Peri-implant diseases and conditions: Peri-implantitis.

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Abstract

Objectives: This narrative review provides an evidence-based overview on peri-implantitis for the 2017 World Workshop on Classification of Peri-implant Diseases.

Material & Methods: A literature review was conducted addressing the following topics: 1) definition of peri-implantitis; 2) conversion from peri-implant mucositis to peri-implantitis, 3) onset and pattern of disease progression, 4) characteristics of peri-implantitis, 5) risk factors/indicators for peri-implantitis, and 6) progressive crestal bone loss in the absence of soft tissue inflammation.

Conclusions:

1) Peri-implantitis is a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone.

2) The histopathological and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood.

3) The onset of peri-implantitis may occur early during follow-up and the disease progresses in a non-linear and accelerating pattern.

4a) Peri-implantitis sites exhibit clinical signs of inflammation and increased probing depths compared to baseline measurements.

4b) At the histological level, compared to periodontitis sites, peri-implantitis sites often have larger inflammatory lesions.

4c) Surgical entry at peri-implantitis sites often reveals a circumferential pattern of bone loss.

5a) There is strong evidence that there is an increased risk of developing peri-implantitis in

patients who have a history of chronic periodontitis, poor plaque control skills and no regular maintenance care after implant therapy. Data identifying "smoking" and "diabetes" as potential risk factors/indicators for peri-implantitis are inconclusive.

5b) There is some limited evidence linking peri-implantitis to other factors such as: post-restorative presence of submucosal cement, lack of peri-implant keratinized mucosa and positioning of implants that make it difficult to perform oral hygiene and maintenance.

6) Evidence suggests that progressive crestal bone loss around implants in the absence of clinical signs of soft tissue inflammation is a rare event.

Introduction

Biological complications affecting osseointegrated implants are a topic of major interest in contemporary dentistry. Such complications mainly refer to inflammatory conditions associated with a bacterial challenge.[1-3] Two clinical varieties may be distinguished: peri-implant mucositis and peri-implantitis. While the presence of an inflammatory lesion is a feature both conditions have in common, only the latter form presents with loss of supporting bone.[4] It is anticipated that mucositis precedes peri-implantitis.[3]

This review addresses the following topics: 1) definition of peri-implantitis; 2) conversion from peri-implant mucositis to peri-implantitis, 3) onset and pattern of disease progression, 4) characteristics of peri-implantitis, 5) risk factors/indicators for peri-implantitis, and 6) progressive crestal bone loss in the absence of soft tissue inflammation.

Methods

Search strategy and data extraction

An electronic and manual search was conducted for each of the addressed topics. The PubMed database of the U.S. National Library of Medicine, the Excerpta Medica database (Embase) by Elsevier, and the Web of Knowledge of Thomson Reuters were screened for relevant articles (i.e. experimental studies in animals and humans/ observational studies, randomized/ controlled clinical studies, systematic reviews/ meta-analyses, consensus reports). Data from identified and relevant publications were extracted and, if indicated, presented in evidence tables. Overall findings were summarized in a narrative manner.

Observations and Discussion

Current definition of peri-implantitis

Peri-implantitis is a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and progressive loss of supporting bone.[1, 4]

In the clinical setting, soft tissue inflammation is detected by probing (bleeding on probing, BOP), while progressive bone loss is identified on radiographs. Studies on peri-implantitis require case definitions and threshold values to distinguish (i) health from disease and (ii)

mucositis from peri-implantitis. It should be noted that, while case definitions for peri-implantitis vary considerably between studies,[5] the definition of the disease remains.

Conversion from peri-implant mucositis to peri-implantitis

Mirroring the progression of gingivitis to periodontitis, peri-implant mucositis is assumed to precede peri-implantitis.[3] Currently, features or conditions characterizing the conversion from peri-implant mucositis to peri-implantitis have not been identified.

The peri-implant soft tissue reactions to plaque formation have been extensively evaluated in both animal[6-13] and human studies.[14-16] Thus, plaque formation consistently resulted in an inflammation of the peri-implant soft tissues,[14-16] associated with clinical signs of inflammation, such as redness and edema.[7]

Zitzmann et al. (2002) examined human biopsies after a plaque formation period of 21 days. The histological analysis revealed the establishment of a B and T cell-dominated inflammatory cell infiltrate (ICT) in the soft tissue lateral to the barrier epithelium, occupying an area of approximately 0.14 mm^2.[16]

Similar findings were made in animal studies, presenting with a varying apical extension of the inflammatory lesion.[7, 9, 10, 12] At most of the implant sites investigated, the lesion was located lateral to the barrier epithelium and separated from the crestal bone by a zone of healthy connective tissue. However, at some sites in one study, the subepithelial connective tissue was infiltrated with inflammatory cells (i.e. CD68 positive cells), thus decreasing the zone of healthy

connective tissue above the peri-implant bone.[7] At 16 weeks of plaque formation, the distance between the apical extension of the ICT and the crestal bone varied between 1.0 and 1.9 mm. At only one implant site did the ICT reach the crestal bone.[7] The exact histopathological mechanisms resulting in apical extension of the ICT and associated crestal bone loss have yet to be determined.

Clinically, the conversion from mucositis to peri-implantitis was evaluated in one retrospective observational study including 80 patients initially suffering from peri-implant mucositis.[17] Over 5 years, the incidence of peri-implantitis was lower in subjects enrolled in a regular maintenance program (18%) than among patients without regular maintenance care (43%). In the "maintained" group, "BOP+ at >50% of all implant sites" (OR 37) and "Probing Depth (PD) ≥4 mm at >5% of sites" (OR 20) were associated with peri-implantitis. In the "not maintained" group, the associated factors were Probing Depth (OR 26) and the presence of periodontitis (OR 11). In the entire patient group, the conversion to peri-implantitis was correlated with BOP (OR 18) and PD scores (OR 16), the lack of regular maintenance therapy (OR 6), as well as the presence of periodontitis (OR 9).

The histopathological and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood.

Onset and pattern of disease progression.

Progression of experimentally induced peri-implantitis

The so-called "ligature model" is often used to study experimental peri-implantitis in animals.[18, 19] The protocol comprises a phase of active tissue breakdown around osseointegrated implants,

including plaque formation and placement of ligatures in a submucosal position.[20] The ligature breaks the mucosal seal to the implant and promotes submucosal bacterial biofilm formation. The ensuing inflammatory lesion initiates tissue destruction, including bone loss. Also after the removal of the ligatures and under continuous plaque formation, progression of disease may occur.[22] This model thus mimicks naturally occurring peri-implantitis. When compared to experimentally induced periodontitis, lesions associated with experimental peri-implantitis demonstrate larger inflammatory cell infiltrates and more rapid and pronounced bone loss.[21] After a period of several weeks of plaque formation subsequent to ligature removal, spontanoues progression of peri-implantitis was associated with severe inflammation and tissue destruction.[22] Disease progression was influenced by implant surface characteristics with more pronounced breakdown at implants with modified than with non-modified surfaces.[21, 23]

Clinical studies on onset and progression of peri-implantitis

Prospective studies evaluating onset and progression of naturally occurring peri-implantitis could not be identified and are for obvious ethical reasons not feasible. However, retrospective observational studies employing *multilevel growth curve models* provided statistical estimates on onset and pattern of peri-implantitis associated bone loss.[24, 25] Fransson et al. evaluated 182 patients with a total of 419 implants (machined/turned surfaces, no bone grafting procedures, fixed restorations) that presented with progressive bone loss.[25] For these implants, bone levels were assessed using intra-oral radiographs obtained between the 1-year examination and a follow-up period of 5 – 23 years (mean: 11.1 years). The average bone loss was 1.7 mm and cumulative percentages of implants with bone loss ≥1 mm, ≥2 mm, or ≥3 mm were 68%, 32% and 10%, respectively. A multilevel growth curve model revealed that the pattern of bone loss was non-linear, accelerating and demonstrating an increased variance over time that was

attributed to subject heterogenity. This was confirmed in a retrospective analysis by Derks et al..[24] Results indicated that the onset of peri-implantitis may occur early, as the majority of implants demonstrated first signs of bone loss (>0.5 mm) already after the second (52%) and third year (66%) in function.[24] At the subject level, these calculations amounted to 70% and 81%, respectively.

