Prevalence of Peri-implantitis in Medically Compromised Patients and Smokers: A Systematic Review

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Purpose: *To verify whether the diversity of systemic medical conditions and smoking act as biologic associated factors for peri-implantitis.* ***Materials and Methods:*** *The PICO question was: "In patients with osseointegrated dental implants, does the presence of smoking habits or a compromised medical status influence the occurrence of peri-implantitis compared with the presence of good general health?" Smoking and systemic conditions such as type 2 diabetes mellitus, cardiovascular diseases, rheumatoid arthritis, lung diseases, obesity, cancer, deep depression, and osteoporosis were screened. Selection criteria included at least 10 patients per condition, 1 year of follow-up after implant loading, and strict cutoff levels (probing pocket depth [PPD], bleeding on probing [BOP] and/or pus, marginal bone loss) to define peri-implantitis.* ***Results:*** *From the 1,136 records initially retrieved, 57 were selected after title and abstract analyses. However, only six papers were considered for qualitative evaluation. No randomized controlled clinical trial was found. Smoking was associated with peri-implantitis in only one out of four studies. Poorly controlled type 2 diabetes accentuated only PPD and radiographic marginal bone level prevalence rates in peri-implant patients (one study). Cardiovascular disease was considered a risk (one out of two studies). The chance of peri-implant patients harboring the Epstein-Barr virus was threefold in one report. No associations were found for rheumatoid arthritis.* ***Conclusion:*** *Data from existing studies point to smoking and diabetes as biologic associated factors for peri-implantitis. However, the body of evidence is still immature, and the specific contribution of general health problems to peri-implantitis requires additional robust epidemiologic and clinical investigations.* Int J Oral Maxillofac Implants 2016;31:111–118. doi:10.11607/jomi.4149

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Although over the years it has become more clear that several professional and patient factors might be responsible for peri-implantitis, with the ultimate theories pointing to probable candidates such as the lack of three-dimensional (3D) implant placement, bad prosthesis design that prevents proper oral hygiene measures, and excess of luting cement,[1,2] there are no common diagnostic criteria; therefore, prevalence figures are still controversial.[3]

For dental practitioners, understanding this impact on peri-implant soft and hard tissues can be even more complicated when medical diseases are added to the equation. The timing of onset, rate of progression, and severity of peri-implantitis in an individual might also be determined by other factors such as systemic risk factors in the host. For example, a review demonstrated that type 2 diabetes mellitus (type 2 DB), which has been considered a contraindication for dental implant placement, generated 0% to 14.3% implant failure

rates (17 studies), but most studies did not report the HbA1c levels.[4]

Also, the effects of smoking cannot be neglected since nicotine depresses the immune system[5] and has a role in osteoclastogenesis.[6] One retrospective study verified that smoking had more impact on implant failure for patients using smooth-surface implants[7] (hazard ratio: 3.1), while one systematic review identified that smoking had an impact on loose trabecular bone.[8] However, a recent review did not demonstrate the impact of smoking on implant failure rates for patients with sinus floor augmentation when only prospective data were considered.[9]

The aim of this review was to assess in a systematic way different systemic conditions as well as smoking as possible risk factors for peri-implantitis.

MATERIALS AND METHODS

This systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10]

Focused Question

In patients with osseointegrated dental implants, does the presence of smoking habits or a compromised medical status influence the occurrence of peri-implantitis compared with the presence of good general health?

- Population: Patients with osseointegrated dental implants
- Intervention or Exposure: Patients who smoke or with compromised medical status
- Comparison: Patients in good general health
- Outcome: Occurrence of peri-implantitis

Search Strategy

An electronic literature search (PubMed) restricted to the English language was conducted until June 4, 2014. No filters were used in order to retrieve the highest number of articles possible.

The following search strategy was performed: (diseases OR conditions OR pathologies OR cardiovascular OR diabetes OR obesity OR metabolic syndrome OR rheumatoid arthritis OR smoking) AND (peri-implantitis OR peri-implant inflammation OR peri-implant disease OR peri-implant infection OR peri-implant bone loss).

