Peri-implantitis: A Systematic Review of Recently Published Papers

Paolo Pesce, DDS, PhD[a]/Maria Menini, DDS, PhD[b]/Tiziano Tealdo, DDS, MS, CDT[c]/
Marco Bevilacqua, DDS[c]/Francesco Pera, DDS, PhD[c]/Paolo Pera, MD, DDS, PhD[d]

Purpose: This systematic review considers possible etiologic factors and definitions of peri-implantitis as reported in the recent literature. ***Materials and Methods:*** An electronic search of databases plus a hand search of the most relevant journals published between January 2005 and September 2012 were performed. ***Results:*** The electronic and manual searches yielded 640 and 14 titles, respectively. From the independent double-check of the titles and abstracts, 24 full texts were downloaded (18 clinical studies and 6 animal studies). After reading the full texts, 10 articles (4 clinical studies and 6 animal studies) were included in this review. None of the human articles selected provided sufficient evidence to address the research question, and no human clinical evidence is available to support a cause-effect relationship between peri-implantitis and bacterial accumulation and/or occlusal overload. The animal literature is also not unanimous regarding a specific peri-implantitis etiology. However, a correlation between periodontitis and smoking histories was cited as contributing to a higher incidence of peri-implantitis. ***Conclusion:*** The available scientific literature is characterized by an absence of a unanimous consensus regarding the etiology of peri-implantitis and its specific relationship to periodontitis. Furthermore, both the choice of the term peri-implantitis and its definition remain controversial. *Int J Prosthodont 2014;27:15–25. doi: 10.11607/ijp.3785*

Documented support for efficacious and effective dental implant therapy outcomes has been recently challenged in publications and lectures on an inflammatory peri-implant reaction associated with loss of supporting bone. The presumed disease "peri-implantitis" was cited in a recent consensus report that stated that bone loss occurring after the initial remodeling response to implant placement is mainly due to bacterial infection.[1] The same report also emphasized similarities regarding both the clinical features and etiology of peri-implantitis and periodontitis.

Other authors[2] refute this premise and note that obvious differences between bone-implant and periodontal ligament–tooth interfaces preclude a specific etiologic connection between bacterial deposits and clinically relevant bone loss. Moreover, other contributors to unpredictable marginal bone loss, such as mechanical overload, have also been proposed. They are presumed to contribute to changes in the integrity of the induced osseointegration response[3,4] and may lead to eventual implant failure.

Peri-implantitis, first described by Levignac[5] in 1965, was defined by Mombelli et al as a "site-specific infection with remarkably similar ecosystems to those encountered in periodontal diseases."[6] This definition was later replaced by the more frequently employed "inflammatory reaction associated with loss of supporting bone around an implant in function."[7]

The controversy regarding the definition and etiology of peri-implantitis clearly demands more robust scientific information. This paper seeks to systematically review relevant recent literature that might better describe the etiology and definition of peri-implantitis.

Materials and Methods

This review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses.[8,9] Medline (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Excerpta Medica Database (EMBASE) searches were performed. The search strategy applied

[a]*PhD Student, Department of Implant and Prosthetic Dentistry, University of Genoa, Genoa, Italy.*
[b]*Assistant Professor, Department of Implant and Prosthetic Dentistry, University of Genoa, Genoa, Italy.*
[c]*Lecturer, Department of Implant and Prosthetic Dentistry, University of Genoa, Genoa, Italy.*
[d]*Full Professor and Head, Department of Implant and Prosthetic Dentistry, University of Genoa, Genoa, Italy.*

Correspondence to: *Dr Paolo Pesce, Department of Implant and Prosthetic Dentistry (DISC - Pad. 4), Ospedale S. Martino, L. Rosanna Benzi 10, 16132 Genova (Italy). Fax: + 39 0103537402. Email: paolo.pesce@unige.it*

