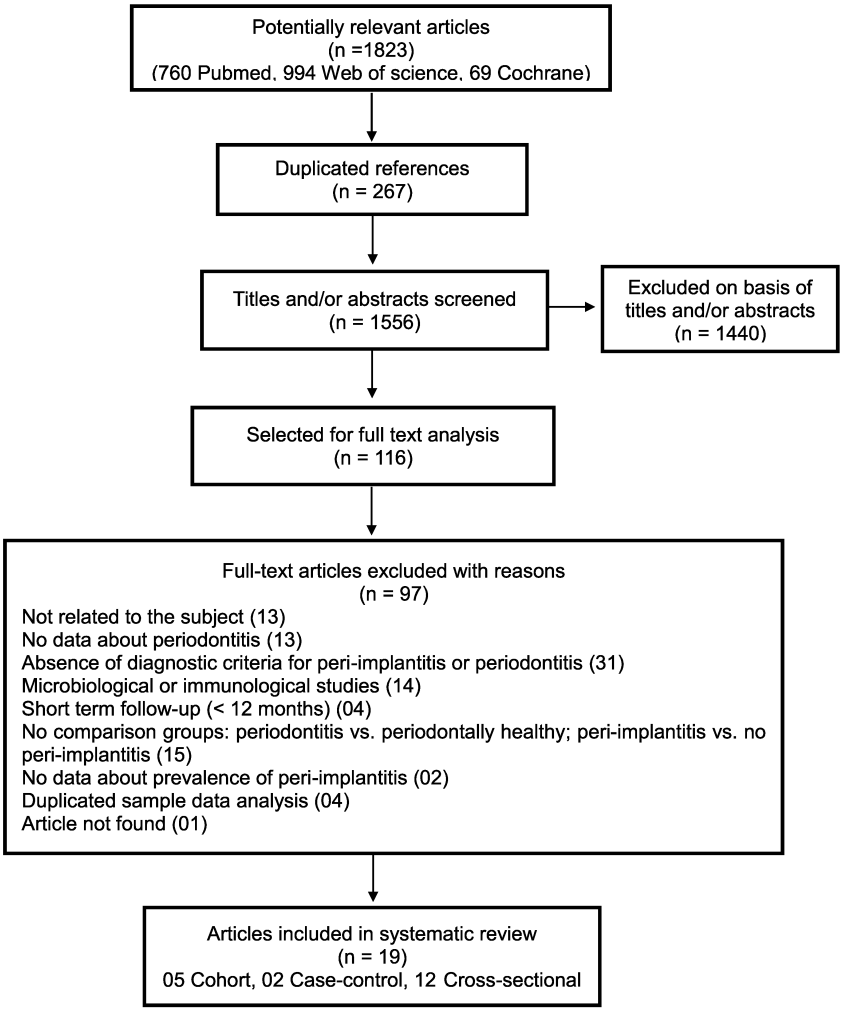

Fig. 1. Flow diagram showing the process of selecting published articles.

reporting data on PE and PI; 5) studies written in English, 6) human studies, and 7) observational, case-control, cross-sectional, and prospective or retrospective cohort studies. Exclusion criteria were: a) case reports, case series, literature reviews, systematic reviews, b) studies that were not original, editorials, book reviews, or letters to the editor, c) animal studies, d) studies from which data extraction was not possible.

Three reviewers (S.A.A., T.R.V., R.P.E.L.) were trained and calibrated to apply the inclusion and exclusion criteria (Kappa Test = 0.83). Each reviewer read all studies independently. Disagreements were resolved by discussion and consensus with a forth reviewer (S.D.F.).

The following data about each study were extracted to a spreadsheet: authors, publication year, country, length of follow-up after prosthesis installation, diagnostic criteria for PE and PI, adjustment for confounding factors, and main findings (Table 1). In order to improve the analysis, articles were grouped by study design: cohort, case-control and cross-sectional studies.

2.2. Article quality analysis

The quality of the studies was analyzed using the modified Newcastle Ottawa scale for cohort, case-control, and cross-sectional studies [22]. Each study received a score from a blind and independent evaluation by 3 researchers. Studies were ranked according to the minimum (0) and maximum scores (cohort = 9; case-control = 9; cross-sectional = 6) (Supplemental files 1, 2, and 3). Studies scoring at or above the median were considered at low risk of bias. The criteria used were: proper definition of cases, representation of cases, selection and definition of controls, comparability of cases and controls based on the study methodology, exposure assessment, method of assessing exposure of cases and controls and non-response rate.