Study Selection

Inclusion Criteria. Prospective and retrospective cohort studies, case-control studies, cross-sectional surveys, and case series, which include cases and controls and split-mouth design, were included in this systematic review.

The additional inclusion criteria for study selection were:

- Human trials with a minimum of 10 subjects and a mean time of functional loading of the implants of at least 1 year
- Studies published in English
- Systemic conditions or diseases such as type 2 diabetes mellitus, also known as hyperglycemia, where blood sugar levels are raised. The body does not use insulin properly (resistance) to control glucose levels (American Diabetes Association: http://www.diabetes.org/diabetes-basics/type-2/facts-about-type-2.html)
- Cardiovascular diseases: a collective term that involves heart and blood vessel diseases, such as hearth valve problems, arrhythmia, heart attack, and stroke (http://www.heart.org/HEARTORG/Caregiver/Resources/WhatisCardiovascularDisease/What-is-Cardiovascular-Disease_UCM_301852_Article.jsp)
- Rheumatoid arthritis: autoimmune disease that causes pain, stiffness, swelling, and limited motion and function of joints (http://www.rheumatology.org/practice/clinical/patients/diseases_and_conditions/ra.asp)
- Lung diseases: a collective term for 40 diseases, including asthma, pneumonia, and chronic obstructive pulmonary disease (http://www.lung.org/lung-disease/list.html)
- Obesity: abnormal or excessive fat accumulation that represents a risk to health (http://www.who.int/topics/obesity/en/)
- Cancer: general name for a group of more than 100 diseases meaning cell growth out of control (http://www.cancer.org/cancer/cancerbasics/what-is-cancer)
- Deep depression
- Osteoporosis, osteopenia: excessive loss of bone and/or body impairment to make substantial bone quantities, leading to weakness and fracture (http://nof.org/articles/7)
- Epstein-Barr virus: active herpesvirus infection that can boost immunosuppression and allows for destructive bacterial overgrowth[11]
- Smoking

Outcome Measures

The presence of peri-implantitis was determined by adopting the definition according to the guidelines from the 7th and the 8th European Workshops on Periodontology[12,13]: evidence of bleeding on probing and/or suppuration with or without deepening

of peri-implant pockets, but with concomitant ≥ 2 mm radiographic bone loss from the expected marginal bone at implant placement.

Disagreement between reviewers (AT, PHOR) was resolved by a third observer (LC). The kappa agreement was calculated.

Quality and Risk of Bias Assessment

Quality assessment of selected studies was performed using the Cochrane tool (for randomized trials)[14] and/or the NewCastle-Ottawa (NO) scale quality assessment for cohort studies.[15] The NO scale is composed of three sections: selection (four items), comparability (two items), and outcome (three items). A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

Data Extraction and Analysis

Meta-analyses were performed from studies on smoking, type 2 diabetes, and cardiovascular disease (odds ratio with random effects model). Three reviewers (AT, PHOR, LC) extracted pertinent information from the selected manuscripts and entered it into a Microsoft Excel worksheet independently from each other. Due to the heterogeneity of study designs, outcome variables, and reporting, no meta-analysis was performed.

Therefore, it was decided to tabulate the data where appropriate and report the findings in a narrative manner. The following information was sought: study design, systemic conditions, smoking habits, number of patients and implants, disease definition, and outcomes on peri-implantitis.

RESULTS

Search Results

Initially, 1,136 references were electronically retrieved. After title and abstract analyses, 57 papers were considered for detailed screening. Then, papers related to laboratorial, systematic reviews, and clinical studies (cases, reports, cohorts) having less than 10 patients per systemic condition were excluded. Examples of other identified (but not included) conditions due to the aforementioned reasons included lung disease, osteoporosis, cancer, depression, osteopenia, hepatitis, Papillon-Lefevre syndrome, human immunodeficiency virus (HIV), immunosuppression conditions, prescription therapy, and chemotherapy. Also, additional exclusion criteria such as no definition/reporting on bone loss and/or lack of cutoff points to characterize peri-implantitis (eg, progressive bone loss) were applied.