Table 1 Studies Excluded After Reading the Full Text

Study	Year	Study design	Reason for exclusion
Leung et al[36]	2001	Case report	Case report
Uribe et al[37]	2004	Case report	Case report
Tawil et al[38]	2008	Case report	Case report
Quirynen et al[43]	1993	Controlled clinical trial	Follow-up period < 6 mo, no reference to bone loss
Pontoriero et al[47]	1994	Controlled clinical trial	No reference to bone loss
Zitzmann et al[48]	2001	Controlled clinical trial	Follow-up period < 6 mo, no reference to bone loss
Wennerberg at al[34]	2003	Controlled clinical trial	Follow-up period < 6 mo
Baldi et al[33]	2009	Controlled clinical trial	Follow-up period < 6 mo
De Freitas at al[49]	2011	Controlled clinical trial	Follow-up period < 6 mo, no reference to bone loss
Hultin et al[50]	2002	Cross-sectional	No information on the implant surgery protocol applied
Shibli et al[51]	2008	Cross-sectional	Implant population not followed since the implant surgery
Sato et al[52]	2011	Cross-sectional	Unknown follow-up period
Casado et al[53]	2011	Cross-sectional	No information on the implant surgery protocol applied
Cho-Yan Lee et al[54]	2012	Case-control	Bone regeneration

was as follows: (((Periimplantitis OR peri-implantitis OR peri implantitis) OR (periimplant or peri-implant OR peri implant)) AND ("bone loss" OR "crestal bone loss" OR disease)) AND etiology. The last search was done on September 15, 2012, and both animal and clinical studies were included. Language limits (English and Italian) were imposed.

The obtained results were combined with manual searches of the bibliographies of all full-text articles and related reviews selected from the electronic search. In addition, content pages of selected journals were manually searched (*Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, Implant Dentistry, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Oral and Maxillofacial Surgery, Journal of Periodontal Research, Journal of Periodontology, Journal of Prosthodontics, The International Journal of Oral and Maxillofacial Implants, The International Journal of Prosthodontics, The Journal of Prosthetic Dentistry,* and *International Journal of Dental Hygiene*) from January 2005 to September 2012.

Exclusion Criteria

Exclusion criteria included orthodontic implants, in vitro studies, guided bone regeneration performed together with implant insertion, bisphosphonates studies, reviews, mini-implants, transmandibular and/or zygomatic implants, pilot studies, case history reports/series, expert opinions, articles with follow-up after implant loading less than 6 months, articles with surgery performed by students, articles with no information on the surgical technique applied, and redundant publications. No publication date restrictions were imposed.

Inclusion Criteria

Only articles investigating peri-implantitis etiology were included. While numerous animal peri-implantitis studies were found, the majority rely only on ligature-induced plaque accumulation and inflammation around implants,[10,11] which the authors regard as offering questionable scientific merit and were therefore excluded from evaluation. Since the two popularly proposed causes of peri-implantitis have been plaque accumulation and occlusal overloading, the animal studies reviewed specifically targeted the combination of these widely quoted etiologic factors.

Screening, Selection, and Data Extraction

The titles and abstracts of the search were screened by two independent reviewers for possible inclusion in the review. Both reviewers performed eligibility assessment independently in a blinded standardized manner. The full text of all studies of possible relevance were obtained for independent assessment by the reviewers (Table 1). Data were extracted independently by the two reviewers using a data form, and any disagreements were resolved by discussion; if an agreement could not be reached, a third reviewer's decision was sought.

Results

Search and Selection Results

The initial electronic search (Fig 1) produced 640 titles, and the manual search found 14 titles. The independent double-check of titles and abstracts yielded 24 full-text articles (18 clinical studies and 6 animal studies).

The main reasons for exclusion were articles with no reference to peri-implantitis (167 papers), reviews (110), articles not investigating peri-implantitis etiology (71), articles that focused on peri-implantitis therapy (62), bone regeneration contextual with implant insertion (57), case report/case series/expert opinion (28), and animal studies based on ligature-induced peri-implantitis without a comparison with overload-induced peri-implantitis (21).

A final selection of 10 articles (4 clinical studies and 6 animal studies) were included in the present review.

Only 4 human studies on peri-implantitis were found to meet the selection criteria, as shown in Tables 2 and 3 (3 cross-sectional studies and 1 prospective).

Six studies on animal models met the criteria and are reported in Table 4 (dog model) and Table 5 (monkey model).