2.3. Synthesis of statistical methods and data

Meta-analyses were conducted using Stata Statistical Software (version 15, College Station, TX: StataCorp LLC). Data consistency was determined by a sensitivity analysis. Heterogeneity was assessed by I^2 and its statistical significance [23,24]. Random effect model (REM) was used when there was statistical significant heterogeneity ($p < 0.05$), because it was assumed that REM considers the variance of the true effect size from one study to the next [24], and also used for subgroup analysis. A fixed effect model was used when there was not any statistically significant heterogeneity ($p > 0.05$). The summary measures were described as OR, 95% CIs and p-values. Data was collected as absolute frequency of individuals or implants with the presence or absence of PI by exposure (exposed to PE or not). In addition, OR and respective 95%CIs were collected for the association between PI and PE when the absolute frequency was not available in the studies.

Meta-analyses were performed on implant- or patient-based data. The primary outcome was PI (presence or absence). Subgroup analysis was conducted by study design. Moreover, meta-analyses were conducted on group of patients with chronic PE, when it was reported on the studies.

Publication bias was qualitatively evaluated by the Egger test and funnel plot when there were at least 10 studies in the meta-analysis [25,26].

3. Results

The initial electronic search found 1823 titles and abstracts (Fig. 1). Ninety-seven articles were eligible for full-text analysis. Fig. 1 summarizes the applied exclusion criteria. The present review included 19 studies: 5 cohort [10,27–30], 2 case-control [31,32], and 12 cross-sectional [33–44] studies.

These 19 studies included 4322 patients (cohort = 481; case-control = 1410; cross-sectional = 2431) and 10,075 implants (cohort = 1885, case-control = 1446; cross-sectional = 6744). Table 1 contains the main findings of the selected studies.

Diagnostic criteria for PI and PE, as well as the prevalence of PI in the selected studies are reported in Table 1. Prevalence of PI ranged from 1.66 to 71.8% in patients and from 1.04 to 68% in implants. PI in PCP was more prevalent (3.0–86.8%) than in PHP (0–39.8%).

3.1. Analysis of study quality

All selected cohort and case-control studies were classified as having low risk of bias. Only one cross-sectional study was considered having high risk of bias [36] (Supplementary tables 1, 2 and 3).

3.2. Summary of study findings

All studies, except from two studies [37,41], found an association between PE diagnosis or PE history and the occurrence of PI. PE history was significantly associated with an increased occurrence of PI in 6 studies [29,31,34,38,39,42]. The presence of PE was statistically associated with a higher risk for PI in 12 studies [10,27,28,30,32,33,35–37,40,43,44].

3.3. Meta-analysis

Fig. 2 shows subgroup meta-analyses by study design on patient data. Sixteen studies were included. Considering all studies designs, patients with PE had 2.29 higher chances of PI than patients without PE (95%CI: 1.34–3.24), showing high statistical heterogeneity (I^2: 72.8%, $p < 0.001$). Variations on the effect estimation was observed in each study design: OR = 22.90 (95%CI: 10.01—35.80; I^2: 11.6%, p = 0.287) for case-control studies, OR = 5.15 (95%CI: -3.35—13.65; I^2: 0%, p = 0.887) for cohort studies and OR = 1.74 (95%CI: 1.10—2.39; I^2: 53.7%, p = 0.017) for cross sectional studies. Funnel plot was created for patient data and visually suggested some publication bias, confirmed by the Egger test (Fig. 3, p = 0.047).

It was possible to extract data for chronic PE in three studies. This meta-analysis is presented on Fig. 4. Patients with chronic PE had 2.89 higher chances of having PI when compared to patients without PE (95%CI: 1.79; 4.00), showing statistically significant heterogeneity (I^2: 0%, p = 0.653).

Fig. 5 shows subgroup meta-analysis by study design on implant data. Five studies were included. Considering all studies designs, implants in individuals with periodontitis had 2.15 higher chances of having PI then implants without PE (95%CI: 1.10; 3.21). Considering the study designs, the effect estimates were: OR = 3.24 (95%CI: -0.05—6.53) for cohort studies and OR = 2.03 (95%CI: 0.92—3.14) for cross sectional studies. Heterogeneity was determined to be low and not significant in all models (0%, $p > 0.05$).

4. Discussion

The presence or history of PE is determined to be a potential risk factor for various complications in implant therapy, including an increased risk of marginal BL, implant loss [15,45] and the occurrence of PI, which may jeopardize the longevity of dental implants. In addition, recent systematic reviews [12,13] have found an increased risk for marginal BL and implant loss in PCP when compared to PHP. However, these reviews assessed different outcomes, including implant failure, postoperative infections and marginal bone loss, while the present review evaluated only whether the presence or history of PE influenced the occurrence and prevalence rates of patients rehabilitated with implants.

The present review found that the presence or history of PE on implant-based data was associated with PI. Meta-analysis on patient-based data also found a significant association between PI and PE.

Table 1
Studies characteristics distributed by study designs.