No randomized controlled clinical trials or controlled clinical studies were found. However, six articles[11,16–20] were considered for qualitative synthesis since they presented soft (probing pocket depth [PPD], bleeding on probing [BOP], suppuration) and hard (marginal implant bone loss) well-defined tissue parameters for peri-implantitis.

The kappa agreement between reviewers was 0.79.

Patient Demographics

The studies were published between 2006 and 2014. Follow-up periods after implant loading ranged from 1 to 14 years. Investigated patient populations were located in Belgium, Italy, Norway, Spain, and mostly in Sweden. Except for patients recruited from local private centers,[17] all patients received implant and prosthodontic treatments performed at university clinics or hospitals.

Implant Demographics

The time period of implant placement to function ranged from 1 year[11] to 14 years.[16] Two studies reported 8.5 years of observation,[18,19] and two other studies reported means of 2 years[17] and 11.8 years.[20] Two studies did not report details on implant surface.[11,18] Overall, machined/turned, moderately rough, and rough surfaces were reported in four studies.[16,17,19,20] Three studies presented data on four implant brands or more,[18–20] while two studies reported on one brand each,[16,17] and just one study did not report on implant surface and brand.[11] The identified implant brands were as follows: Brånemark (Nobel Biocare),[16–20] Astra Tech (Dentsply),[18,20] Straumann,[18–20] Biomet 3i,[18] Frialit-2 (Dentsply),[19] Ankylos (Dentsply),[19] Steri-Oss (Nobel Biocare),[19] Screw-Vent (Zimmer Dental),[19] IMZ,[19] ImplaMed (Sterngold).[20]

Two studies did not present the absolute numbers of implants placed,[17,20] while four studies[11,16,18,19] reported the following implant/patient ratios, respectively: (999/218), (354/109), (266/103), and (46/23).

Definition of Peri-implantitis: Cutoff Points

Three parameters were used to define peri-implantitis: PPD, BOP and/or pus, and radiographic marginal bone levels (BL). One article[20] reported BOP 60 seconds after measurement of PPD and the other 15 seconds later.[17] For BL, three articles[11,18,19] used 2 mm and even 0.4 mm as threshold values. Also, three articles[11,16,17] reported on the number of exposed threads (≥ 3 or ≥ 4 threads) since the implant thread pitch was known. Different radiographic techniques (eg, panoramic, periapical, long-cone parallel) and measurement starting points (eg, implant-abutment junction, most coronal implant portion) were used to provide bone loss values. Finally, two articles[18,19] provided different definitions

Table 1 Systemic Conditions as Biologic Factors for Peri-implantitis: Outcomes and Criteria

Study	Study design	Systemic condition(s)	No. of patients	No. of implants
Roos-Jansåker et al[16] (2006)	Retrospective, cross-sectional study 9–14 y follow-up	Smoking	218 patients: Ne-S: 80; Ex-S: 81; S: 57	999 implants: Ne-S: 301; Ex-S: 383; S: 303
Venza et al[17] (2010)	Case control cross-sectional study	Type 2 DB C-P P-IM	170 patients: No DB; C-P: 25; P-IM: 15	NR
			Type 2 DB (good glycemic control): C-P: 27; P-IM: 18	NR
			Type 2 DB (poor glycemic control): C-P: 30; P-IM: 20	NR
			Control: 35	NR
Koldsland et al[18] (2011)	Cross-sectional study 8.4 y	CVD Smoking	109 patients CVD: 17; Ex-S: 41; S: 18; Ne-S: 50	354 implants: NR
Marrone et al[19] (2013)	Cross-sectional study At least 5 y	Smoking	103 patients: S: 20; NS: 83	NR
Renvert et al[20] (2014)	Cross-sectional retrospective study	Comorbid conditions for the risk of peri-implantitis	164 patients with peri-implantitis: 98 mucositis/healthy; S: 22; NS: 24	NR
			172 patients with peri-implantitis: CVD: 47; RA: 11; Type 2 DB: 10	NR
Verdugo et al[11] (2015)	Case control, split-mouth study At least 1 year	EB virus	23	23: peri-implantitis 23: healthy