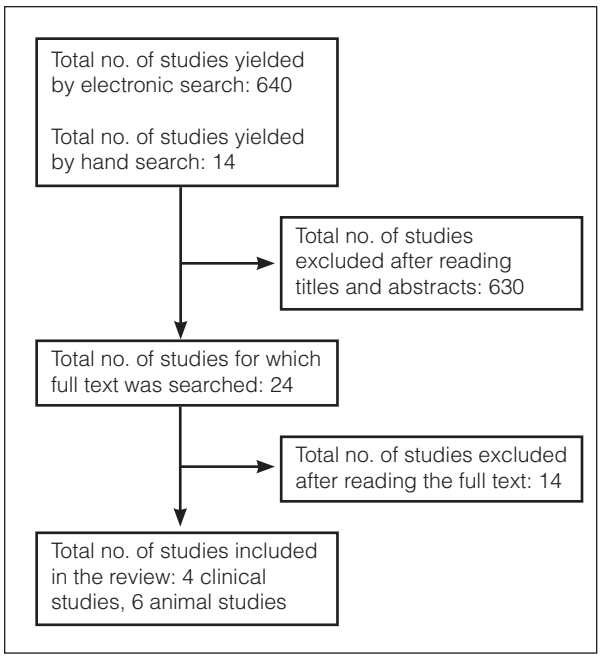

Fig 1 Study selection flowchart.

Outcome Results

Human Studies. A total of 491 patients were examined in the four selected studies. The included papers also reported different definitions of peri-implantitis (Table 6). In fact, for some authors to define an implant as affected by peri-implantitis, the probing depth (PD) had to be ≥ 5 mm[12] or ≥ 6 mm[13]; for some authors bleeding on probing (BoP) and presence of pus were necessary[12,14,15] to diagnose peri-implantis, while for others these signs were not indispensable.[13] Regarding bone loss, some authors required ≥ 3 threads,[14,15] while other authors diagnosed peri-implantitis when general bone loss or a peri-implant lesion was present.[12,13]

Two papers[14,15] examined microbiologic samples from both healthy and diseased peri-implant sites and reported contrasting results. Leonhardt et al[14] reported that patients with peri-implantitis harbored periodontal pathogens next to the implants affected by peri-implantitis. Renvert et al[15] did not find any difference between the two groups and affirmed that their data suggest a past history of periodontitis as a risk for mucositis (a reversible inflammatory reaction in the soft tissues surrounding a functioning dental implant) and that current poor oral hygiene does not increase the risk of presence of pathogenic microbiota at titanium implants.

The Roccuzzo et al[13] prospective study followed a cohort of periodontally healthy and periodontally compromised (moderate or severe periodontitis) patients for 10 years. They reported that biologic complications (peri-implantitis) occurred in all three groups, but significantly more biologic complications were observed in severe periodontally compromised patients compared with periodontally healthy patients ($P = .002$).

In a cross-sectional study, Rinke et al[12] examined 89 patients (17 smokers, 72 nonsmokers). Patients affected by aggressive periodontitis were excluded. The statistical analysis identified a significant association of peri-implantitis with ''smokers'' and ''compliance.'' Periodontal history in general showed no significant association with peri-implantitis.

Animal Studies. Six studies evaluating the relationship between overloading and/or plaque accumulation and peri-implantitis were included in the review. Three of these studies were based on a dog model (Table 4), and the other three on a monkey model (Table 5).

Overloading was simulated creating a supraocclusion[16–20] or connecting two implants with an expansion screw.[21]

Studies based on the dog model[16,19,21] did not find any relationship between overloading and bone resorption. Conversely, an increased bone-implant contact (BIC) was found when overload was applied on implants in absence of ligature-induced inflammation.

Table 2 Included Studies: Microbiologic Evaluation

Study	Year	Study design	Patients	Surgery/follow-up	Outcomes
Leonhardt et al[14]	1999	Cross-sectional	37 diseased* subjects (6 edentulous, 31 dentate) 51 healthy subjects (control). Teeth were lost due to periodontitis. All individuals were systemically healthy.	Implant positioned ad modum Brånemark. Mean follow-up since implant surgery: 7 y	BoP, PPD, subgingival microbiologic evaluation of plaque samples, radiographic examination
Renvert et al[15]	2007	Cross-sectional	213 subjects	Patients treated with Brånemark implants by experienced clinicians	Microbiologic evaluation of plaque samples, BoP, PPD radiographic evaluation, PI

BoP = bleeding on probing; PPD = probing pocket depth; PI = Plaque Index.
*Patients affected by peri-implantitis.

