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Prevalence and Mechanisms of Peri-implant Diseases

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Abstract

The aim of the present critical review is to summarize recent evidence on the prevalence of peri-implant diseases and their similarities and differences with periodontal diseases with a focus on their pathogenetic mechanisms. Reports on the extent and severity of peri-implant diseases are influenced by different case definitions. The prevalence of peri-implant diseases is reported at the subject or implant level and affected by the type of population samples analyzed (e.g., randomly selected population samples or convenience samples). The outcomes of studies on animals and humans indicate that experimental biofilm accumulation leads to a higher frequency of bleeding sites around implants as compared with teeth. Despite the proof of principle that experimentally induced mucositis may be reversible, early diagnosis and management of naturally occurring peri-implant mucositis are clinically relevant. Tissue destruction at experimental peri-implantitis sites is faster and more extensive when compared with that at experimental periodontitis sites. Although human periodontitis and peri-implantitis lesions share similarities with respect to etiology and clinical features, they represent distinct entities from a histopathologic point of view. To avoid implant loss, patients diagnosed with peri-implantitis should be treated without delay.

Keywords: periodontal disease(s)/periodontitis, implant dentistry/implantology, inflammation, peri-implant infection(s), epidemiology, plaque/plaque biofilms

Introduction

Upon completion of hard and soft tissue integration following implant placement (Salvi et al. 2015), peri-implant diseases have been defined as 1) development of mucosal inflammation around implants without loss of supporting bone (i.e., peri-implant mucositis) and 2) presence of inflammation with additional loss of supporting bone (i.e., peri-implantitis; Lindhe and Meyle 2008). Peri-implant diseases are initiated by the presence of similar etiologic factors as those involved in the onset of periodontal diseases (Heitz-Mayfield and Lang 2010). In patients diagnosed with moderate/severe peri-implantitis, onset of disease occurred within 3 y of function and followed a nonlinear accelerating pattern over a 9-year period (Derks et al. 2016b).

For the purpose of the present critical review, recent evidence on the prevalence/incidence of peri-implant mucositis and peri-implantitis was summarized. In addition, peri-implant mucositis and peri-implantitis were compared with their counterparts around natural teeth (i.e., gingivitis and periodontitis), focusing on similarities and differences between the pathogeneses of periodontal and peri-implant diseases.

Prevalence of Peri-implant Diseases

Currently, the prevalence of peri-implant diseases represents a controversial issue (Tarnow 2016). Patient-based estimated weighted mean prevalences and ranges for peri-implant mucositis and peri-implantitis were reported in a systematic review with meta-analysis (Derks and Tomasi 2015). The prevalence for peri-implant mucositis was reported at 43% (range, 19% to 65%), whereas for peri-implantitis it amounted to 22% (range, 1% to 47%; Derks and Tomasi 2015). Moreover, results from recent cross-sectional studies not included in the systematic review mentioned above reported prevalences for peri-implantitis within ranges comparable to those reported by Derks and Tomasi (2015): 20% (Rokn et al. 2016), 15.1% (Aguirre-Zorzano et al. 2015), 13.9% (Schwarz et al. 2015), 26% (Daubert et al. 2015), 16.4% (Dalago et al. 2016), 12.9% (Konstantinidis et al. 2015), and 28% (Filho et al. 2014).

Clearly, these outcomes indicate a wide range in the prevalence of peri-implant diseases, making it difficult to globally estimate the magnitude of the disease. These inadequacies may rely on methodological inconsistencies and shortcomings of the reported studies (Sanz and Chapple 2012; Tomasi and Derks 2012). One of the major inconsistencies reflecting the lack of consensus in epidemiologic research is found in the differences applied for case definitions.