DB = Diabetes mellitus; CAL = clinical attachment level; C-P = chronic periodontitis; P-IM = peri-implantitis; EB = Epstein-Barr; PPD, PD = pocket probing depth (mm); BOP = bleeding on probing; BL = bone loss; mPI = modified Plaque Index; mGI = modified Gingival Index; RA = rheumatoid arthritis; CVD = cardiovascular disease; S = smokers; Ne-S = never smoker; Ex-S = ex-smoker; NS = nonsmoker; NR = not reported; OR =odds ratio; RR = relative risk.

for peri-implantitis based on the aforementioned parameters.

Description of Studies

No randomized controlled clinical trials were found. Only prospective and/or retrospective, cross-sectional studies were identified,[11,16–20] with one split-mouth design reported.[11] Overall, the accounted systemic conditions were: smoking (four articles[16,18,19,20]), type 2 diabetes (two articles[17,20]), cardiovascular diseases (two articles[18,20]), rheumatoid arthritis (one article[11]), and Epstein-Barr virus (one article[11]). Cardiovascular disease/rheumatoid/smoking (one article[19]), and cardiovascular disease/smoking (one article[18]) were also collectively reported. Details on study design, number of patients, number of implants, outcomes, and criteria used to define peri-implantitis can be found in Table 1.

Smoking

Smoking was the most prevalent condition identified in this systematic review. In a large population (218 patients, 999 implants), Roos-Jansåker et al[16] verified after logistic regression that 47 smoker patients (303 implants) presented a greater chance (univariate analysis: OR: 7.7; [95% CI: 2.5–14, $P < .001$]; multivariate analysis: OR: 4.6 [95% CI: 1.1–19]) for peri-implantitis than patients who had never smoked (OR: 1.0 for both) or ex-smoker patients (OR: 0.52 and 0.42, respectively). On the other hand, another two cross-sectional studies[18,19] (109 patients, 8.4 years; 103 patients; at least 5 years, respectively) still using a multilevel logistic regression approach did not verify the same outcome probably due to the small proportion of smokers present (18 smokers vs 91 non/ex-smokers[18]; 20 smokers vs 83 nonsmokers[19]). Also, the second largest retrospective study[20] (172 individuals) did not verify the same association after bivariate logistic regression (unadjusted OR: 2.5 [95% CI: 1.4–4.2]) because a significantly higher number of individuals in the healthy/peri-implant mucositis group were smokers.

Type 2 Diabetes Mellitus

One cross-sectional study[17] verified whether type 2 diabetes mellitus (DB) altered the levels of inflammatory mediators in a cohort population of chronic periodontitis (C-P) and peri-implantitis (P-IM) patients according to good (HBA1c < 8%) and poor (HBA1c ≥ 8%) glycemic status. It was demonstrated that poor glycemic control abolished differences between chronic periodontitis and

Outcomes on peri-implantitis	Criteria used to define peri-implantitis
Ne-S: 12 implants; Ex-S: 7 implants; S: 47 implants Smoking identified as a risk factor	PPD ≥ 4 mm, BOP and/or pus, BL ≥ 3 threads 1 y after placement of suprastructure
mPI, mGI, PD, CAL, BOP (significantly higher in inflamed than healthy sites) mGI, PD, CAL, BL higher in poorly than well-controlled diabetic patients with P-IM Levels of mPI and BOP unaffected by diabetes	Moderate: PD and CAL: 3 to 4 mm, BOP and BL involving 4 implant threads Advanced: PD and CAL ≥ 5 mm, BOP and BL involving fewer than 4 implant threads
Ex-S/S (composite): Detectable: 28 implants Overt: 15 implants No association between smoking and peri-implant disease	Detectable: Inflammation, BL > 0.4 mm Overt: BOP, suppuration, PPD ≥ 4 mm, BL ≥ 2 mm
S: 30% peri-implantitis Overall, 16 from 266 implants with peri-implantitis May be no association due to the higher number of nonsmokers	BOP, PPD > 5 mm, BL > 2 mm
History of CVD contributed Smoking did not contribute	PPD ≥ 4 mm, BOP, BL ≥ 2 mm
Peri-implantitis lesions three times more likely to harbor EB virus	PD ≥ 5 mm, BOP, suppuration, BL > 3 threads