Author, year, Country	Sample subjects (implants) Implant type	Age in years min-max (mean ± SD)	Evaluation time range in years* (mean)	Parameters for Periodontitis diagnosis (PE form)	Peri-implantitis diagnosis	Peri-implantitis incidence/ prevalence (frequency in implants)	Adjusted for confounding factors	Findings
Cohort								
Karoussis et al. (2003) Switzerland	53 (112) ITI® Dental Implant System	NR	1-10 (NR)	Tooth loss due to PE (Chronic)	PPDi ≥ 5 mm + BOPi + BL	NR (1160%) (PCP: 28.6% PHP: 5.8%)	Smoking	PCP had significantly higher incidence of peri-implantitis (28.6% vs. 5.8%) than PHP ($p = 0.0001$)
Roos-Jansaker et al. (2006) Sweden	218 (999) Branemark System®, Nobelpharma	NR	9-14 (NR)	Teeth BL 0-30% 31-100% (PFNR)	Radiographic BL ≥ 3 threads when comparing the final exam with 1 year after placement of suprastructure, + BOP and/or pus.	7.15% PCP:9.17% PHP:2.16% (NR)	Smoking, age, keratinized mucosa, gender, general disease, visits to dental hygienist, visits to dentist.	PCP had more peri-implantitis $OR_{crude} = 7.0$ (95% CI: 1.5–39) $OR_{adj} = 4.7$ (95% CI: 1.0-22).
Gatti et al. (2008) Sweden	62 (227) Nobel Biocare®, Zimmer Dental, Straumann®, Dentsply Friadent	18-85 (No PE = 40; severe and moderate PE = 56)	NR (5)	Periodontal screening and recording index. PPD between 3.5 to 5.5 mm and/or furcation involvement degree 1 PPD > 5 mm and or furcation involvement degree 2 or more (PFNR)	BL > 2 mm, last radiographic assessment, presence of pus or another sign of infection and PPDi > 5 mm	3.57% (1.76%) Only in PCP group	NR	Patients with history of severe and moderate PE had twice more BL compared with patients without history of PE (2.6 mm vs.1.2 mm) ($p < 0.001$)
Renvert et al. (2012) Sweden	54 (234)† 41 (164)‡ Tioblast Astra Tech™, Branemark Nobel Biocare®	33-80 (NR)	2 exams (7 and 13 years)	PE treatment and teeth loss due to PE (PFNR)	BL > 2 mm, BOPi + PPDi ≥ 4 mm e Si	Years 1-7 = 56.6% years 7-13 = 18.6% years 1-13 = 71.8% (68%)	Smoking, age, gender, medical conditions, plaque scores	RR = 6.4 (95% CI: 2.5-16.3). RR = 4.1 (95% CI: 2.0-8.4) of having PI in PCP at year -1-7 and -1-13 respectively.
Swierkot et al. (2012) Germany	53 (149) Branemark System, Nobel Biocare®; Osseotite, Biomet 3i®	5-16 (8.25)	5-16 (8.25)	CAL, mild (1-2 mm), moderate (3-4 mm) and severe (≥ 5 mm) PE (Aggressive)	PPDi > 5 mm with or without BOP and annual BL > 0.2 mm.	17% (23%) 15% (PCP = 26%) 2% (PHP = 10%;	Sex, age, tobacco smoking, implant topography, implant length, prosthetic appliances, bone quality and atrophy regenerated bone and prevalence of pathogenic bacteria	Higher risk of PI for GAgP patients compared to PHP $OR_{crude} = 6$ (95% CI 1.193-30.174) ($OR_{adj} = 14.09$ (95% CI: 2.051-96.772)
Case-control								
de Araujo Nobre et al. (2014) Portugal	1350 (1350) 270 cases; 1080 controls Nobel Biocare®	28-88 (55.8 ± 102)	NR (NR)	PE history collected from patient's records and radiographs. Recorded as present and absent (PFNR)	PPDi ≥ 5 mm, BOPi, vertical BL and CAL ≥ 2 mm	PCP 39.9% PHP 6.97% (NR)	Smoking, systemic conditions	PE history ($OR_{crude} = 25$ (95% CI 17.82-35.32) was associated to a higher probability of having PI.
Wang et al. (2017) China	60 (96) Straumann®	NR (49.87 ± 9.03)	NR (7.69)	1999 International Workshop (Chronic)	PPDi ≥ 5 mm, suppuration and/or BOPi + bone loss > 2 mm	1.66% (1.04%)	NR	PI more prevalent in individuals with PE
Cross-sectional								
Ferreira et al. (2006) Brasil	212 (578) Nobel Biocare®, Biomet 3i®, Intralok®	NR (NR)	1-5 (NR)	Presence of 4 or more teeth with one or more sites with PPD ≥ 4 mm and CAL ≥ 3 mm at the same site (Chronic)	PPDi ≥ 5 mm BOPi and/or pus + radiographic BL	8.9% (744%)	Diabetes, oral hygiene. Non-smokers.	PCP tended to have more implants with PI $OR_{adj} = 3.1$ (95% CI: 1.1-3.5)
Simonis et al. (2010) France	55 (131) Straumann®	29-88 (687 ± 12)	10-16 (NR)	NR (PFNR)	PPDi ≥ 5 mm BOPi/pus BL ≥ 2.5 mm or BL ≥ 3 threads	PCP 37.93% PHP 10.53% (1694%)	Smoking	Patients with PE history were at a higher risk of PI $OR_{crude} = 5.1$ (95% CI 1.92-14,06)