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In cases with missing baseline radiographs, the presence of clinical inflammation with peri-implant bone-level changes of 2 mm after remodeling was suggested as definition criteria for peri-implantitis (Sanz and Chapple 2012). In cases with baseline radiographs, incidence of peri-implantitis was defined as the presence of clinical inflammation and a bone loss of 1 to 1.5 mm (Sanz and Chapple 2012). Despite these recommendations for case definitions, varying thresholds were employed for the assessment of peri-implant bone loss and reference time points from which the specified bone loss occurred. Of course, when different crestal bone loss thresholds are used, various outcomes are reported. In the review by Derks and Tomasi (2015), the study reporting the lowest peri-implantitis prevalence (1%) considered, for the case definition, a threshold for bone loss of 5 mm (Zetterqvist et al. 2010), whereas the study reporting the highest prevalence (47%) applied a threshold for bone loss of 0.4 mm (Koldsland et al. 2010).

A retrospective cross-sectional analysis of a randomly selected Swedish population sample defined peri-implantitis as the presence of bleeding on probing/suppuration and crestal bone loss >0.5 mm and reported a 45% patient-based prevalence for peri-implantitis after 9 y of loading (Derks et al. 2016a). However, in terms of the severity of the disease when the threshold for bone loss was >2 mm, 14.5% of the patients exhibited moderate to severe peri-implantitis (Derks et al. 2016a).

The fact that several studies reported only implant-based data and lacked subject-based outcomes was emphasized in a systematic review on the quality of studies reporting prevalence, incidence, and risk factors of peri-implant diseases (Tomasi and Derks 2012). The consensus report of the Eighth European Workshop on Periodontology (EWP) considered the outcome of interest to be the impact of peri-implant diseases on individuals—not that on individual implants—thereby emphasizing that research assessing the prevalence of peri-implant diseases should focus on subject-level analysis (Sanz and Chapple 2012). This is reflected by the fact that recent investigations adopted the recommendations of the Eighth EWP and included patient-level analyses (Meijer et al. 2014; Aguirre-Zorzano et al. 2015; Daubert et al. 2015; Konstantinidis et al. 2015; Schwarz et al. 2015; Dalago et al. 2016; Derks et al. 2016a, 2016b; Rokn et al. 2016).

Time of implant function is another relevant parameter influencing the reported values for prevalence of peri-implantitis. In this respect, the consensus report of the Eighth EWP recommended the inclusion of implants with a function time "of sufficient duration" without specifying a predetermined time threshold (Sanz and Chapple 2012). However, since establishment of any type of chronic diseases (e.g., peri-implantitis) requires time, reports on prevalence based on cases with an implant function time <5 y seem inappropriate (Gianserra et al. 2010). Consistent results with respect to the prevalence/incidence of peri-implantitis were reported when a function time of 5 y and a threshold for bone loss >2 mm were included (Meijer et al. 2014; Konstantinidis et al. 2015).

Another critical issue in several studies reporting on the prevalence/incidence of peri-implant diseases is the fact that their analysis relies on convenience samples from universities or private clinics of limited sample size rather than large randomly selected population samples (Patten 2000; Sanz and Chapple 2012; Tomasi and Derks 2012). This bears the risk for selection bias and limits external validity with respect to the true prevalence/incidence of peri-implant diseases. In fact, few studies reporting on the prevalence/incidence of peri-implant diseases included patients treated in both private and university settings (Renvert et al. 2014; Schwarz et al. 2015; Derks et al. 2016a, 2016b) or analyzed a randomly selected population sample (Derks et al. 2016a, 2016b).

Pathogenesis of Gingivitis versus Peri-implant Mucositis

Experimental Studies in Animal Models

The host response to experimental biofilm accumulation around teeth and osseointegrated implants has been investigated in dogs (Berglundh et al. 1992; Ericsson et al. 1992; Ericsson et al. 1995; Abrahamsson et al. 1998) and monkeys (Schou et al. 2002), respectively. A comparison of the histopathologic similarities and differences between experimental gingivitis and peri-implant mucositis was summarized by Lang et al. (2011).