Table 3 Included Studies: Periodontally Compromised Subjects/Smoking

Study	Year	Study design	Patients	Surgery/follow-up	Outcomes
Roccuzzo et al[13]	2012	Cohort	28 PHP 37 mPCP 36 sPCP	Patients treated with TPS dental implants, full body screws, hollow screws and hollow cylinders (Straumann) Follow-up since the implant surgery: 10 years	PPD, PI, BoP, radiographic evaluation
Rinke et al[12]	2011	Cross-sectional	89 patients (17 smokers; 49 nonsmokers and 15 smokers had a history of periodontal disease)	Patients treated with Ankylos implants Mean follow-up: 68.2 mo	PPD, BoP, radiographic evaluation

PHP = periodontally healthy patients; mPCP = moderate periodontally compromised patients; sPCP = severe periodontally compromised patients; TPS = titanium plasr
PI = Plaque Index; BoP = bleeding on probing.

Overloading significantly increased angular bone loss only when combined with ligature-induced inflammation.[19]

In contrast, the monkey studies[17,18,20] reported that occlusal overload can induce bone loss or loss of osseointegration.

Isidor[20] concluded that an occlusal overload can determine a loss of osseointegration, while plaque accumulation can cause bone loss (loss of contact between bone tissue and implant) but not loss of osseointegration (described as "bone resorption starting at a short distance from the implant surface").

	Methods	Findings
	Diseased sites (1–4 sites/patient) and 2–3 sites/patient in the control group were isolated. Supra- and subgingival plaque samples were collected.	60% of patients with peri-implantitis harbored periodontal pathogens. None of the healthy edentulous patients had pathogens that were present in affected edentulous patients. Enteric bacteria were found in diseased patients.
	Plaque samples were collected from 4 sites of 1 implant and 1 tooth for each patient. Both teeth and implants were examined, and the selected sites were the ones with the largest PPD.	No differences were identified in microbial samples from teeth and implants of patients affected by mucositis or peri-implantitis.

	Findings	Results
	PI PHP: 16.1% ± 2.4%, mPCP: 29.0% ± 2.4% sPCP: 23.1% ± 2.3% BOP PHP: 12.3% ± 2.1% mPCP: 31.0% ± 2.5% sPCP: 30.9% ± 2.6%. PPD PHP 3.1 ± 0.5 mm mPCP 3.5 ± 0.9 mm sPCP 3.9 ± 0.7 mm Peri-implantitis (BoP, suppuration, PPD > 5, Rx defect) PHP 10.7% of patients mPCP 27% sPCP 47,2%	sPCP subjects had significantly more peri-implantitis than PHP subjects (P = .002).
	10 patients exhibited peri-implantitis. 8 of 17 smokers suffered from peri-implantitis (prevalence rate: 47%)	Statistical analysis identified a significant association of peri-implantitis with "smoker" (OR: 31.58; Po0.001) and "compliance" (OR: 0.09; P1/40.011). Periodontal history in general showed no significant association with peri-implantitis (note: Patients with aggressive periodontitis were excluded)

ma sprayed; PPD = probing pocket depth;

Miyata et al[18] created an occlusal interference of various degrees to demonstrate the tendency for bone resorption to increase only in models with 180 µm or more of excess height.

Discussion

A systematic review may be regarded as a reliable method of collecting information to provide a solid basis for clinical decision-making.[22]

Several outcome studies have been reported on this topic but they are usually designed to evaluate cumulative survival rate (CSR) or bone loss, without focusing on considerations of peri-implantitis per se and/or its etiology.

The choice of inclusion criteria in this study may have led to an unintended selection bias since only studies that met the aim to determine peri-implantitis definition and etiology were included. Consequently, the search strategy identified papers dealing with implant sites affected by bone loss and inflammation (and therefore matching the Albrektsson and Isidor[7] definition of peri-implantitis) and excluded papers in which the condition was not explicitly mentioned. On the other hand, the definition of peri-implantitis, which led to the inclusion of the selected studies, differed for each study (Table 6). All the definitions reported are based on the one proposed by Abrektsson and Isidor,[7] but histologic (or even clinical) proof of inflammation is difficult in clinical cases. As a consequence, only the resultant radiographic bone loss was a common feature considered necessary to define an implant as affected by peri-implantitis. The other parameters required to define peri-implantitis (bleeding on probing, probing depth, etc) differed between studies (Table 6).