(*continued on next page*)

Table 1 (*continued*)

Author, year, Country	Sample subjects (implants) Implant type	Age in years min-max (mean ± SD)	Evaluation time range in years* (mean)	Parameters for Periodontitis diagnosis (PE form)	Peri-implantitis diagnosis	Peri-implantitis incidence/ prevalence (frequency in implants)	Adjusted for confounding factors	Findings
Rinke et al. (2011) Germany	89 (NR) Ankylos® Dentslpy Friadent	NR (518 ± 103)	2-11.3 (5.6 ± 2.0)	Having a "PE history" if they had received active periodontal therapy (SRP or surgical therapy) within 5 years before implant placement (Chronic)	PPDi ≥ 5 mm, BOPi/pus, radiographic BL	11.2% PCP smokers 53.3% PCP non smokers 2.8% PHP 0% (NR)	Smoking, compliance to regular prophylaxis, gender, follow-up period.	Smokers patients with PE had more chance to have PI OR 31.58 (95% CI 5.13-194.25).
Cho-Yan Lee et al. (2012) Australia	60 (117) Straumann®	PCP (65.35) PHP (6648)	PCP group 5.04-14.40 (7.99); PHP group 5.00-13.46 (8.20)	CAL, mild (1-2 mm), moderate (3-4 mm) and severe (≥ 5 mm) PE (Chronic)	PPDi > 5 mm, BOPi	PCP 6.7% (26.7%) PHP 16.7% (13.1%)	NR	Increased risk OR 163 (95% CI 0,41-6,47) of having PI in PCP
Marrone et al. (2013) Belgium	103 (266) SteriOss™ Nobel Biocare®, Straumann®, Nobel Replace®, Branemark System®, Frialit 2®, Ankylos®, IMZ®, Screw Vent	26-86 (62 ± 134)	NR (8.5 ± 3.2)	PE history: BOP < 25%, PPD < 5 mm. Active PE: BOP > 25% and PPD ≥ 5 mm (PFNR)	BL > 2 mm, BOPi + PPDi > 5 mm.	Overall sample 37% (23%), PE history 39.3%, Active PE 57.1% PHP 33.3%	Smoking, compliance to SPT and diabetes	Patients with active PE had positive correlation with PI OR 1.98 (95% CI 0.525-7.531). No association between PE history and PI OR = 0.98 (95% CI 0.338-2.388)
Renvert et al., (2014) Sweden	270 (NR) Branemark® Nobel Biocare, Astra Tech®, Straumann®, ImplaMed®, others	Patients with PI (68.2) Patients with implant health/ mucositis (44.7)	5 (NR)	NR (PFNR)	BL ≥ 2 mm, increased PPDi ≥ 4 mm and pus	PCP 86.8% PHP 39.8% (NR)	Smoking habits and history of systemic diseases	PE history associated to a higher risk of having PI. OR_{crude} = 10.8 (95% CI: 5.8-20.0) OR_{adj} = 4.5 (95% CI 2.1-9.7)
Kostantinidis et al. (2015) Germany	186 (597) Dentsply Friadent®, Straumann®, Nobel Biocare®, Wi.Tal®, IMZ®	21-9 (63)	1-16.5 (5.5 ± 3.8)	History of periodontal disease, tooth loss due to PE (PFNR)	BOPi, PPDi > 5 mm, BL > 2 mm	12.9% (6.2%) e 13.3% ≥ 5 years of function.	Smoking and diabetes	Association between PE history (p = 0.0322) and tooth loss due PE OR = 1.063 (95% CI 1.006-1.123) and PI.
Daubert et al. (2015) United States	96 (225) Biomet 3i®, Straumann®, Nobel Biocare®, Branemark System®, Centerpulse®, Astra Tech®, Sulzer Dental®, Steri-Oss®.	31-86 (67.6 ± 10.6)	8.9-14.8 (10.9 ± 1.5)	CAL, mild (1-2 mm), moderate (3-4 mm) and severe (≥ 5 mm) PE (Chronic)	BOPi, Si, 2 mm of detectable BL and PPDi ≥ 4 mm	26% (16%)	Smoking, regular maintenance and diabetes	The frequency of PI in implants was statistically significant in mild PE, RR = 3 (p = 0.05), In moderate and severe PE (RR = 2.2 and 2.1 respectively; p > 0.05) association was not statistically significant. The prevalence of PI was significantly associated with severe PE at follow-up RR = 7.3 (95% CI 3.0-17.3)
Canullo et al. (2016) Spain	534 (1507) Straumann®, Phibo Dental Solutions®, Mozo-Gran®, Sweden & Martina®, Klockner®, Dentsply Friadent®, Nobel Biocare®, AstraTech®, Biomet 3i®	PI: 30-85 (59.7 ± 10.3) Without PI: 24-87 (55.1 ± 11.5)	PI: NR (5.9 ± 3.3) Without PI: NR (5.0 ± 3.8)	> 30% teeth with BOP, PD ≥ 4 mm + radiographic image of bone loss (PFNR)	Radiographic bone loss > 3 mm, PPDi ≥ 4 mm + BOPi and/or suppuration	10.3% (7.3%)	NR	No differences between the non peri-implantitis and the peri-implantitis subjects in terms of periodontitis. OR = 1.129 (95% CI: 0.452-2.816)