Although the early host response to the bacterial challenge (e.g., after 3 wk) displayed similar characteristics comparing peri-implant mucosa with gingiva, after a period of up to 9 mo of biofilm accumulation, the apical extension and the size of the inflammatory infiltrate were more pronounced in the peri-implant mucosa as compared with those in the gingiva. This indicated a stronger host response to the bacterial challenge in the soft tissues adjacent to implants as compared with that around teeth.

In addition, the location and composition of inflammatory lesions in the peri-implant mucosa were investigated for 3 implant systems with different geometry and dimensions (i.e., ITI Dental Implant System, Astra Tech Dental Implant System, Brånemark System) following 5 mo of experimental biofilm accumulation in dogs (Abrahamsson et al. 1998). The outcomes of that study (Abrahamsson et al. 1998) revealed similar inflammatory lesions in terms of extension and composition around the 3 implant systems tested, suggesting that the host-response mechanisms to the bacterial challenge are not system specific.

From a diagnostic point of view, results from a study on cynomolgus monkeys revealed deeper penetrations of a periodontal probe in the soft tissues around implants with mild and severe mucositis as compared with those around teeth with mild and severe gingivitis (Schou et al. 2002).

Analysis of Biopsies from Cross-sectional Human Studies

Analysis of animal biopsies of the supracrestal connective tissue compartment revealed quantitative and qualitative differences in terms of density of collagen fibers and fibroblasts, collagen fiber

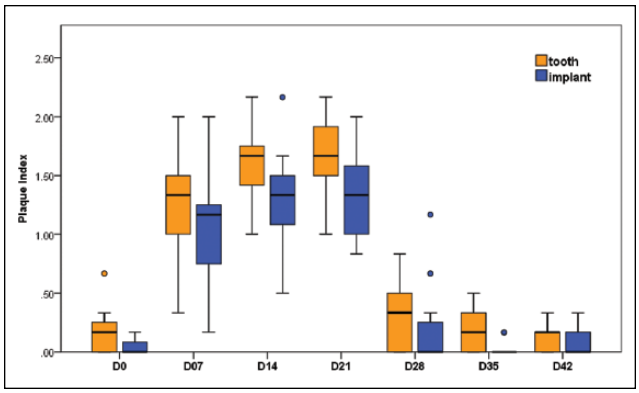

Figure 1. Comparative boxplots of Plaque Index scores at tooth and implant sites during 21 d of experimental gingivitis/mucositis (D0 to D21) and 21 d of reinstituted oral hygiene practices (D21 to D42; adapted from Salvi et al. 2012).

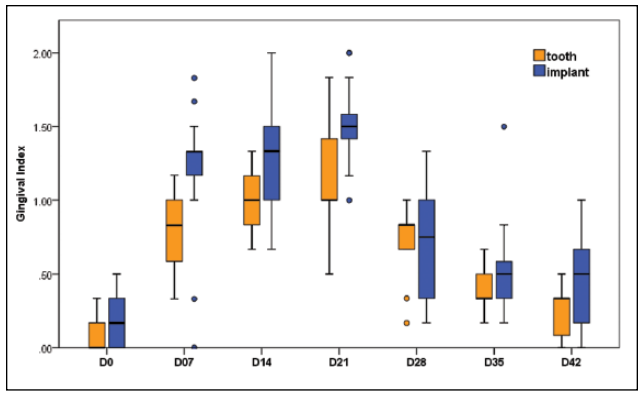

Figure 2. Comparative boxplots of Gingival Index scores at tooth and implant sites during 21 d of experimental gingivitis/mucositis (D0 to D21) and 21 d of reinstituted oral hygiene practices (D21 to D42; adapted from Salvi et al. 2012).

orientation, and vascular structures between the gingiva around teeth and the mucosa around titanium implants (Berglundh et al. 1991; Berglundh et al. 1994). Human biopsies of gingival and peri-implant mucosal tissues characterized by clinical health or inflammation have been harvested to investigate the expression of vascular cell adhesion molecules and the cellular composition in the connective tissue (Schmid et al. 1992; Tonetti et al. 1994; Mackenzie and Tonetti 1995; Tonetti et al. 1995; Liljenberg et al. 1997; Zitzmann et al. 2002). Similarities and differences were observed in the expression of cell adhesion molecules, cytokeratins, and inflammatory cell populations between gingival and peri-implant soft tissue biopsies.