When evaluating the above studies, it must be kept in mind that the onset of peri-implantitis was estimated on the basis of radiographic bone loss alone, not considering other clinical parameters.[24, 25] Nevertheless, these analyses suggest that peri-implantitis may commence early during follow-up and that the progression of peri-implantitis appears to be faster than what is observed in periodontitis.[26-28]

The concept of a potentially early onset of peri-implantitis is further supported by findings from studies evaluating peri-implant conditions already after comparatively short follow-up periods (≤2 years). A cross-sectional analysis of 238 patients with a total of 512 implants revealed that peri-implantitis (case definition: BOP+ and changes in radiographic bone level compared to baseline) was frequently noted in all implant age groups investigated.[29] At the implant level, its frequency amounted to n=18 at 1-12 months of follow-up, n=34 at 12-48 months and n=12 at >48 months, respectively. For the diagnosis of peri-implant mucositis, the number of affected implants in respective age groups was n=25, n=157 and n=32, respectively. Becker et al. recently studied the incidence of biological complications at zirconia implants over a 2-year period in 52 patients.[30] BOP values significantly increased from 21% at baseline (i.e. 10-12 weeks after implant placement) to 38% and 64% at 6 and 12 months, respectively. Based on the given case definition (BOP+ and changes in the radiographic bone level compared to baseline), 18 patients were diagnosed with initial peri-implantitis between 12 and 24 months.[30]

Characteristics of peri-implantitis

Histopathological characteristics of naturally occurring peri-implantitis

The histopathological features of naturally occurring peri-implantitis lesions have been extensively assessed in human biopsy materials.[31-39]

When compared with peri-implant mucositis, the lesions at peri-implantitis sites (case definition: BOP+, suppuration, radiographic bone loss) harbored more neutrophil granulocytes and larger "proportions of B cells (CD19+)".[35] Similar to periodontitis, the lesions at peri-implantitis sites were also dominated by plasma cells and lymphocytes,[33, 34, 36] but characterized by larger proportions of polymorphonuclear leukocytes and macrophages.[31, 38] Recently, it was also shown that the size of peri-implantitis lesions (case definition: interproximal implant sites with BOP+ and PD ≥7 mm) was more than twice as large as that noted at periodontitis sites (3.5 mm^2 vs. 1.5 mm^2).[39] Moreover, peri-implantitis lesions were characterized by larger area proportions, numbers and densities of plasma cells, macrophages and neutrophils, as well as a higher density of vascular structures outside and lateral to the cell infiltrate.[39] Another study using immunohistochemical analysis of harvested soft tissue biopsies showed that IL-1α was a dominant osteoclast activating cytokine at peri-implantitis sites.[37] It must be emphasized that the above analyses of human peri-implant tissue biopsies did, for ethical reasons, not include the osseous component of the sites.

Microbiological and immunological characteristics of naturally occurring peri-implantitis

Using conventional DNA probe and cultural analyses, common periodontopathogenic bacteria have been isolated at both healthy and diseased implant sites,[40] and the distribution of the detected species did not markedly differ by clinical implant status (i.e. healthy, peri-implant mucositis, peri-implantitis).[41] However, when compared with healthy implant sites alone, peri-implantitis was associated with higher counts of 19 bacterial species, including *Porphyromonas gingivalis* and *Tannerella forsythia*.[42] Moreover, observational studies have indicated that peri-implantitis was more frequently linked with opportunistic pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* (*S. aureus*),[43, 44] fungal organisms (e.g. *Candida albicans, Candida boidinii, Penicillum spp., Rhadotorula laryngis, Paelicomyces spp.*),[43, 45, 46] and viruses (i.e. human cytomegalovirus, Epstein-Barr virus)[47], thus pointing to a rather complex and heterogenous infection.[48, 49] It should be emphasized that the submucosal microbiota of peri-implantitis lesions have not been extensively studied using culture-independent techniques. Thus, the microbial picture associated with peri-implantitis should be regarded as incomplete.

Most recent systematic reviews have focused on the correlations between various cytokines (i.e. proinflammatory/ anti-inflammatory/ osteoclastogenesis-related) and chemokines measured in the peri-implant crevicular fluid (PICF) and the clinical condition at implant sites.[50, 51] Most of the included studies focused on the assessment of IL-1β and tumor necrosis factor alpha (TNF-α). Based on a meta-analysis,[50] the release of IL-1β was reported to be significantly increased at mucositis and peri-implantitis sites, when compared with healthy implant sites. However, no significant difference in IL-1β levels was noted between peri-implant mucositis and peri-implantitis sites. Peri-implantitis sites were also associated with a significant increase in TNF-α

levels over healthy implant sites.[50] In contrast, the majority of included studies failed to identify any significant differences in the levels of either IL-4, IL-10 or osteoclastogenesis-related (RANKL) cytokines between healthy and peri-implantitis sites.[51] Accordingly, the systematic reviews indicated that the assessment of proinflammatory cytokines (mainly IL-1β) in the PICF might be of beneficial value to differentiate between peri-implant health and disease, but inappropriate to determine the onset of peri-implantitis.

Clinical characteristics of naturally occurring peri-implantitis

Clinical signs of inflammation including redness, edema, mucosal enlargement, BOP+ with or without suppuration along with increases in PD and radiographic bone loss are commonly used in case definitions for peri-implantitis.[31, 33-39]

Implant sites diagnosed with peri-implantitis commonly show increased PD. In a study evaluating 588 patients with 2277 implants after a function time of 9 years, a PD ≥6 mm was recorded at 59% of all implants presenting with moderate/severe peri-implantitis (case definition: BOP+ and bone loss >2 mm).[52] Out of the implants classified as healthy (case definition: BOP-) or diagnosed with mucositis (case definition: BOP+ but no bone loss >0.5 mm), 3% and 16% showed PD ≥6 mm, respectively. It was also noted that the frequency of implants demonstrating PD ≥6 mm increased with increasing severity of peri-implantitis.

In a cross-sectional analysis, Schwarz et al. evaluated a total of 238 patients (n=512 implants) after a median function time of 23 months (1-80 months).[29] At peri-implant mucositis sites (Case definition: BOP+ on at least one aspect of the implant), the frequency of BOP scores mainly ranged between 33% and 50%, while the peak was 67% at peri-implantitis sites (Case definition: BOP+ and/or suppuration and changes in the radiographic bone level compared to

baseline). Diseased implant sites were associated with higher frequencies of 4-6 mm PD than implants with a healthy peri-implant mucosa, with an equal distribution between mucositis and peri-implantitis sites. PD values of ≥7 mm were only observed at one implant diagnosed with peri-implantitis.[29]

In this context, it must be realized that the determination of what constitutes a physiological PD at implant sites is difficult. A recent analysis described a high degree of variation in the vertical mucosal thickness measured at healthy implant sites, ranging from 1.6 mm to 7.0 mm (i.e. mucosal margin to the crestal bone level).[53] One cross-sectional analysis also evaluated and compared the horizontal mucosal thickness (hMT) at healthy and diseased implant sites. Median hMT were significantly increased at diseased-, when compared with healthy implant sites (1.1 mm), but were similar at mucositis and peri-implantitis sites (i.e. 1.7mm vs. 1.6 mm), respectively. In all groups investigated, these values did not markedly differ by implant location (i.e., upper/lower jaws) or position (i.e., anterior/posterior sites).[54]

Several consensus statements pointed towards suppuration as a common finding at sites diagnosed with peri-implantitis.[1, 4] One study examined 197 implants in 97 patients demonstrating progressive bone loss on radiographs.[55, 56] The authors compared these implants with 285 implants in the same patients not exhibiting bone loss. It was observed that, while 94% of the implants presenting with bone loss also were positive for BOP, suppuration on probing was identified at 19%. Only 5% of implant sites without bone loss showed suppuration.