It appears that the definition of peri-implantitis is not a unanimously employed one. As a consequence, implants defined as affected by peri-implantitis by some authors might not be considered affected by other authors if another definition is used. Consequently, the prevalence of this "disease" could vary enormously between studies using different definitions. According to Klinge,[23] since there appears to be a clustering effect, and implants in the same mouth cannot be considered independent from each other, it is recommended to use the patient as a unit. The different cutoff values for clinical parameters reported in different studies will exert a significant influence on the magnitude of the reported incidence of peri-implantitis.

The selected papers also presented a great variability in study design, making the results difficult to compare and a specific meta-analysis impossible.

The outcomes analyzed in the four clinical studies included in this review were similar: bone loss, bleeding on probing, probing depth, histologic and microbiologic analysis, and Plaque Index.

Table 4 Included Studies: Dog Model

Study	Year	Study design	Model	Methods
Gotfredsen et al[21]	2002	Controlled trial	5 beagle dogs; 3 machined implants in one side of the mandible and 3 sand-blasted, large-grit, acid-etched surface implants in the other	Implants: 3.3 × 8 mm Vitalium crowns without occlusal contacts were fitted to the implants. 3 mo after surgery, central and posterior implants were connected with an expansion screw (not activated); cotton ligatures were placed around the neck of the anterior and posterior implants and plaque control program ended. After 4 mo, ligatures were removed; after 2 mo, the expansion screws were activated for a 3-month period.
Heitz-Mayfield et al[16]	2004	Controlled trail	6 dogs; 2 TPS and 2 sandblasted, large-grit, acid-etched implants in each side of the mandible	Implants: 4.1 × 8 mm 6 mo after surgery, gold crowns were fitted on implants in the test side of the mandible to create premature contacts. Crowns were left in function for 8 mo. Control implants and remaining front teeth did not yield occlusal contacts during mastication. Hygiene was constantly maintained.
Kozlovsky et al[19]	2007	Controlled trial	4 dogs; 4 screw-shaped machined implants in each side of the mandible	Implants: 3.75 × 10 mm After 3 mo of healing, all implants were exposed and healing screws were connected. After 3 wk, healing screws were substituted with abutments (5- or 8-mm long). 5-mm abutments were free of any occlusal contact, while supraocclusal contacts were created between the 8-mm abutments and opposite teeth. Ligatures were placed around abutments on one side of the mandible for 12 mo. The other abutments were brushed 3 times/wk.

BIC = bone-implant contact; TPS = titanium plasma sprayed; BoP = bleeding on probing; PPD = probing pocket depth; mPI = modified Plaque Index; mGI = modified Gingival Index.

Table 5 Included Studies: Monkey Model

Study	Year	Study design	Model	Methods
Isidor[20]	1997	Controlled trial	4 macaca fascicularis 5 screw-type implants in the mandible. 2 in each molar-premolar area (1 machined, 1 TiO-blasted), 1 in the incisor zone	Implants 3.5 × 8 mm 6 mo after insertion, abutments were connected and a fixed partial prosthesis was mounted on the 2 implants in one side of the mandible to create an overload. The prosthesis caused a lateral displacement of the mandible. These 2 implants were brushed once per wk. In the other side, ligatures were positioned around abutments for 18 mo.
Miyata et al[17]	1998	Controlled trial	5 macaca fascicularis; 2 implants in one side of the mandible	Implants 2.8 × 8 mm 3 mo after implant insertion, a superstructure was realized so that a lateral force from lingual to buccal could be applied (occlusal interference of 100 μm) under conditions of good oral hygiene.
Miyata et al[18]	2000	Controlled trial	4 macaca fascicularis; 2 implants in one side of the mandible	Implants 2.8 × 8 mm 3 mo after implant insertion, a superstructure was realized so that a lateral force from lingual to buccal could be applied (occlusal interference of 100, 180, or 250 μm). Loading was applied for 4 wk under conditions of good oral hygiene.