Because of the cross-sectional nature of the human studies cited above, information on the temporal exposure of implants to the oral environment was lacking, suggesting that a prolonged exposure of implants to the bacterial challenge may yield quantitative and qualitative changes in the composition of the inflammatory infiltrate.

Consequently, differences in the outcomes of comparative cross-sectional studies in humans should be interpreted with caution.

Pathogenesis of Gingivitis versus Peri-implant Mucositis

Experimental Studies in Humans

The effects of experimental biofilm accumulation on the development of an inflammatory response in the soft tissues adjacent to titanium dental implants were investigated in humans (Pontoriero et al. 1994; Zitzmann et al. 2001; Salvi et al. 2012; Meyer et al. 2016). In a first study, 20 partially edentulous patients received dental implants following successful completion of periodontal therapy (Pontoriero et al. 1994). After 6 mo of closely supervised oral hygiene, the patients were asked to abstain from oral hygiene practices for a period of 3 wk. At the end of this period, optimal plaque control was reinstituted. The comparison of experimental biofilm accumulation and the host response expressed at gingival and peri-implant tissues yielded no differences in the development of experimental gingivitis and mucositis, respectively (Pontoriero et al. 1994).

A second study of humans involved 12 partially edentulous patients (Zitzmann et al. 2001). The inflammatory response to the experimental bacterial challenge was characterized by the enumeration of the proportions of T and B cells in gingival and peri-implant tissues. Biopsies harvested around implants and teeth in a clinically healthy situation and after 21 d of experimental biofilm accumulation indicated that the connective tissue surrounding teeth and implants displayed an increased volume of T and B lymphocytes as a consequence of abolished oral hygiene practices (Zitzmann et al. 2001). However, the size of the inflammatory cell infiltrate and the number of several immune cell populations were not statistically significantly different when gingival and mucosal biopsies were compared, respectively.

Outcomes of a comparative study of humans indicated that following 3 wk of experimental biofilm accumulation, significantly more bleeding sites were observed around implants than around teeth (Salvi et al. 2012). Absence of bleeding sites, however, was not achieved around implants after 3 wk of reinstituted plaque control, indicating that complete resolution of experimental mucositis in humans either takes >3 wk or may not be achieved (Salvi et al. 2012; Figs. 1, 2).

In contrast to the study by Salvi et al. (2012), recent findings indicated that all clinical parameters assessed in a sample of subjects ≥70 y old returned to preexperimental levels after 3 wk of reinstituted plaque control, documenting reversibility of experimentally induced peri-implant mucositis in elderly subjects (Meyer et al. 2016).

Furthermore, complete resolution of experimental mucositis was documented in both studies at the host biomarker level, as identified by the decrease to preexperimental values of crevicular fluid inflammatory biomarkers (Salvi et al. 2012; Meyer et al. 2016).

Despite the proof of principle that experimentally induced mucositis may be reversible, early diagnosis and management

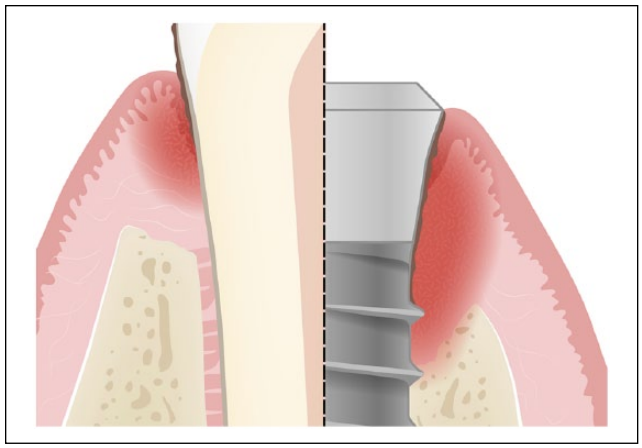

Figure 3. Extension of the inflammatory connective tissue (ICT) infiltrate at tooth and implants sites in relation to the alveolar crest after ligature removal. At implant sites, the ICT reached the alveolar crest and extended into the bone marrow, whereas at tooth sites the ICT was separated apically from the alveolar crest by a layer of supracrestal collagen fibers (adapted from Lindhe et al. 1992).