Clinical studies also reported on the configuration of peri-implantitis defects.[57-59] In 79% of all sites investigated, naturally occurring peri-implantitis lesions featured a combined supra- (Class II) and intra-bony (Class I) defect configuration.[58] The intrabony component most frequently (55%) exhibited circumferential bone loss with maintenance of the buccal and lingual contours of the supporting crestal bone (i.e. Class Ie). This was followed by buccal dehiscence-type

defects revealing a semicircular defect to the middle of the implant body (i.e. Class Ib) (16%), and buccal dehiscence-type defects with circular bone resorption in the presence (i.e. Class Ic) (13%), or absence (i.e. Class Id) (10%) of the lingual bone plate. The lowest frequency was noted for isolated buccal dehiscence-type defects (i.e. Class Ia) (5%).[58] Similar intraoperative findings were also reported by Serino et al.[57] The majority (66%) of the implants investigated (n=59) exhibited a uniform bone loss at all four aspects.[57] The remaining peri-implantitis defects mainly featured a more advanced bone loss at the buccal site. These data were recently confirmed in a cross-sectional analysis, also pointing to an uniform bone loss at all four implant aspects with a high frequency of Class Ie defects (15/46, 33%).[59] Based on the above studies, it is assumed that peri-implantitis lesions commonly progress circumferentially around the affected implants.

Studies reporting on clinical characteristics of implants diagnosed with peri-implantitis are summarized in Table 1.

Periapical peri-implantitis

Apart from peri-implant infections at sites with deepened probing depths, a number of case series also reported on the occurrence of periapical peri-implantitis lesions. The affected implants were commonly characterized by a periapical radiographic radiolucency with or without concomitant clinical signs of inflammation, such as redness, edema, fistula and/ or abscess formation.[60-72] These clinical and radiographic signs of inflammation were noted between 2 - 8 weeks[68, 71] and up to 4 years[65] after implant placement. The majority of the studies reported a direct correlation between retrograde peri-implantitis and the existence of periapical endodontic lesions at adjacent teeth.[61-63, 65, 67, 68, 70, 72]

Oral-mucosa lesions mimicking peri-implantitis

Case reports have described a variety of oral-mucosa lesions at dental implants that may mimic peri-implant diseases. Such lesions include primary malignant tumors (i.e. oral squamous cell carcinoma)[73-76] or metastases[77] as well as giant cell and pyogenic granuloma.[78-86]

While these pathologic conditions share several clinical features with peri-implant diseases, they reveal distinct differences to a nonspecific inflammation at the histopathological level.[86]

Risk factors/indicators for peri-implantitis

Interventional studies of longitudinal design are required to identify true risk factors for a disease. Observational studies, cross-sectional or retrospective in nature, may only describe risk indicators.

In the following text, potential risk factors/indicators with substantial evidence are addressed in dedicated sections, while factors with limited evidence are summarized under "Areas of future research".

History of periodontitis

Periodontitis is a common disease. Its severe form ranks 6th among the most prevalent disorders.[87] In a recent survey carried out in the US, Eke et al. reported that roughly 50% of the

adult population (aged ≥30 years) presented with periodontitis.[88] In individuals ≥65 years of age, the corresponding number was 68%. Studies reporting on the potential association between history of periodontitis (chronic or aggressive) and peri-implantitis are described in Table 2.

In two 10-year longitudinal studies, peri-implantitis was assessed and correlated with a history of periodontitis. Karoussis et al. provided implant therapy to 45 patients without a history of periodontitits.[89] A total of 8 patients were treated with implants after having successfully completed periodontal therapy. The 10-year incidence of peri-implantitis (case definition: PD ≥5 mm, BOP+ and annual bone loss >0.2 mm) in the non-periodontitis group was 6% (implant level) compared to 29% in subjects with a history of periodontitis. Roccuzzo et al. followed 101 patients provided with dental implants after having been categorized as (i) periodontally not compromised, (ii) moderately compromised and (iii) severely compromised.[90, 91] The authors reported that both the frequency of implant sites demonstrating PD ≥6 mm (2%, 16%, 27%, respectively) and bone loss ≥3 mm (5%, 11%, 15%, respectively) differed significantly between groups. The results also showed that treatment of peri-implantitis was more time consuming in patients with a history of periodontitis. In a follow-up study of 80 patients presenting with mucositis at baseline, the incidence of peri-implantitis over 5 years was assessed by Costa et al.[17] The authors observed an overall incidence of peri-implantitis of 31%. Patients suffering from periodontitis at the final examination had significantly higher odds to also have developed peri-implantitis when compared to individuals without periodontitis (OR 9).

A number of cross-sectional studies reported on prevalence of peri-implantitis and analyzed associations with either a history of periodontitis or current periodontitis. In a study including 216 patients 9-14 years after implant therapy, Roos-Jansåker et al. reported that implants placed in patients with a history of periodontits had significantly higher odds (OR 5) for peri-

implantitis when compared to implants in patients without.[92, 93] Koldsland et al. reported similar findings after examining 109 subjects with 1 to 16 years of follow-up.[94, 95] Thus, patients with a history of periodontitis were found to be at higher risk for peri-implantitis (OR 6). Several subsequent studies confirmed this association with varying degrees of strength.[96-100] Other studies correlated current periodontitis with peri-implantitis, also reporting strong associations.[52, 101, 102] In fact, Daubert et al. found that severe periodontitis at follow-up was the strongest indicator for peri-implantitis of all variables examined, presenting with an unadjusted risk ratio of 7.[101] Derks et al., in a 9-year follow-up including 588 patients reported an odds ratio of 4 for patients with current periodontitis.[52]

While the majority of publications is in general agreement when examining the association between periodontitis and peri-implantitis, it should also be noted that conflicting reports exist.[29, 103-106] Thus, Marrone et al. examined 103 patients with implant-supported restorations in function for at least 5 years.[103] Neither current periodontitis nor history of periodontitis were statistically significant predictors for peri-implantitis. Also Rokn et al., in a cross-sectional study on 134 patients failed to demonstrate a higher risk for peri-implantitis in patients with a history of periodontitis.[104] Disagreement between studies may be explained by differences in case definitions for (i) (history of) periodontitis and (ii) peri-implantitis (see Table 2).

Conclusion: There is strong evidence from longitudinal and cross-sectional studies that a history of periodontitis constitutes a risk factor/indicator for peri-implantitis.

Smoking

Smoking has been strongly associated with chronic periodontitis, attachment loss as well as tooth loss,[107, 108] Studies reporting on the potential association between smoking and peri-

implantitis are described in Table 3.

Lindquist et al. reported that smokers presented with substantially more crestal bone loss than non-smokers.[109] In line with this observation, several subsequent studies observed a strong association between smoking and peri-implantitis. In a 10-year cohort study, Karoussis et al. found that 18% of all implants in smokers developed peri-implantitis, while only 6% of implants in non-smokers were affected.[89] Three cross-sectional studies confirmed these findings, reporting odds ratios of 32[110], 3[30] and 5[93], respectively.

The majority of publications, however, failed to identify smoking as a risk factor/indicator for peri-implantitis. Aguirre-Zorzano et al. examined 239 implant-carrying individuals after a mean follow-up time of about 5 years and found an overall prevalence of peri-implantitis of 15%.[111] Smokers were not at higher risk. Results from other cross-sectional studies confirmed their findings.[95, 96, 99-101, 103-106] It should be observed that three different studies reported on an association between smoking and peri-implantitis in their respective initial univariate analyses.[52, 97, 98] However, in the following calculations with adjustments for confounding and interaction (multivariate analyses), smoking was not retained as a relevant predictor for peri-implantitis. This indicates that smoking may be confounded by other background variables, e.g. history of periodontitis. The reasons for the conflicting findings and the apparent weak association between smoking and peri-implantits are currently not understood but may be related to differences in categorization of smokers and non-smokers. Thus, criteria for the factor "smoking" varied considerably from study to study. Furthermore, all of the identfied studies relied solely on patient-reported information for the assessment of smoking status.

Conclusion: There is currently no conclusive evidence that smoking constitutes a risk factor/indicator for peri-implantitis.

Diabetes

Diabetes mellitus comprises a group of metabolic diseases where type 1 describes an autoimmune destruction of insulin-producing β-cells and type 2 is characterized by insulin resistance.[112] The global prevalence of diabetes in the adult population is estimated at around 8%,[113, 114] and the disorder has been identified as a risk factor for periodontitis.[115, 116] Table 4 summarizes studies on its potential association with peri-implantitis.