(*continued on next page*)

Table 1 (*continued*)

Author, year, Country	Sample subjects (implants) Implant type	Age in years min-max (mean ± SD)	Evaluation time range in years* (mean)	Parameters for Periodontitis diagnosis (PE form)	Peri-implantitis diagnosis	Peri-implantitis incidence/ prevalence (frequency in implants)	Adjusted for confounding factors	Findings
Dalago et al. (2017) Brazil	183 (916) Implacil De Bortoli	27-89 (59.30)	1-14 (5.64)	PPD > 4 mm CAL ≥ 2 mm, BL (PFNR)	PPDi > 5 mm, at least one point BOPi/pus and BL > 2 mm	16.4% (7.3%)	System of retention, artificial gingiva, type of prosthesis, and periodic maintenance care, heart disorders, hypertension, smoking habits, alcoholism, liver disorders, hepatitis, gastrointestinal disease, diabetes mellitus I and II, hyperthyroidism or hypothyroidism, radiation therapy, chemotherapy, menopause, osteoporosis, active and history of periodontal disease and bruxism	Positive relationship between PI and PE history OR = 2.2 (95% CI 1.2–4.1).
Seki et al. (2017) Japan	55 (130) Novel Biocare®, AstraTech®, Biomet 3i®	NR (63.53 ± 10.51)	NR (6.6)	AAP classification of Periodontal Diseases (1999) (Chronic)	PPDi ≥ 6 mm, suppuration, BOPi + bone loss ≥ 25% of the implant length	10.9% (10.8%) PCP 162% PHP 0%	NR	PI more prevalent in individuals with history of PE
Derks et al. (2016) Sweden	588 (2277) Straumann®, Nobel Biocare, Astra Tech®, Biomet 3i®, LifeCore, Cresco Ti, XiVE.	62.3 ± 9.3	9 (8,9 ± 0.8)	≥ 2 teeth BOP/Pus and CAL ≥ 2 mm PPD ≥ 6 mm (PFNR)	BOPi/Pus and BL > 0,5 mm (initial) > 2 mm (moderate/severe)	45% (NR)	Smoking; Diabetes; Jaw of treatment; Position; Installation procedure; Bone augmentation procedure; Retention of supraconstruction; Design of supraconstruction Implant length, diameter and brand.	Significantly higher OR = 4.1 (95% CI 1.88-8.86).for moderate/severe PI were found for PCP

PI, peri-implantitis; BL, bone Loss; PPD, pocket probing depth; PPDi, peri-implant probing depth; BOP, bleeding on probing; BOPi, peri-implant bleeding on probing; CAL, clinical attachment loss; SCR, scaling and root planning; PFNR, periodontitis form not reported; NR, not reported; NS, not statistically significant; PCP, periodontally compromised patients; PHP, periodontally healthy patients; HP history of periodontitis; SH, smoking habits, SPT supportive periodontal therapy.

*After placement of suprastructure; †1-7 years / ‡1–13 years.