of naturally occurring peri-implant mucositis is clinically relevant. This is documented by findings indicating that preexisting peri-implant mucositis in conjunction with lack of adherence to maintenance care was associated with a higher incidence of peri-implantitis over a 5-y follow-up period (Costa et al. 2012). The outcomes of that study yielded a 5-y incidence of peri-implantitis of 18.0% in the group of patients with maintenance care and 43.9% in the group without (Costa et al. 2012).

Pathogenesis of Periodontitis versus Peri-implantitis

Experimental Studies in Animal Models

Experimental studies comparing the pathogenesis of periodontitis with that of peri-implantitis were conducted through the ligature model in dogs (Lindhe et al. 1992; Marinello et al. 1995; Zitzmann et al. 2004) and in monkeys (Lang et al. 1993; Schou et al. 1993; Warrer et al. 1995). A comparison of the histopathologic similarities and differences between experimental ligature-induced periodontitis and peri-implantitis was summarized by Berglundh et al. (2011).

Collectively, the results of these experimental animal studies indicated that placement of ligatures around teeth and osseointegrated implants resulted in loss of supporting tissues and large inflammatory connective tissue (ICT) infiltrates surrounding teeth and implants. Furthermore, the results of these studies indicated that ligature removal resulted in a self-limiting process around teeth characterized by a connective tissue encapsulation separating the ICT from the alveolar crest. In peri-implant tissues, however, the ICT extended to the alveolar crest and was associated with a high density of osteoclasts (Fig. 3).

Although arrest of disease progression occurred in 20% of cases, it was demonstrated that, following ligature removal, the majority of the established peri-implantitis lesions experienced additional bone loss within a period of 1 y (Zitzmann et al. 2004).

Thus, it has been suggested that spontaneous progression of experimental peri-implantitis following ligature removal may be further influenced by implant surface characteristics. Hence, the influence of implant surface roughness on the amount of bone loss occurring in the period following ligature removal was investigated (Carcuac et al. 2013). The outcomes of that study demonstrated that the amount of bone loss was significantly larger at implants with a modified surface as compared with 1) implants with a turned surface and 2) teeth (Carcuac et al. 2013). Moreover, the histologic analysis revealed that peri-implantitis lesions exhibited ICTs that 1) were larger, 2) extended closer to the alveolar crest, and 3) contained larger proportions of neutrophils and osteoclasts as compared with those of periodontitis lesions (Carcuac et al. 2013).

Peri-implant Mucositis and Peri-implantitis in Humans

Influence of Material Wear, Implant Design, and Surface Roughness

Titanium wear particles from implant surfaces are found in hard and soft peri-implant tissues, but their role in the pathogenesis of peri-implant diseases remains unclear. Outcomes of an in vitro study, however, indicated that peri-implant granulation tissue fibroblasts challenged with TiO_2 particles in combination with a *Porphyromonas gingivalis* infection significantly enhanced the inflammatory response, as measured by TNF-α secretion (Irshad et al. 2013).

Yet, it has to be pointed out that evidence for the influence of implant surface roughness on the incidence of peri-implant mucositis and peri-implantitis in humans is still limited (Renvert et al. 2011; Renvert et al. 2012; Renvert and Polyzois 2015). Outcomes of an experimental study humans and a systematic review indicated that peri-implant mucositis does not seem to be associated with implant or abutment systems with a specific design or surface roughness (Wennerberg et al. 2003; Renvert and Polyzois 2015). Moreover, outcomes of a clinical study including 3 implant systems failed to detect differences in the incidence of peri-implantitis as an effect of implant surface and design over a period of 13 y (Renvert et al. 2012).