A number of authors have indicated that diabetic patients are at higher risk for peri-implantitis. Thus, Ferreira et al. recorded peri-implantitis in 24% of individuals who either medicated for glycaemic control or presented with fasting blood sugar ≥126 mg/dl at the final examination [117] In contrast, only 7% of non-diabetic patients were diagnosed accordingly. The authors reported an OR of 1.9. Recent findings from a study involving 96 patients with 225 implants demonstrated, after a mean follow-up of 11 years, a 3-fold risk (Risk ratio 3, implant level) for peri-implantitis in subjects who were diagnosed with diabetes at time of implant placement.[101] This analysis, however, was not adjusted for potential confounding. Tawil et al. followed 45 diabetic patients for a mean of 42 months (range 1-12 years).[118] In subjects with a mean HbA1c level ≤7%, no implants were diagnosed with peri-implantitis. In patients with elevated HbA1c levels (7% - 9%), 6 out 141 implants developed peri-implantitis.

A number of studies failed to identify diabetes as a risk for peri-implantitis. In the retrospective study by Costa et al., diabetic patients diagnosed with mucostis were not at higher risk to develop peri-implantitis when compared to non-diabetics.[17] Similarly, a lack of assocation between peri-implantitis and diabetes was reported in the majority of available cross-sectional

studies.[52, 93, 98-100, 103, 104, 106] It should be pointed out that the assessment of diabetes in all but three studies[17, 102, 118] was solely based on patient-reported information. In two of the three reports an association was found between diabetes[102] or HbA1c levels[118] and peri-implantitis.

Conclusion: Available evidence is inconclusive as to whether diabetes is a risk factor/indicator for peri-implantitis.

Poor plaque control/lack of regular maintenance therapy

As demonstrated in classical studies on periodontal diseases, lack of regular maintenance therapy is associated with tooth mortality and clinical attachment loss at teeth.[119-123] These findings have highlighted the importance of self-performed and professionally-administered infection control measures in the prevention of periodontal diseases. Studies on the potential association between poor plaque control or lack of regular maintenance therapy and peri-implantitis are presented in Table 5.

Results from one longitudinal study including patients diagnosed with mucositis indicated the importance of plaque control in the prevention of peri-implantitis.[17] The analysis showed that the incidence of peri-implantitis over a 5-year period was lower in patients attending maintenance therapy (18%) when compared to individuals without supportive care (44%). These findings are in aggreement with Roccuzzo et al.[90] The authors reported that patients who, during a 10-year period, failed to adhere to the recommended maintenance therapy required substantially more treatment for peri-implantitis (41%) than those attending the follow-up visits (27%). Results from a cross-sectional study are also in agreement. Patients complying to

maintenance therapy following implant therapy during a mean obersvation time of 3.8 years were less likely to be diagnosed with peri-implantitis than non-compliers (OR 0.14).[124]

Cross-sectional reports assessing self-performed plaque control and its association with peri-implantitis demonstrated a strong correlation. In four studies, poor plaque control at the final examination was the strongest statistical predictor for peri-implantitis with ORs ranging from 5 to 14.[29, 102, 104, 111] A more modest assocation (ORs 3 to 4) was described by one additional cross-sectional[105] and one case-control study.[97]

Contradictory data have also been reported. A total of four publications were identified that failed to observe correlations between cross-sectional assessments of plaque scores and peri-implantitis.[93, 95, 103, 106] In this context, it should be considered that a one-time assessment of plaque may not necessarily reflect the long-term level of self-performed plaque control.

Other factors related to oral hygiene measures at implants may also be considered. Recently, Souza et al. reported that brushing at implant sites with keratinized mucosa (KM) <2 mm was associated with considerably more discomfort when compared to brushing at sites with KM ≥2 mm.[125] The authors also noted higher scores for plaque and bleeding at sites with reduced KM. Serino and Ström evaluated the accessibility of implant-supported restorations for oral hygiene measures in patients diagnosed with peri-implantitis.[126] The authors noted that only few sites with access for oral hygiene were affected (18%), while 65% of the non-cleansable sites showed peri-implantitis.

Conclusion: There is evidence that poor plaque control and lack of regular maintenance therapy constitute risk factors/indicators for peri-implantitis.

Areas of future research

Keratinized mucosa

The evidence that there is a need of a keratinized mucosa (KM) to maintain peri-implant health is still limited.[127, 128] Previous systematic reviews have indicated that a KM of <2 mm was associated with more plaque accumulation and peri-implant soft tissue inflammation when compared with implants that were surrounded by a KM of ≥2 mm.[128, 129] In particular, a meta-analysis pointed to statistically significant differences in terms of plaque scores, modified gingival index, mucosal recession and attachment loss in favour of sites with a wider KM.[129]

These findings were also supported by recent observational studies.[105, 125, 130-132] In a cross-sectional analysis, Ladwein et al. evaluated 211 patients (n=967 implants) after a mean observation period of 8 years.[132] Implant sites lacking KM were associated with significantly higher plaque scores, marginal bleeding and BOP scores than sites with KM. However, no significant differences were noted with regard to PD and radiographic bone levels.

Another cross-sectional analysis of 36 patients (n=110 implants) after an observation period of at least 6 months also pointed to significantly more plaque, marginal bleeding and mucosal inflammation as well as greater mucosal recession at sites where KM was ≤2 mm.[131] Souza et al. observed that implant sites with a KM of <2 mm had significantly higher plaque and BOP scores and were associated with an increased brushing discomfort than implant sites with a KM of ≥2 mm.[125] This finding was also supported by data from another cross-sectional analysis (n=60 patients) indicating that implants with a KM of <2 mm revealed a significantly higher levels of plaque accumulation as well as increased BOP+ and PD values when compared with implant sites with a KM of ≥2 mm.[130] Canullo et al. reported that periodontally healthy patients diagnosed with peri-implantitis (53 out of 534 patients) had higher plaque and BOP scores as well as higher percentages of implants with a KM of <2 mm.[105] Recently, in a cross-sectional

analysis at 10 years after implant placement, Rocuzzo et al. reported that, even in patients with a sufficient oral hygiene, the absence of KM was associated with higher plaque scores.[133]

Conclusion: While studies suggest that the absence or a reduced width of KM may negatively affect self-performed oral hygiene measures, there is limited evidence that this factor constitutes a risk for peri-implantitis.

Excess cement

Several observational studies have reported on a correlation between excess cement and the prevalence of peri-implant diseases. Employing a variety of different case definitions, it was suggested that the presence of excess cement was closely linked to the occurrence of either peri-implant mucositis or peri-implantitis.[134-138] However, the proportions of diseased implant sites showing showing excess cement varied considerably among studies and ranged between 9% and 81%. Accordingly, several implant sites showing excess cement exhibited no disease.[134-138] Furthermore, cement-retained restorations were not found to be at higher risk for peri-implantitis when compared to screw-retained reconstructions.[52, 101, 103, 139] Nevertheless, a systematic review emphasized that the rough surface structure of cement remnants may facilitate retention and biofilm formation.[140]

Conclusion: It is suggested that excess cement is a potential risk factor/indicator for peri-implantitis.

Genetic factors

Gene polymorphisms may affect gene expression, protein production and cytokine secretion.[141] Several observational studies have addressed the potential association between various gene polymorphisms and the occurence of peri-implantitis, with the majority focussing on IL-1.[142-146] Based on a cross-sectional analysis, Gruica et al. reported that 64 out of 180 patients revealed a

positive IL-1 composite gene polymorphism (IL-1α +4845; IL-1β +3954) and a total of 34 patients (51 implants) were associated with biological complications (unclear case definition) at 8-15 years after implant therapy.[143] An association between a positive IL-1 composite gene polymorphism and the occurrence of biological complications was, however, observed only in a subgroup of heavy smokers (≥20 cigarettes per day). In another cross-sectional analysis, Laine et al. identified a significantly higher prevalence of IL-1 receptor antagonist (IL-1RA) polymorphisms in patients that were diagnosed with peri-implantitis (case definition: BOP+ and/or suppuration, bone loss >3 threads at machined implants) when compared with patients showing healthy control implants (57% vs. 33%; OR 3).[142] Similar findings were reported by Hamdy & Ebrahem, showing that a positive IL-1 composite gene polymorphism (IL-1α -889; IL-1β +3954) was significantly higher among patients suffering from peri-implantitis.[145] However, this association was not confirmed in other cross-sectional analyses.[144, 146, 147] Recent observational studies have also pointed to a potential association with gene polymorphisms of osteoprotegerin,[148, 149] IL-6,[150] CD14-159 C/T and TNFα -308 A/G.[151]

Conclusion: While prospective clinical studies and studies with sufficient sample size are still lacking, the available evidence points to a potential influence of various gene polymorphisms in the pathogenesis of peri-implantitis.