peri-implantitis regarding the expression of mediators, but peri-implantitis patients without diabetes and with well-controlled diabetes expressed more TNF-α, CCR5, and CXCR3 ($P < .01$). Also, IL-6 and IL-8 levels were elevated in patients without diabetes and with well-controlled diabetes ($P < .01$). It was noteworthy that mGI, PD, and BL were higher in poorly controlled versus well-controlled diabetic peri-implantitis patients. On the other hand, the study by Renvert et al[20] found no association between peri-implantitis and type 2 diabetes, due to the low prevalence rates, although within what can be expected for a normal population (5%).

Cardiovascular Diseases

Two articles[18,20] investigated the role of cardiovascular disease (CVD) as a risk factor for peri-implantitis. The second paper identified that the odds ratio for peri-implantitis and cardiovascular disease (after adjustment for confounding factors) was 8.7 (95% CI: 1.9– 40.3, $P < .006$).

Rheumatoid Arthritis

One article[20] reported 11 patients (out of 172) with peri-implantitis, but statistical analysis demonstrated no associations (OR: 6.5 [95% CI: 0.9–52.8], $P = .07$).

Epstein-Barr Virus

In a cross-sectional, split-mouth study[11] with 46 implants, patients with peri-implantitis (n = 23) were found to have a 3 times greater chance to harbor Epstein-Barr virus (OR: 14.2, RR: 9.75).

Quality and Risk of Bias Assessment

Since no randomized clinical trial was identified, the NewCastle-Ottawa scale provided the results for quality assessment of cohorts. Results can be seen in Table 2. None of the studies reached the maximum of selection and comparability items. However, all selected studies reached the maximum score for outcome.

DISCUSSION

Smoking and Systemic Factors

The aim of this systematic review was to verify whether medical conditions and smoking could act as biologic factors for the occurrence of peri-implantitis. Based on the available evidence, this hypothesis cannot be confirmed.

Table 2 Results of NewCastle-Ottawa Quality Assessment Tool

	Selected studies					
Items	Roos-Jansåker et al[16] (2006)	Venza et al[17] (2010)	Koldsland et al[18] (2011)	Marrone et al[19] (2013)	Renvert et al[20] (2014)	Verdugo et al[11] (2015)
Selection						
Representativeness of the exposed cohort	b (*)	b (*)	b (*)	b (*)	b (*)	b (*)
Selection of the nonexposed cohort	c	a (*)	c	a (*)	c	a (*)
Ascertainment of exposure	b (*)	a (*)	b (*)	b (*)	b (*)	a (*)
Demonstration that outcome of interest was not present at start of study	No	No	No	No	No	No
Comparability	N/A	N/A	N/A	N/A	a (*) age, smoking, sex	N/A
Outcome						
Assessment of outcome	b (*)	b (*)	b (*)	b (*)	b (*)	b (*)
Was follow-up long enough for outcomes to occur?	Yes (*)	Yes (*)	Yes (*)	Yes (*)	Yes (*)	Yes (*)
Adequacy of follow-up cohorts	b (*) 76 out of 294 lost (26%)	a (*)	a (*)	a (*)	a (*)	a (*)

A recent systematic review and meta-analysis identified the harmful influence of smoking on radiographic, peri-implant marginal bone loss.[21] In the present review, although just one article demonstrated association between smoking and peri-implantitis,[16] the use of history/frequency of smoking could have underreported risks,[22,23] especially in female smokers.[24] Instead, it was demonstrated that serum cotinine levels are a more reliable parameter[25] and were also correlated with the severity of periodontal attachment loss.[26] In addition, two articles demonstrated that dentate smokers had less BOP than nonsmokers,[27,28] with those findings recently confirmed by multilevel logistic analysis (601 patients, 88,960 sites).[29] For sites with peri-implantitis and keeping BL ≥ 3 threads, the complementary material[30] of Roos-Jansåker et al[16] also demonstrated that BOP prevalence significantly diminished (from 7.0% to 0.9%) with just a 2-mm increase in PPD values. A recently published systematic review and meta-analysis demonstrated a higher risk at implant level (RR: 2.1) but no differences at patient level (RR: 1.17).[31]