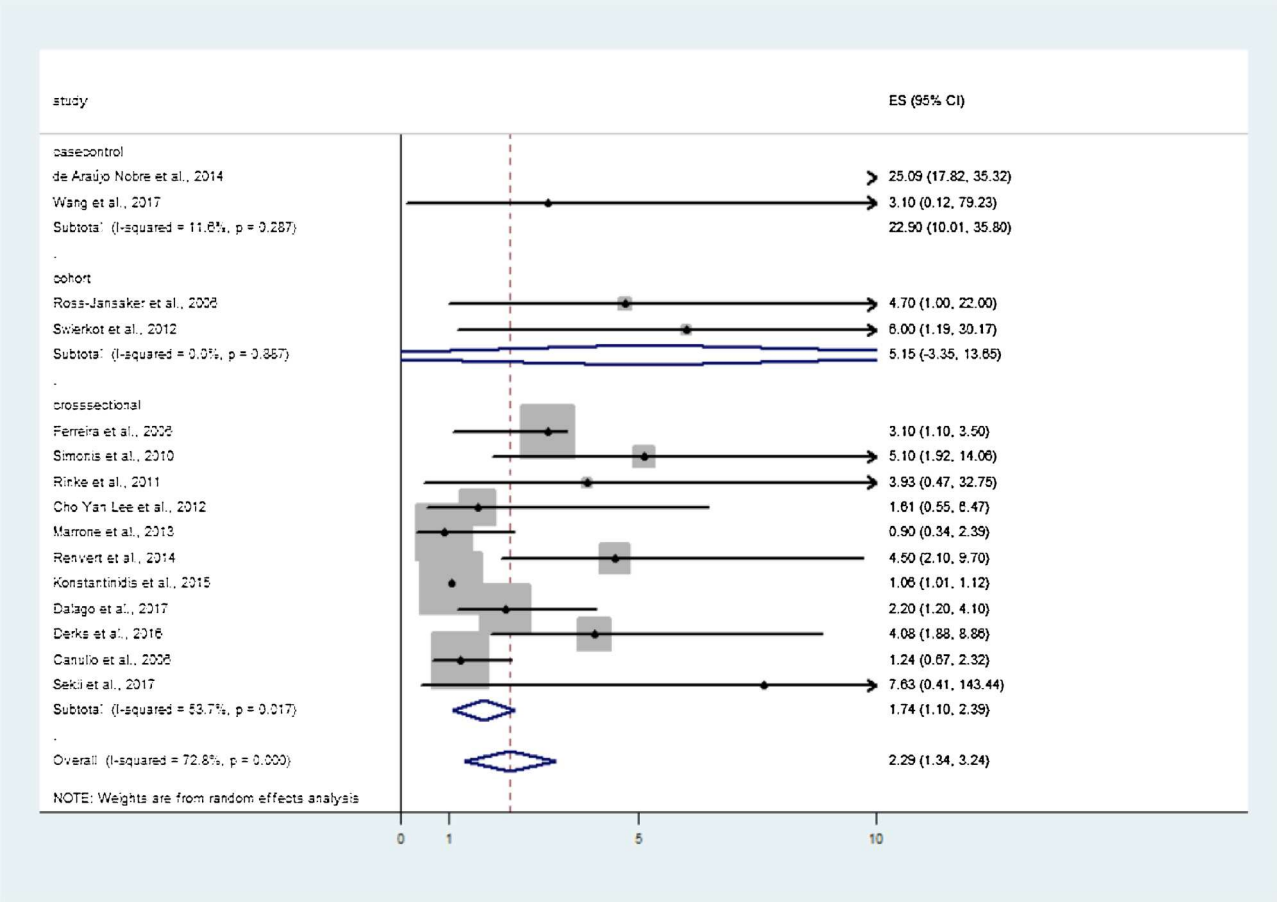

Fig. 2. Subgroup meta-analysis by study design for patient data. OR > 1 shows increased chance of PI for patients with PE. Random effect model.

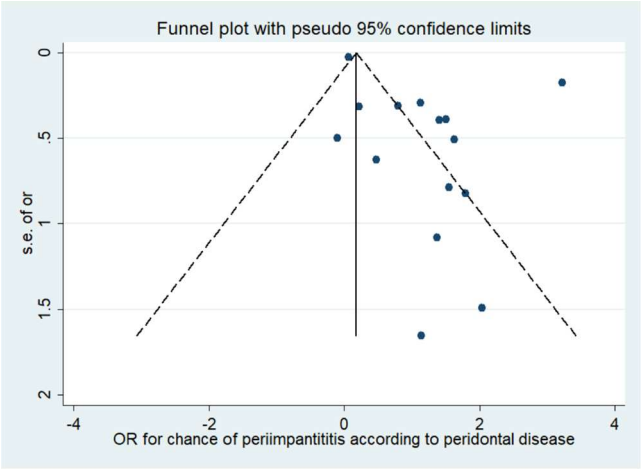

Fig. 3. Funnel plot for patient design. Egger test showed statistically significant publication bias (p = 0.047).

However, this association was not demonstrated in the meta-analysis of cohort studies for patient-based or implant-based data. These results from cohort studies are divergent from those on previous systematic reviews [2,6,16,18,45] that found an increased risk for PI in patients who had lost teeth due to PE. However, comparisons between the present systematic review and others in the literature are difficult due to methodological differences, especially as regards the assessment of the primary outcome (PI). One paper [2] found limited evidence of a greater predisposition to PI in patients with chronic PE. However, both reviews [2,18] included only two studies each, which could limit their conclusions. Another paper [16] reported an increased prevalence of PI in patients with history of PE. However, authors considered PI as implant failure and used marginal BL as a measure. Two papers [2,6] evaluated only prospective studies and reported that PCP were at a higher risk for developing PI than were PHP. Therefore, using stricter criteria for selecting articles can improve the homogeneity of those included in the review. Despite the fact that cross-sectional and case-controls studies present evidence with a lower level when compared to other study designs, they should not be neglected. Most of retrospective studies included in the present review had low risk of bias and overall good quality. Moreover, retrospective studies can identify associations. Finding associations with PI is as important as determining causal relationships.