Systemic conditions

The association of systemic conditions (other than diabetes) with peri-implantitis has rarely been studied and is therefore unclear. A cross-sectional study reported a higher risk for peri-implantitis in patients diagnosed with cardiovascular disease (OR 9) and rheumatoid arthritis (OR 7).[152] Koldsland et al. evaluated cardiovascular disease but failed to observe an association with peri-implantitis.[95] Roos-Jansåker et al.[93], Casado et al.[96] and Canullo et al.[105] combined

different systemic diseases into one parameter and found no elevated risk for peri-implantitis in their respective analyses. Other studies considered osteoporosis[100, 106], osteopenia[100, 106], thyroid disease[99, 106], hepatitis[99, 103], BMI[100] as well as radiation and chemotherapy.[97] No association with peri-implantitis was observed. It may be questioned whether existing studies evaluating risk factors/indicators for peri-implantitis are adequately powered to detect associations with rare disorders.

Conclusion: Evidence suggesting systemic conditions (other than diabetes) to be a risk factor/indicator for peri-implantitis is limited.

Iatrogenic factors

The Consensus report of the 7th European Workshop on Periodontology recognized that the onset and progression of peri-implantitis may be influenced by iatrogenic factors such as "inadequate restoration-abutment seating, overcontouring of restorations or implant-malpositioning".[1] It appears reasonable that the implant position and design of the suprastructure should facilitate access for self-performed oral hygiene and professionally administered plaque removal.[3] However, studies examining the role of iatrogenic factors in the development of peri-implant diseases are still scarce.

In a restrospective analysis, it was suggested that peri-implantitis was linked with malpositioning (OR 48) and bone augmentation (OR 2).[153] The potential association between bone augmentation procedures and peri-implantitis was also addressed in two cross-sectional studies. [105, 154] Canullo et al. reported that in patients (n=53) diagnosed with peri-implantitis (case definition: BOP+ and/or suppuration, PD ≥4 mm, radiographic bone level >3 mm), 18% of the diseased implants had received a bone grafting procedure at installation while the percentage of healthy implants sites with a history of bone augmentation was significantly smaller (7%).[105]

In another cross-sectional study, Schwarz et al. evaluated the impact of the outcome of guided bone regeneration in dehiscence-type bone defects on peri-implant health.[154] The residual defect height was assessed 4 months following grafting. After 4 years of follow-up, it was observed that implants with residual defects of >1 mm were at a higher risk of developing peri-implant disease.

Conclusion: In the absence of sufficient data, it appears reasonable to suggest that implant position and design of the suprastructure may influence the access for home care- and professionally administered plaque removal.

Occlusal overload

In the presence of plaque, the potential influence of excessive occlusal overload[155] and lateral static load[156] on peri-implantitis has been addressed in animal studies. In particular, employing the ligature model in dogs, Kozlovsky et al. subjected titanium abutments connected to machined implants to either a supra- (i.e. overload), or infra-occlusion (i.e. unloaded) over a period of 12 weeks.[155] At control sites (i.e. implants with plaque control), overload was associated with an improved osseointegration over unloaded implants. No data on changes of crestal bone levels were presented. In the study by Gotfredsen et al., implants with mucositis and experimental peri-implantitis were exposed to lateral static load by means of expansion screws.[156] There was no difference in terms of bone level changes between loaded and unloaded implants. Lateral load did not induce bone loss at mucositis sites. These findings were supported by Heitz-Mayfield et al.[157], since in their study occlusal overload at implant sites with plaque control in the dog did not result in increased PD or BOP scores over unloaded (i.e. no crowns) control implants at 8 months.

A cross-sectional analysis revealed that clinical signs of occlusal overload (e.g. abutment fracture, loss of retention, chipping, dynamic occlusal measurements) were identified at 3 out of 207 implants with healthy peri-implant conditions, whereas the ratio changed to 27/125 at peri-implantitis sites (OR 19).[153] It should be noted that only patients diagnosed with peri-implantitis were considered in the analysis. In a population of 183 patients with a total of 916 implants, Dalago et al.[99] identified that wear facets on the implant supported crowns were associated with peri-implantitis (OR 2).

Conclusion: There is currently no evidence that occlusal overload constitutes a risk factor/indicator for the onset or progression of peri-implantitis.

Titanium particles

In an analysis of archive material of human biopsies, it was reported that the inflammatory cell infiltrate at peri-implantitis sites occasionally (i.e. 7 out of 36 biopsies) revealed residues of particles featuring titanium peaks in the energy dispersive x-ray spectroscope.[32] Similar findings were also reported by Fretwurst et al.[158], since metal particles (i.e. titanium and iron) were identified in 9 out of 12 human hard and soft tissue biopsies taken at peri-implantitis sites. Both studies, however, were lacking tissue biopsies retrieved from clinically healthy implant sites (e.g. taken during the removal of malpositioned or fractured implants).

In a cytological analysis of oral smears taken from the peri-implant mucosa of 30 patients, Olmedo et al. identified metal-like particles at both healthy and diseased (i.e. peri-implantitis) implant sites.[159] However, the titanium concentration appeared to be higher in patients suffering from peri-implantitis.

Conclusion: At the time being, the available evidence does not allow for an evaluation of the role of titanium or metal particles in the pathogenesis of peri-implant diseases.

A number of additional factors have been associated with peri-implantitis in case reports, finite-element analyses or pre-clinical research (e.g. bone compression necrosis[160,161], over-heating[162], micro-motion[163] and bio-corrosion[164]). The importance of such factors should be evaluated in future research.

Does progressive crestal bone loss around implants occur in the absence of soft tissue inflammation?

It is important to distinguish between initial physiological bone remodeling and progressive crestal peri-implant bone loss, with the latter implying that a pathological process is ongoing. The initial remodeling of the crestal bone is considered to be a physiological process following implant placement.[1] This process is influenced by a variety of biological (e.g. mucosal thickness[165]), technical (e.g. prosthetic connections[166]) and surgical (e.g. implant positioning[167, 168]) factors.

Observational studies have indicated that crestal bone level changes at implants are commonly associated with clinical signs of inflammation. In a retrospective analysis, Fransson et al. evaluated the prevalence of subjects with progressive bone loss (bone level >3 threads and bone loss ≥0.6 mm with year 1 as baseline) at machined/turned implants.[56] Between 5 and 23 years after loading, the prevalence of progressive bone loss amounted to 28% at the subject- and 12% at the implant level. In an analysis of a subgroup of these patients, clinical signs of

inflammation (i.e. BOP+, suppuration, PD >6 mm) were more frequent at sites demonstrating "progressive bone loss".[55] In particular, the percentages of BOP+, suppuration and PD ≥6 mm at implant sites without progressive bone loss were 91%, 5% and 12% compared to 94%, 19% and 35% at implant sites with progressive bone loss.

In another cross-sectional analysis including 427 patients, Derks et al. observed that, over a 9-year period, bone loss (>0.5 mm) had occured at 629 (40%) out of 1578 implants.[52] Of these 629 implants, 393 (63%) also presented with soft tissue inflammation (BOP+) at the final examination. At implants presenting with more pronounced bone loss (>1 mm, >2 mm, >3 mm, >4 mm), BOP+ was recorded at 72%, 80%, 87% and 88%, respectively.

Similarly, a prospective analysis of implants with a modified surface over a period of 10 years indicated, that crestal bone level changes (>0.5 mm; >1.0 mm; >2.0 mm) were commonly associated with clinical signs of inflammation (BOP+).[169, 170]

Conclusion: Evidence suggests that progressive crestal bone loss around implants in the absence of clinical signs of soft tissue inflammation is a rare event.

Conclusions

1) Peri-implantitis is defined as a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone.