The effects of type 2 diabetes on healing have been studied for a long time, and their effects on implants are still uncertain.[32] However, Venza et al[17] demonstrated that BOP prevalence for patients with poorly and well-controlled peri-implantitis does not differ (91.4% vs 88.9%). On the other hand, differences in BL prevalence of individuals with poorly controlled peri-implantitis were found to be significant when compared to that of healthy peri-implantitis and good glycemic peri-implantitis patients (60.2% vs 46.3% vs 45.5%). In this way, type 2 diabetes can potentially aggravate the level of peri-implantitis. Even so, its role as a biologic factor has to be elucidated with more controlled studies.

The findings on the Epstein-Barr virus regarding the etiopathogenesis of peri-implantitis are interesting. Possibly, a mechanism similar to that proposed for severe periodontitis can be assumed: *(1)* herpes virus presence at periodontal sites, *(2)* reactivation of latent periodontal herpes viruses, *(3)* inadequate antiviral cytotoxic T-lymphocyte response, *(4)* presence of specific pathogenic bacteria, and *(5)* insufficient level of protective antibacterial antibodies.[33]

A history of cardiovascular diseases was found in 27.3% of individuals with peri-implantitis and in only 3% of subjects with peri-implant mucositis or good peri-implant health.[20] This was in contrast with the results reported by Koldsland et al,[18] where variables not reported as risk indicators might have been identified as such in a larger population since the statistical method chosen was best suited for large populations.

Furthermore, Renvert et al[20] attempted to determine whether rheumatoid arthritis represents a significant risk factor to the long-term clinical performance of dental implants. However, when the age of the subjects, smoking, and sex were entered as confounding factors, no association between the autoimmune disease and peri-implantitis was observed.

Sources of Bias

Most of the documentation used in this review was composed of studies with large retrospective and/or cross-sectional designs made at different time periods.[11,16–20] Thus, the influence of industrial development on implant design and surface could be a confounding factor. Of clinical interest, the implant coronal portion in particular has a direct influence on radiographic bone loss measurements; factors such as reference levels (subcrestal, at bone level), collar length, presence of threads, thread pitch, and the adoption of the first bone-to-implant contact are all variables reported in different ways. Also, the studies[11,16–20] considered in this review reported two different forms of cutoff values: millimeters and/or based on the number of implant threads. Besides, it cannot be determined from patient records whether those implants were inserted more to the labial/buccal or to the lingual/palatal aspects since this is now an issue for peri-implantitis. Implants with more time in function are prone to more plaque accumulation, inflammation, and peri-implant disease.

Also, oral hygiene levels and the degree of patient education play a considerable role. Two sources of bias, ie, nonuniform professional supportive treatment and missing information on bone loss of 344 dental implants surely had an impact on the significance of the smoking effect and peri-implantitis.[16] Another common feature is that most retrospective studies contain populations not balanced for implant brands.[18,20] In addition to smoking being based on self-reporting, current smokers may not have developed the disease yet at the time of clinical evaluation.[18]

Patients with rheumatoid arthritis use anti-inflammatory drugs, a confounding factor that affects PPD levels and bleeding on probing.[20] On the other hand, more than one systemic disease can be found in the same patient (ie, diabetes and atherosclerosis), and some are aggravated by cigarette smoking, such as diabetes and lung cancer. As such, the levels of inflammation and bone loss found at the peri-implant sulcus may be more influenced by those factors and not bacterial loads.

CONCLUSIONS

Data from existing studies point to underlying smoking and diabetes as systemic associated factors for peri-implantitis. However, the body of evidence is still immature, and the specific contribution of general health problems to peri-implantitis requires additional robust epidemiologic and clinical investigations.

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