A limitation of the present meta-analysis is the inclusion of crude OR. The results should be interpreted with caution as they can have the effect of confounding variables. A systematic review of 9 studies [14] evaluated the increased risk of PI in well-maintained PCP. Six of the 9 evaluated studies presented a high risk of bias and only 3 evaluated PI as the primary outcome. In addition, the reviews included studies that did not clearly reported the diagnostic criteria for PI, which may result in some overestimation of the disease, since implants may experience BL or failure from causes not related to PI [46,47]. Thus, these systematic reviews provided limited data about the risk for PI in PCP, because the relationship between PE and PI cannot be measured using only the variables cited above, since implant failure or BL do not indicate an association between PE and PI events. Unlike other previous reviews, a review [45] reported that PCP receiving regular maintenance therapy had no significant increase in the frequency of PI.

It was possible to perform a subgroup analysis for chronic PE using

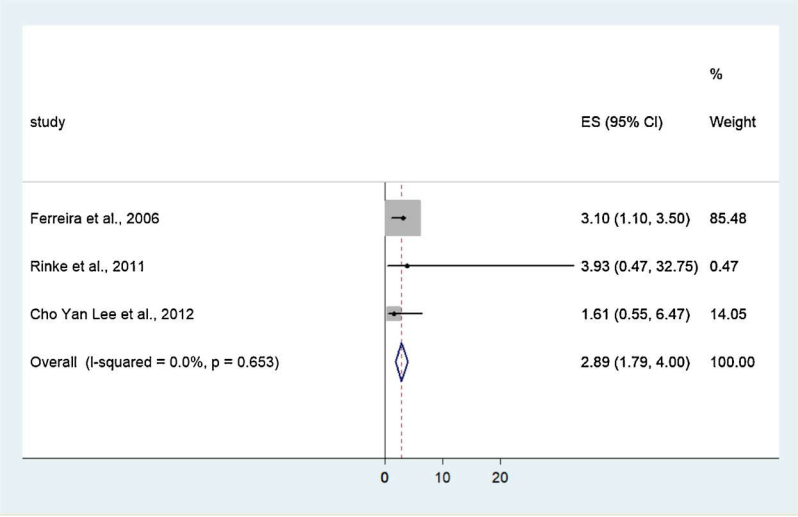

Fig. 4. Meta-analysis of cross-sectional studies for patients with chronic PE. OR > 1 shows increased chance of PI for patients with chronic PE. Fixed effect model.

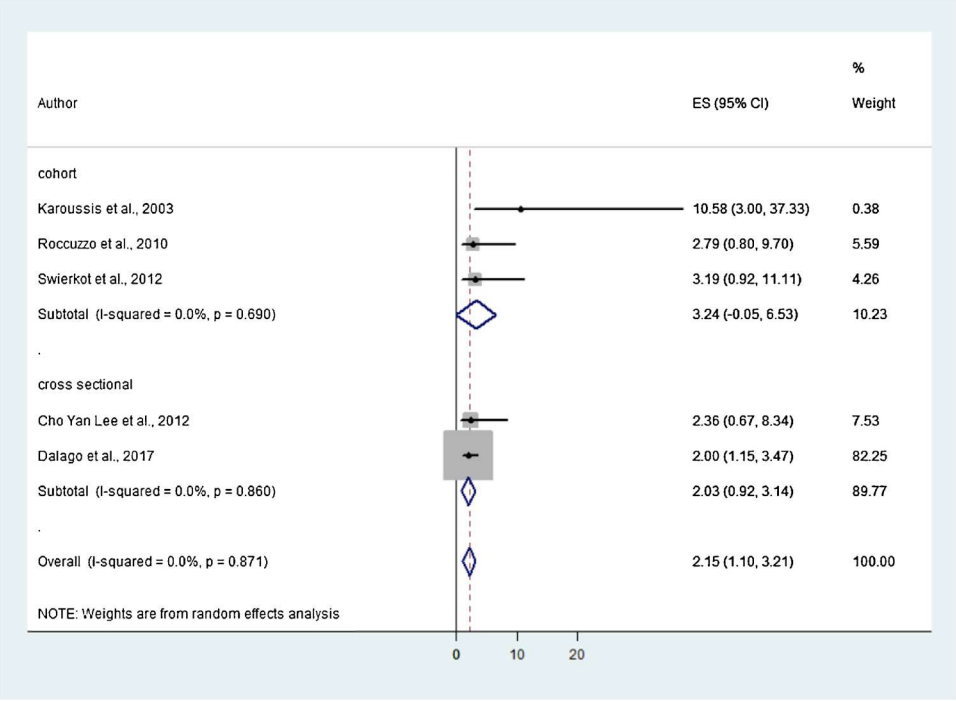

Fig. 5. Subgroup meta-analysis by study design for implant data. OR > 1 shows increased chance of PI for patients with PE. Random effect model.

three studies [33,35,36]. Any significant association between chronic PE and PI was demonstrated. Since the analysis was performed on crude OR, interpretation of data limited. The other studies included in the meta-analysis did not specify PE form or presented mixed data. For this reason, it was not possible to run subgroup analysis for the remaining of the forest plots. This is a limitation of the present systematic review as it was not possible to identify PE form in many analyses. Moreover, only one study presented data on aggressive PE [10], therefore, precluding a meta-analysis on aggressive PE.