2) The histopathological and clinical conditions leading to the conversion from peri-implant mucositis to peri-implantitis are not completely understood.

3) The onset of peri-implantitis may occur early during follow-up and the disease progresses in a non-linear and accelerating pattern.

4a) Peri-implantitis sites exhibit clinical signs of inflammation and increased probing depths compared to baseline measurements.

4b) At the histological level, compared to periodontitis sites, peri-implantitis sites often have larger inflammatory lesions.

4c) Surgical entry at peri-implantitis sites often reveals a circumferential pattern of bone loss.

5a) There is strong evidence that there is an increased risk of developing peri-implantitis in patients who have a history of chronic periodontitis, poor plaque control skills and no regular maintenance care after implant therapy. Data identifying "smoking" and "diabetes" as potential risk factors/indicators for peri-implantitis are inconclusive.

5b) There is some limited evidence linking peri-implantitis to other factors such as: post-restorative presence of submucosal cement, lack of peri-implant keratinized mucosa and

positioning of implants that make it difficult to perform oral hygiene and maintenance.

6) Evidence suggests that progressive crestal bone loss around implants in the absence of clinical signs of soft tissue inflammation is a rare event.

Tables

Table 1. Clinical characteristics of peri-implantitis

Study	Type of study	Study sample	Case definition/ Inclusion criteria	Findings
Fransson et al. 2005[56] & 2008[55]	Cross-sectional 5-20 years mean: 9.4 years	82 patients 197 implants identified with progressive bone loss 285 implants with no progressive bone loss	Progressive bone loss Bone level ≥3 threads & bone loss >0.6 mm	Clinical examination PD ≥6 mm/Suppuration (% of implants) No progressive bone loss: 12%/5% Progressive bone loss: 35%/19%
Schwarz et al. 2007[58]	Cross-sectional	24 patients 40 implants diagnosed with moderate to advanced peri-implantitis	Case definition PD >6 mm BOP/SUP+ Bone loss	Intraoperative assessment Combination of intrabony and supracrestal defects; circumferential-type intrabony defects most frequent (55.3%).
Serino et al. 2013[57]	Cross-sectional	29 patients 89 implants diagnosed with peri-implantitis	Case definition PD >4 mm BOP/SUP+ Bone loss ≥2 mm	Clinical examination and intraoperative assessment Circumferential-type bone defects most frequent (66.0%).

Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 137 patients diagnosed with mucositis 62 patients diagnosed with moderate/severe peri-implantitis	Case definition BOP/SUP+ Bone loss >2 mm	Clinical examination PD ≥6 mm (% of implants) Healthy: 3% Mucositis: 16% Moderate/severe peri-implantitis: 59%
Garcia-Garcia et al. 2016[59]	Cross-sectional	25 patients 46 implants diagnosed with peri-implantitis	Case definition BOP/SUP+ Bone level >2 mm	Radiographic and intraoperative assessment Circumferential-type intrabony defects most frequent (32.6%).
Schwarz et al. 2016[54]	Cross-sectional	60 patients 229 implants diagnosed with moderate to advanced peri-implantitis	Case definition BOP/SUP+ Bone loss	Clinical assessment with validated ultrasonic A-sacnner Horizontal mucosal thickness (median) Healthy sites 1.1 mm Mucositis: 1.7 mm Peri-implantitis: 1.61 mm
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients 216/512 implants diagnosed with mucositis 46/512 implants diagnosed with peri-implantitis	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	Clinical examination Higher BOP scores at peri-implantitis sites when compared to mucositis sites. Similar PD scores.

Table 2. History of periodontitis and peri-implantitis

Study	Type of study	Study sample	History of periodontitis	Peri-implantitis	Association
Karoussis et al. 2003[89]	Cohort study 8-12 years	53 patients 8 patients with history of periodontitis 45 patients with no history of periodontitis	Case definition for periodontitis not specified. Successfully treated prior to implant therapy.	Case definition PD ≥5 mm BOP+ Annual bone loss >0.2 mm	10-year incidence of peri-implantitis (implant level) History of periodontitis: 28.6% No history of periodontitis: 5.8%
Ferreira et al. 2006[102]	Cross-sectional 0.5-5 years mean: 3.5 years	212 patients 30 patients with current periodontitis 182 patients with no current periodontitis	Case definition ≥4 teeth with PD ≥4 mm and CAL ≥3 mm (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) Periodontitis: OR 3.1
Roos-Jansåker et al. 2006[92, 93]	Cross-sectional 9-14 years mean: 11.0 years	216 patients Number of patients with/without history of periodontitis not reported	Case definition % remaining teeth with bone loss ≥4 mm (prior to implant therapy) Categories: 0-30% and 31-100%	Case definition BOP/SUP+ Bone loss ≥1.8 mm	Odds for peri-implantitis (implant level) History of periodontitis: OR 4.7
Máximo et al. 2008[100]	Cross-sectional ≥1 year mean: 3.4 years	113 patients 33 edentulous patients 21 patients with no history of periodontal bone loss 59 patients with history of periodontal bone loss	Case definition Number of quadrants showing crestal bone loss (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level ≥3 threads	Peri-implantitis most common in patients presenting with periodontal bone loss in all 4 quadrants.

Study	Type of study	Study sample	History of periodontitis	Peri-implantitis	Association
Koldsland et al. 2010[94] **& 2011**[95]	Cross-sectional 1-16 years mean: 8.4 years	<u>103 patients</u> 24 patients with history of periodontitis (6 patients with current periodontitis) 77 patients with no history of periodontitis	<u>Case definition for current periodontitis</u> ≥2 teeth with PD ≥5 mm, BOP % bone loss ≥6 mm (at final examination) <u>Definition for history of periodontitis</u> Tooth loss due to periodontitis and bone loss ≥4 mm at ≥30% of remaining teeth.	<u>Case definition</u> PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	<u>Odds for peri-implantitis (implant level)</u> History of periodontitis: OR 6.2
Roccuzzo et al. 2010[91] **& 2012**[90]	Cohort study 10 years	<u>101 patients</u> 28 patients not periodontally compromised 37 patients moderately compromised 36 patients severely compromised	Case definition for periodontitis not specified. Based on clinical examination at baseline. Periodontally compromised patients categorized according to number and depth of periodontal pockets.	Case definition for peri-implantitis not reported. Number of sites with increased PD and bone loss as well as patients treated for peri-implantitis by means of systemic antibiotics and/or surgery are presented.	Association between (i) % of sites with PD ≥6 mm, (ii) % of sites with bone loss ≥3 mm, (iii) % of patients treated for peri-implantitis and baseline periodontal status.
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	<u>203 patients</u> Number of patients with/without history of periodontitis not reported	Case definition for periodontitis not specified. Patient-reported.	<u>Case definition</u> PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.
Costa et al. 2012[17]	Cohort study 5 years	<u>80 patients with mucositis</u> 28 patients with current periodontitis 52 patients with no current periodontitis	<u>Case definition</u> ≥4 teeth with PD ≥4 mm and CAL ≥3 mm (at final examination)	<u>Case definition</u> PD ≥5 mm BOP/SUP+ Bone level (no threshold)	<u>Odds for peri-implantitis (patient level)</u> Periodontitis: OR 9.2

Study	Type of study	Study sample	History of periodontitis	Peri-implantitis	Association
Casado et al. 2013[96]	Cross-sectional 1-8 years mean: 5.6 years	215 patients 88 with history of periodontitis 127 with no history of periodontitis	Case definition Bone loss and PD ≥4 mm at ≥30% of remaining sites (prior to implant therapy). Patient records.	Case definition BOP+ Annual bone loss >0.2 mm (1 mm for first year)	Odds for peri-implantitis (patient level) History of periodontitis: OR 4.0
Marrone et al. 2013[103]	Cross-sectional 5-18 years mean: 8.5 years	103 patients 62 patients with history of periodontitis (15 patients with current periodontitis) 41 patients with no history of periodontitis	Case definition for current periodontitis BOP ≥25% & PD ≥5 mm (at final examination). Definition for history of periodontitis not reported.	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Renvert et al. 2014[98]	Cross-sectional mean: 10.1 years	270 patients 137 with history of periodontitis 133 with no history of periodontitis	Case definition for periodontitis not specified. Based on patient records, interview and clinical examination.	Case definition PD ≥4 mm BOP/SUP+ Bone level >2 mm	Odds for peri-implantitis (patient level) History of periodontitis: OR 4.5
Daubert et al. 2015[101]	Cross-sectional 9-15 years mean: 10.9 years	96 patients Number of patients with current severe periodontitis not reported	Severe periodontitis defined as the presence of periodontitis with attachment loss ≥5 mm (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	Risk for peri-implantitis (implant level) Severe periodontitis: RR 7.3
de Araujo Nobre et al. 2015[97]	Case-control ≥1 year	1275 patients 198/255 cases with history of periodontitis 57/1020 controls with history of periodontitis	Tooth loss due to periodontitis.	Case definition PD ≥5 mm BOP+ Bone loss ≥2 mm	Odds for peri-implantitis (patient level) History of periodontitis: OR 19.0