BoP = bleeding on probing; PPD = probing pocket depth; MO = implant mobility.

Experimental sites	Outcomes	Findings
1. Plaque accumulation without ligatures with load 2. Plaque accumulation with ligatures without load 3. Plaque accumulation with ligatures and load	Radiographs, histologic evaluations (BIC)	Load applied to implants exhibiting peri-implantitis did not result in additional bone loss; on the contrary, it seemed to promote bone modeling and remodeling (implants with load and no ligatures exhibited a higher BIC).
No plaque without load; no plaque with load	BoP, radiographs, PPD, histologic evaluation	Implants subjected to 8 mo of excessive overload in conjunction with a plaque control regimen were stable.
1. Plaque accumulation with ligatures and load 2. Plaque accumulation with ligatures without load 3. No plaque with load 4. No plaque without load	Radiographs, Periotest evaluation, mPI, mGI, PPD, histologic evaluation.	Load applied to no plaque implants did not result in bone loss but had a positive effect on BIC. Occlusal overloading, when combined with plaque accumulation, significantly increased the angular bone loss on the buccal and lingual aspects.

Experimental sites	Outcomes	Findings
1. Plaque accumulation with ligatures without load 2. No plaque with load	Radiographs, BoP, histologic evaluation, Periotest	Occlusal overload could be the main factor for an already osseointegrated implant to fail (6 of the 8 occlusally loaded implants in 3 different monkeys lost osseointegration). Plaque accumulation caused bone loss but no loss of osseointegration. Occlusal overloading can result in a complete or partial loss of osseointegration.
No plaque, each animal received a different loading period: 1. Control: no load 2. 1-wk load 3. 2-wk load 4. 3-wk load 5. 4-wk load	Radiographs, histologic evaluation, PPD	None of the implants failed and a similar amount of bone loss was identified at all implant sites, although the implants had not completely integrated with the bone in the 1-week specimen. No signs of inflammation were identified.
No plaque 1. No load 2. 100-µm occlusal interference 3. 180-µm occlusal interference 4. 250-µm occlusal interference	Radiographs, histologic evaluation, PPD, MO	Bone loss around implants tended to increase with 180 µm or more of excessive height of a functioning superstructure. There is the possibility of bone loss even with no inflammation.

Table 6 Included Studies: Peri-implantitis Definition

Study	Year	Peri-implantitis definition
Roccuzzo et al[13]	2012	CIST protocol (PPD ≥ 6 mm, plaque deposits, BoP/pus may or may not be present, a peri-implant lesion is usually radiographically evident)
Rinke et al[12]	2011	PPD ≥ 5 mm, BoP/pus, radiographic bone loss
Leonhardt et al[14]	1999	≥ 3 threads of bone loss, BoP/pus
Renvert et al[15]	2007	≥ 3 threads of bone loss between the 1st year and the final radiographic examination, BoP

CIST = Cummulative Interceptive Supportive Therapy; PPD = probing pocket depth; BoP = bleeding on probing.

However, the value of applying periodontal parameters in the monitoring of peri-implant tissue health remains unclear and is far from compelling.[24,25] In fact, teeth and implants are very different clinical entities and the osseointegrated implant-host interface and the tooth-host interface differ in their anatomical and histologic characteristics. As a consequence, it seems simplistic and perhaps even misleading to presume that their biologic and functional reactions in the functional human oral environment are identical.[26,27]

Nonetheless, it is generally accepted that gentle probing (< 0.25 N), including recording of bleeding on probing, appears to be a guide for the presence of soft tissue inflammation. Increased probing pocket depth and bleeding is an indicator for supplementary radiographic examination.[23]

In regard to radiographic analysis,[28] the distance from the implant shoulder to the alveolar bone crest represents a reliable radiographic parameter for long-term monitoring in clinical practice.[29–31] Even if minor changes in bone morphology in the crestal area may not be revealed until they reach a significant size and shape, conventional periapical radiographs yield high specificity for the detection of peri-implant bone loss[28] and are believed to accurately evaluate crestal bone levels around implants clinically in a high percentage (89%) of cases.[32] According to Klinge,[23] it is suggested that the composite variables including bone loss ≥ 2 mm compared with initial radiographs at delivery of the prosthetic device, in combination with bleeding on probing, should be interpreted as a red flag for the clinician.