Diagnostic criteria are a crucial factor in evaluating PI and can directly influence the prevalence rates. Unlike previous systematic reviews, the present one attempted to reduce bias related to PI diagnosis by including only studies that reported PI diagnosed through specific clinical criteria associated or not with radiographic findings. According to the consensus of the 8th European Workshop on Periodontology, different criteria are used to define PI cases, making studies comparison difficult. PI can be defined as peri-implant inflammatory changes accompanied by BOPi and increased PPDi, always associated with BL [48]. Therefore, the parameters of BOPi, PPDi, and BL can be considered the gold standards indispensable to the accurate diagnosis. In the present review, three studies [28,36,43] did not use all three of these parameters to diagnose PI, and not doing so could affect the results by increasing diagnostic error, usually disease overestimation.

PE diagnostic criteria can also affect the accurate evaluation of the association between PE and PI. The lack of uniformity in the criteria to define the form, severity, and extent of PE hinders the comparison among studies. In addition, studies included assessed PE history in various ways, including dental loss [27], prior PE treatment [30,35], and analysis of dental records [31]. Thus, PE history may carry strong biases and patients exhibiting "active" PE may have a greater chance of

developing PI than patients who undergo regular periodontal maintenance therapy. The implications of these issues in the evaluation of PE can act as confounding factors for the outcome of interest (PI). Studies comparing patients with PE history to those with "active" disease are needed to identify any differences in the occurrence of PI under these distinct circumstances.

Research on risk factors for peri-implant disease is in early stages and studies using different designs are needed [49]. First, cross-sectional and case-control studies, using uni and multivariate analysis with consequent identification of confounding factors, should be implemented followed by cohort studies, ideally using various and different populations. The present review identified 14 cross-sectional and case-control studies and 5 cohort studies, indicating the need for more cohort studies using appropriate methodologies to contribute to more consistent conclusions.

Studies included in crude meta-analyses for implant-based data found a high risk for PE. The crude analysis should be interpreted with caution, as there may be the effect of the confounding variables such as smoking that is an important risk factor for PE. Other limitation is the analysis on implant-based data that can be clustered within patients, and therefore can increase the risk for type-I error in the summary effect measure.

Considering only the adjusted analysis for patient-based data, there was a high statistical heterogeneity (I^2: 72.8%, $p < 0.001$) that should be interpreted with caution [24]. Additionally, the funnel plot and Egger test suggested publication bias. Confronting with individual results of the included studies, PCP had a greater chance of having PI in the majority of studies what reinforces the association between PE and PI [10,27–31,33–36,38–40,42,43].

The present review may present some language bias [50] since only English studies were included although there were no restrictions regarding language during studies search. The majority of the studies reported a positive significant association between PE and PI, and only two did not find any significant association. This can represent a publication bias that is the non-publication of a research depending on the nature and direction of the results [50]. To overcome this limitation, grey literature was searched and manual search was also performed. The systematic review was limited by the lack of subgroups analysis to distinguish studies with PE history and PE presence. Moreover, the lack of a clear definition of the time interval for periodontal maintenance visits and the procedures that were performed makes the comparison between data impossible.

To provide more consistent data on PE as a risk factor for PI, future prospective studies must clearly define the diagnostic criteria for PI definition and use gold-standard parameters to define PI cases, as well as control for confounding factors. Using only PPDi or BOPi without associating radiographic findings can cause diagnostic error due to differences in implant positions in relation to the alveolar bone crest (above or at crest level) make identification of BL due to PI less precise. Furthermore, some types of prosthetic connections (e.g., the Morse taper or the platform switch) may cause underestimation of PPDi values because they prevent correct probing. Therefore, in these cases, radiographic examination to identify BL is mandatory.

It is important to emphasize that future studies should use clear and uniform criteria to define PE diagnosis. Prospective studies should clearly define PE history and accurately assess the reason for dental loss and any periodontal treatment. In addition, when defining individuals without PE, studies should include only patients with no history of PE.

Individuals with active periodontitis should undergo effective periodontal therapy prior to implant rehabilitation, reducing the risk of developing peri-implantitis. In addition, individuals with a history of periodontitis, rehabilitated with implants, should remain in a rigorous maintenance program due to their susceptibility.

5. Conclusions

There is evidence that patients with diagnosis or history of PE were associated with the occurrence of PI. However, this association was not observed when cohort studies were analyzed. Better-designed prospective studies are needed to confirm these findings.

Declarations of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdent.2018.09.010.

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