Study	Type of study	Study sample	History of periodontitis	Peri-implantitis	Association
Canullo et al. 2016[105]	Cross-sectional mean: 5.1 years	534 patients 140 patients with current periodontitis 394 patients with no current periodontitis	Case definition >30% of remaining teeth with BOP, presence of PD ≥4 mm and bone loss (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone level >3 mm	No association.
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 140 patients with current periodontitis 352 patients with not current periodontitis 96 edentulouspatients	Case definition ≥2 teeth exhibiting BOP/SUP+, attachment loss ≥2 mm and PD ≥6 mm (at final examination)	Case definition BOP/SUP+ Bone loss >2 mm	Odds for peri-implantitis (patient level) Periodontitis: OR 4.1
Rokn et al. 2016[104]	Cross-sectional 1-11 years mean: 4.4 years	134 patients 17 patients with history of periodontal treatment 117 patients with no history of periodontal treatment	Case definition for periodontitis not specified.	Case definition BOP/SUP+ Bone level >2 mm	No association.
Dalago et al. 2017[99]	Cross-sectional 1-14 years	183 patients 33 patients with history of periodontitis 150 with no history of periodontitis	Case definition Tooth loss, bone loss >5 mm, mobility degree III and/or PD >4 mm (prior to implant therapy)	Case definition PD >5 mm BOP/SUP+ Bone level >2 mm	Odds for peri-implantitis (implant level) History of periodontitis: OR 2.2
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients 39 with history of periodontitis 199 with no history of periodontitis	Case definition for periodontitis not specified.	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	No association.

Table 3. Smoking and peri-implantitis

Study	Type of study	Study sample	Smoking	Peri-implantitis	Association
Karoussis et al. 2003[89]	Cohort study 8-12 years	53 patients 41 non-smokers 12 smokers	Patient-reported Smoker: smoking at time of implant installation.	Case definition PD ≥5 mm BOP+ Annual bone loss >0.2 mm	Incidence of peri-implantitis (implant level) Non-smokers: 6.0% Smokers: 17.9%
Roos-Jansåker et al. 2006[92, 93]	Cross-sectional 9-14 years mean: 11.0 years	216 patients Number of smokers/former smokers not reported.	Patient-reported Smoker: smoking at final examination.	Case definition BOP/SUP+ Bone loss ≥1.8 mm	Odds for peri-implantitis (implant level) Smoking OR 4.6
Máximo et al. 2008[100]	Cross-sectional ≥1 year mean: 3.4 years	113 patients 60 never-smokers 32 former smokers 21 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD ≥5 mm BOP/SUP+ Bone level ≥3 threads	No association.
Koldsland et al. 2010[94] **& 2011**[95]	Cross-sectional 1-16 years mean: 8.4 years	103 patients 87 non-smokers 16 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	No association.
Rinke et al. 2010[110]	Cross-sectional 2-11 years mean: 5.7 years	89 patients 72 non-smokers 17 smokers	Patient-reported Smoker: smoking at final examination and former smokers (cessation <5 years).	Case definition PD ≥4 mm BOP+ Bone loss ≥3.5 mm	Odds for peri-implantitis (patient level) Smoker: OR 31.6
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	203 patients Number of smokers not reported.	Patient-reported Smoker: smoking at final examination.	Case definition PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.

Casado et al. 2013[96]	Cross-sectional 1-8 years mean: 5.6 years	<u>215 patients</u> 194 non-smokers 21 smokers	Patient-reported Smoker: smoking at final examination.	<u>Case definition</u> BOP+ Annual bone loss >0.2 mm (1 mm for first year)	No association.
Marrone et al. 2013[103]	Cross-sectional 5-18 years mean: 8.5 years	<u>103 patients</u> 83 non-smokers 20 smokers	Patient-reported Smoker: smoking at final examination.	<u>Case definition</u> PD >5 mm BOP+ Bone level >2 mm	No association.
Renvert et al. 2014[98]	Not reported	<u>270 patients</u> 155 non-smokers 110 smokers	Patient-reported Smoker: smoking at final examination and former smokers (cessation ≤10 years).	<u>Case definition</u> PD ≥4 mm BOP/SUP+ Bone level >2 mm	Signficant association in unadjusted but not in adjusted analysis.
Aguirre-Zorzano et al. 2015[111]	Cross-sectional 6 months - 17 years mean: 5.3 years	<u>239 patients</u> 164 non-smokers 75 smokers	Patient-reported Smoker: smoking at final examination.	<u>Case definition</u> BOP+ Bone loss >1.5 mm	No association.
Daubert et al. 2015[101]	Cross-sectional 9-15 years mean: 10.9 years	<u>96 patients</u> 89 non-smokers 7 smokers	Patient-reported at time of implant installation and final examination. Smoker: smoking at initial/final examination. Calculation of pack/years.	<u>Case definition</u> PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	No association between peri-implantitis and (i) smoking status at initial/final examation, (ii) pack/years.
de Araujo Nobre et al. 2015[97]	Case-control ≥1 year	<u>1275 patients</u> 95/255 cases are smokers 242/1020 controls are smokers	Patient-reported Smoker: smoking at final examination.	<u>Case definition</u> PD ≥5 mm BOP+ Bone loss ≥2 mm	No association.
Canullo et al. 2016[105]	Cross-sectional mean: 5.1 years	<u>534 patients</u> 393 non-smokers 141 smokers	Patient-reported Smoker: smoking at final examination.	<u>Case definition</u> PD ≥4 mm BOP/SUP+ Bone level >3 mm	No association.

Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 467 non-smokers 121 smokers	Patient-reported Smoker: smoking at time of implant installation.	Case definition BOP/SUP+ Bone loss >2 mm	Signficant association in unadjusted but not in adjusted analysis.
Rokn et al. 2016[104]	Cross-sectional 1-11 years mean: 4.4 years	134 patients 126 non-smokers 8 smokers	Patient-reported Smoker: smoking at final examination.	Case definition BOP/SUP+ Bone level >2 mm	No association.
Dalago et al. 2017[99]	Cross-sectional 1-14 years	183 patients 162 non-smokers 21 smokers	Patient-reported Smoker: smoking at final examination.	Case definition PD >5 mm BOP/SUP+ Bone level >2 mm	No association.
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients 204 non-smokers 34 smokers	Patient-reported Smoker: smoking at time of implant installation.	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	Odds for peri-implantitis (patient level) Smoking: OR 2.7

Table 4. Diabetes and peri-implantitis

Study	Type of study	Study sample	Diabetes	Peri-implantitis	Association

Ferreira et al. 2006[102]	Cross-sectional 0.5-5 years mean: 3.5 years	<u>212 patients</u> 183 non-diabetic patients 29 diabetic patients	Fasting blood sugar ≥126 mg/dl or intake of anti-diabetic medicine (at final examination)	<u>Case definition</u> PD ≥5 mm BOP/SUP+ Bone level (no threshold)	<u>Peri-implantitis (patient level)</u> Diabetes: OR 1.9
Roos-Jansåker et al. 2006[92, 93]	Cross-sectional 9-14 years mean: 11.0 years	<u>216 patients</u> Number of patients with/without diabetes not reported.	Patient-reported (at final examination) Diabetes considered in factor "General disease"	<u>Case definition</u> BOP/SUP+ Bone loss ≥1.8 mm	No association.
Máximo et al. 2008[100]	Cross-sectional ≥1 year mean: 3.4 years	<u>113 patients</u> 111 non-diabetic patients 2 diabetic patients	Patient-reported (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level ≥3 threads	No association.
Tawil et al. 2008[118]	Cohort study 1-12 years mean: 3.5 years	<u>45 diabetic patients patients</u> 22 patients with HbA1c level ≤7% 22 patients with HbA1c level 7% - 9% 1 patient with HbA1c level >9%	Regular assessments of HbA1c levels during pre- and postoperative period.	Case definition for peri-implantitis not reported.	<u>Peri-implantitis (implant level)</u> HbA1c level ≤7%: 0% HbA1c level 7% - 9%: 4.3% HbA1c level >9%: 9.1%
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	<u>203 patients</u> Number of patients with/without diabetes not reported.	Patient-reported (at final examination)	<u>Case definition</u> PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.
Costa et al. 2012[17]	Cohort study 5 years	<u>80 patients with mucositis</u> 69 non-diabetic patients 11 diabetic patients	Fasting blood sugar ≥126 mg/dl or intake of anti-diabetic medicine (at final examination)	<u>Case definition</u> PD ≥5 mm BOP/SUP+ Bone level (no threshold)	No association.