The two microbiologic studies[14,15] meeting the inclusion criteria of the present review reported contrasting results about the plaque composition/quantity of healthy and diseased peri-implant sites. Microbiologic studies are not unanimous about the flora around diseased peri-implant sites. But different methods were applied in these studies; different titanium surfaces have been tested, and the optimal bacterial sampling method has not yet been established. In particular, Renvert et al[15] affirmed that poor oral hygiene does not predispose a patient to the establishment of a pathogenic microbiota at titanium implants. Some authors found that rough abutments harbored a greater amount of plaque than machined abutments, but no differences in plaque composition, nor in other periodontal parameters evaluated, were found.[33,34]

Balshe et al[35] reported that the increased risk of implant failure in smokers is abrogated by use of implants with a modified implant surface; in this case, an anodized, rough surface. Indeed, it appears that whereas the combination of a smoker host and a smooth, machined titanium surface reduced the implant survival rate, the combination of a smoker host and a modified titanium surface is just as likely to survive as the combination of a nonsmoker host and a modified titanium surface. These data suggest scientific evidence that implant survival over the short and long term is influenced by properties of both the host and the implant.[4]

Some authors[36–39] state that in some cases of peri-implantitis, bone loss ended after an occlusal modification of the prosthesis. However, these kinds of case history reports provide very low scientific evidence and can be regarded as mere anecdotal evidence.

Engel et al[39] indirectly analyzed occlusal overload considering the relation between occlusal wear and bone level. The authors did not find any correlation, but a strict recall program with a careful control of the occlusal conditions was performed; if supraocclusion or side interferences were found, they were immediately corrected. In the authors' opinion, this is a too indirect way to evaluate the possible role of occlusal overload in peri-implant bone loss.

In dental literature, prosthodontic factors such as individual occlusal force, the characteristics of the prosthesis or of the opposite dentition, and their influence on bone resorption and implant rehabilitation success have been frequently neglected.[40] In fact, these factors could be difficult to standardize in clinical practice and the many variables involved are difficult to isolate and evaluate using clinical trials.

In the same way, it is not possible to assume a bacterial etiology for peri-implantitis by just underlining a correlation between history of periodontal disease and peri-implantitis. In fact, it is important to distinguish between correlation and causation. While causation implies a cause-effect relationship, correlation does not necessarily imply causation. Two events occurring in close proximity does not imply that one caused the other, even if it appears to make sense.

For this reason, bruxism, a history of periodontitis,[13] and smoking[12] are currently considered risk factors correlated with peri-implantitis. They are already recognized detrimental factors in implant surgery as they are associated with the risk of greater bone resorption and lower CSR, but these risk factors do not have a demonstrated cause-effect relationship with peri-implantitis.

Smoking, in particular, appears to be shared between diseases affecting attachment loss around teeth and crestal bone loss around implants.[3] Rinke et al[12] also showed a significant association of peri-implantitis with "smoker" and "compliance" (Table 3). However, this paper described a cross-sectional study, which is a study design not suitable for identifying a cause-effect relationship. The animal studies literature is far from unanimous about peri-implantitis etiology; moreover, data on animal studies should be used with caution when discussing clinical evidence.[41]

The complexity of the different phenomena (both chemical and physical) that dental implants are exposed to in human and animal oral cavities includes diet, oral hygiene, and occlusal function. On the other hand, it is important to emphasize the difficulties that a well-designed and ethically acceptable human study on peri-implantitis etiology would entail. Data from animal studies should be subjected to careful interpretation if applied in the clinical environment when reliable clinical evidence is absent.[42]

In particular, the use of ligatures (as in three of the included animal studies[19–21]) results in a foreign body reaction and induces a destructive process around implants that does not represent clinical reality.[42]

In the same way, overloading research designs used in the animal model do not adequately simulate the human situation. The majority of patients are extremely sensitive to even minute occlusal imperfections in occlusion on implant-supported restorations and would demand an immediate corrective action by the dentist.

Some included animal articles[17,18,20,21] share a shortcoming of lacking appropriate controls. In some studies, the control group did not match the test group since they differed in several aspects, not only with respect to the investigated parameters.