Marrone et al. 2013[103]	Cross-sectional 5-18 years mean: 8.5 years	103 patients 96 non-diabetic patients 7 diabetic patients	Patient-reported (at final examination)	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Renvert et al. 2014[98]	Not reported	270 patients 259 non-diabetic patients 11 diabetic patients	Patient-reported (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone level >2 mm	Association in unadjusted (OR 6.1, p=0.09) but not in adjusted analysis.
Daubert et al. 2015[101]	Cross-sectional 9-15 years mean: 10.9 years	96 patients 91 non-diabetic patients 5 diabetic patients	Patient records/Patient-reported (prior to implant therapy)	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	Risk for peri-implantitis (implant level) Diabetic at baseline: RR 3.0 (unadjusted analysis)
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 254 non-diabetic patients 14 diabetic patients	Patient records/Patient-reported (prior to implant therapy)	Case definition BOP/SUP+ Bone loss >2 mm	No association.
Rokn et al. 2016[104]	Cross-sectional 1-11 years mean: 4.4 years	134 patients 130 non-diabetic patients 4 diabetic patients	Patient records/Patient-reported	Case definition BOP/SUP+ Bone level >2 mm	No association.
Dalago et al. 2017[99]	Cross-sectional 1-14 years	183 patients 167 non-diabetic patients 16 diabetic patients	Patient records/Patient-reported (prior to implant therapy)	Case definition PD >5 mm BOP/SUP+ Bone level >2 mm	No association.

Table 5. Poor plaque control/lack of regular maintenance therapy and peri-implantitis

Study	Type of study	Study sample	Plaque control/ Maintenance therapy	Peri-implantitis	Association
Ferreira et al. 2006[102]	Cross-sectional 0.5-5 years mean: 3.5 years	212 patients 43 patients with good plaque control 123 patients with poor plaque control 46 patients with very poor plaque control	Plaque score (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) Poor plaque control: OR 3.8 Very poor plaque control: OR 14.3
Roos-Jansåker et al. 2006[92, 93]	Cross-sectional 9-14 years mean: 11.0 years	216 patients Number of patients with/without good plaque control not reported.	Presence of plaque at implant level (at final examination)	Case definition BOP/SUP+ Bone loss ≥1.8 mm	No association.
Koldsland et al. 2010[94] **& 2011**[95]	Cross-sectional 1-16 years mean: 8.4 years	103 patients 10 patients with plaque score ≥30% 93 patients with plaque score <30%	Plaque score and presence of plaque at implant level (at final examination) Recall visits Patient-reported	Case definition PD ≥4 mm BOP/SUP+ Bone loss ≥2 mm	No association.
Rinke et al. 2010[110]	Cross-sectional 2-11 years mean: 5.7 years	89 patients 58 patients attending recommended maintenance visits 31 patients not attending recommended maintenance visits	Maintenance therapy	Case definition PD ≥4 mm BOP+ Bone loss ≥3.5 mm	Odds for peri-implantitis (patient level) Regular maintenance therapy: OR 0.09
Dvorak et al. 2011[106]	Cross-sectional 1-24 years mean: 6.0 years	177 patients Number of patients with/without good plaque control not reported.	Presence of plaque at implant level (at final examination)	Case definition PD >4 mm BOP/SUP+ Bone loss/level (no threshold)	No association.

Costa et al. 2012[17]	Cohort study 5 years	80 patients with mucositis 39 patients with maintenance therapy 41 patients without maintenance therapy	Maintenance therapy Patient-reported and patient records Plaque index (at final examination)	Case definition PD ≥5 mm BOP/SUP+ Bone level (no threshold)	Odds for peri-implantitis (patient level) No maintenance therapy: OR 1.8
Roccuzzo et al. 2010[91] **& 2012**[90]	Cohort study 10 years	101 patients 79 patients adhering to maintenance therapy 22 patients not adhering to maintenance therapy	Maintenance therapy	Case definiton for peri-implantitis not reported. Treatment for peri-implantitis (surgery and/or systemic antibiotics).	Treatment for peri-implantitis (patient level) Adherence to maintenance therapy: 27% Non-adherence to maintenance therapy: 41%
Marrone et al. 2013[103]	Cross-sectional 5-18 years mean: 8.5 years	103 patients 16 patients with plaque score ≥30% 87 patients with plaque score <30%	Plaque index (at final examination)	Case definition PD >5 mm BOP+ Bone level >2 mm	No association.
Aguirre-Zorzano et al. 2015[111]	Cross-sectional 6 months - 17 years mean: 5.3 years	239 patients 50 patients with plaque score ≥25% 189 patients with plaque score <25%	Plaque index (at final examination)	Case definition BOP+ Bone loss >1.5 mm	Odds for peri-implantitis (implant level) Plaque ≥25%: OR 5.4
de Araujo Nobre et al. 2015[97]	Case-control ≥1 year	1275 patients Plaque present in 108/255 cases Plaque present in 67/1020 controls	Presence of plaque at patient level (at final examination)	Case definition PD ≥5 mm BOP+ Bone loss ≥2 mm	Odds for peri-implantitis (patient level) Plaque: OR 3.6
Canullo et al. 2016[105]	Cross-sectional mean: 5.1 years	534 patients Number of patients with/without good plaque control not reported.	Plaque index (at final examination)	Case definition PD ≥4 mm BOP/SUP+ Bone level >3 mm	Odds for peri-implantitis (patient level) Plaque >30%: OR 3.4
Derks et al. 2016[52]	Cross-sectional 9 years	588 patients 474 patients attending annual	Recall visits Patient records	Case definition BOP/SUP+	No association.

		maintenance visits 101 patients not attending annual maintenance visits		Bone loss >2 mm	
Rokn et al. 2016[104]	Cross-sectional 1-11 years mean: 4.4 years	134 patients Number of patients with/without good plaque control not reported.	Plaque index (at final examination)	Case definition BOP/SUP+ Bone level >2 mm	Odds for peri-implantitis (implant level) Plaque index (categorization not reported): OR 5.4
Schwarz et al. 2017[29]	Cross-sectional 1 month - 6.7 years mean: 2.2 years	238 patients Number of patients with/without good plaque control not reported.	Plaque index (at final examination)	Case definition BOP/SUP+ Changes in the radiographic bone level compared to baseline (i.e. prosthesis installation)	Odds for peri-implantitis (patient level) Plaque ≥33%: OR 9.3
Monje et al. 2017[124]	Cross-sectional 3-4.5 years mean: 3.8 years	153 patints Patients categorized according to frequency of maintenance visits	Plaque index (at final examination) Recall visits Patient records on early marginal bone loss	Case definition BOP/SUP+ Changes in the radiographic bone level (≥2 mm) compared to baseline (i.e. prosthesis installation) Alternative case definitions were further explored (i.e. ≥3 mm and ≥4 mm with signs of inflammation)	Prevalence of peri-implantitis: Regular compliers: 72.7% were healthy, 4.5% had peri-implantitis. Non-compliers: 53.5% were healthy, and 23.9% had periimplantitis (OR=0.14)

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