Gotfredsen et al[21] used a split-mouth approach with turned implants on one side and sand-blasted, large-grit, acid-etched implants on the other, but their results combined the two implant groups with an evident bias. A similar problem is evident in the study by Isidor,[20] who used machined and titanium-oxide–blasted implants without reporting separate results. This is particularly important. Different titanium surfaces have been reported to affect the amount of plaque accumulation and peri-implant bone resorption.[33,34,43] As a consequence, different implant surfaces could have biased the results.

On the other hand, the studies by Miyata et al[17,18] lack an appropriate sample size: each animal analyzed received a different treatment (a different loading time or overloading amount), resulting in two implants only per test group.

These limits in study design make it impossible to draw any scientifically sound conclusion. Regardless, the three studies on a dog model suggested a plaque-related etiology. On the contrary, the studies on the monkey model showed an overloading etiology or a synergism between plaque accumulation and overloading. The different study designs and different animal models could account for this inconsistency.

The studies by Heitz-Mayfield et al[16] and Kozlovsky et al[19] reported that no bone loss is evident if an overload is placed in a regimen of plaque control (Kozlovsky also reports an increased BIC next to overloaded implants). In contrast, the positioning of ligature induced massive bone loss even without overloading.

Gotfredsen et al[21] used a different model. They did not use an occlusal overload but an expansion screw connected to two implants. In the present authors' opinion, this is not a correct system to evaluate overload because the constant force applied was not similar to occlusal loading, which is characterized by force peaks and reductions to which dental implants in the mouth are normally subjected.

Finally, Isidor[20] and Miyata et al[17,18] focused their attention on a monkey model. Both found a correlation between occlusal overload and bone loss in a regimen of plaque control. It is worth underlining that, according to Miyata et al, an occlusal overload of less than 100 μm does not appear to be capable of causing bone loss. Only an overload of 180 μm or more can result in vertical bone loss.

As Isidor[44] suggested in a review, it seems possible that if the strain in the bone surrounding an oral implant is in the mild overload range (1,500 to 3,000 microstrain), apposition of bone appears to be the biologic response. On the other hand, strain in the bone beyond this range will at some point result in fatigue fracture and bone resorption.

The clinical and animal studies analyzed focused on two possible causes of peri-implantitis: plaque accumulation and overloading. However, multifactorial aspects (host general health, bone quality and quantity, surgical procedure, implant macro- and microcharacteristics, parafunctional habits, occlusal overloading, medications, bacterial insult, etc) potentially affect bone healing and induce peri-implant bone damage.[4]

Some authors have also suggested a cause-effect correlation between the incidence of peri-implantitis and osseointegration failure and the surgeon who performed the intervention.[45,46]

It is acknowledged that neither the selected clinical or animal studies proved to be useful in addressing the current controversy regarding a definition or a specific etiology for peri-implantitis. This may be regarded as alarming given the therapeutic intervention risk associated with the frequent and loose use of such a term.[27] Some authors have even questioned the existence of such a so-called disease.[3]

Ligature studies, inducing a destructive process around implants correlated with peri-implant tissue inflammation, describe a disease matching the definition of peri-implantitis. But ligature studies do not properly simulate clinical reality and the question remains: If such a disease does exist, can it be identified in human beings?

Conclusion

It is possible that the inclusion criteria may have led to an unintended selection bias. Given this context, the following conclusions are proposed: *(1)* No clinical evidence is available of a cause-effect relationship between peri-implantitis and bacterial accumulation or occlusal overload. *(2)* Animal studies report contrasting results depending on the model employed (dog or monkey). *(3)* Peri-implantitis might be correlated with a history of periodontitis, although the evidence is far from robust and compelling. *(4)* Smoking and poor compliance with regular prophylaxis appear to be detrimental factors associated with peri-implantitis. *(5)* The definition of peri-implantitis is not a unanimously employed one and this makes it difficult to compare the outcomes of different studies.

These considerations suggest that a more rigorous approach is required when addressing this topic in the scientific literature. The term peri-implantitis appears to have been improperly used to describe any peri-implant bone loss, irrespective of the complexity of the numerous factors that may contribute to loss of marginal bone around implants.

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