Pathogenesis of Periodontitis versus Peri-implantitis

Analysis of Biopsies from Cross-sectional Human Studies

Studies analyzing histopathologic and functional data from sites with periodontitis and peri-implantitis were conducted in humans (Gualini and Berglundh 2003; Berglundh et al. 2004; Bullon et al. 2004; Venza et al. 2010; Becker et al. 2014; Carcuac and Berglundh 2014).

The immunohistochemical analysis and comparison of soft tissue biopsies from patients with peri-implant mucositis and peri-implantitis lesions were reported by Gualini and Berglundh (2003). It was observed that peri-implantitis lesions contained a significantly greater proportions of B cells and neutrophils as compared with mucositis lesions, indicating that peri-implantitis and mucositis differed with respect to not only the size of the lesion but also a specific cell profile.

Although periodontitis and peri-implantitis share common etiologic factors (Heitz-Mayfield and Lang 2010), comparative analyses of human gingival and mucosal biopsies revealed critical histopathologic differences. Compared with periodontitis lesions, peri-implantitis lesions 1) extended apically from the pocket epithelium and 2) were not encapsulated by healthy connective tissue (Carcuac and Berglundh 2014). Thus, from a clinical point of view, peri-implantitis lesions may display a more aggressive character and may be expected to progress more rapidly when compared with periodontitis lesions (Fig. 4).

Furthermore, peri-implantitis lesions displayed enhanced densities of vascular structures in the noninfiltrated versus the infiltrated connective tissue areas, suggesting that host-response cells need to cover a longer distance to target the bacterial challenge (Carcuac and Berglundh 2014).

From a functional point of view, comparative analyses of gingival and mucosal biopsies by means of genetic signatures indicated that periodontitis and peri-implantitis represent 2 distinct entities (Venza et al. 2010; Becker et al. 2014).

Conclusions and Clinical Implications

Prevalence of Peri-implant Diseases

- Controversial prevalences of peri-implant diseases are reported in the literature.
- Differences in case definitions influence the extent and severity of peri-implant diseases and make comparisons among studies difficult.
- Convenience samples, rather than randomly selected population samples, are often analyzed to estimate the prevalence of peri-implant diseases.
- Recent studies report the prevalence of peri-implant diseases on both implant- and subject-based analyses.

Peri-implant Mucositis

- Long-standing experimental plaque accumulation in animals leads to a more severe lesion in the peri-implant as compared with the periodontal soft tissues.
- Experimental plaque accumulation around implants in humans yields a stronger inflammatory response when compared with that around natural teeth.
- Complete resolution of experimental mucositis has been shown in subjects ≥70 y. In younger subjects, complete resolution takes >3 wk or may not be achieved.
- Early diagnosis and management of peri-implant mucositis should be implemented to prevent the onset of peri-implantitis.

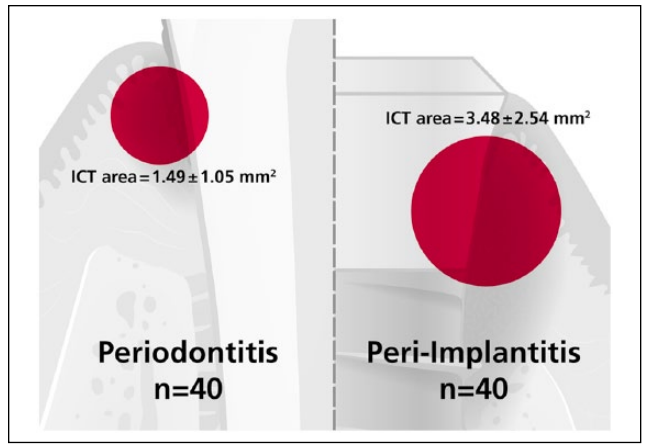

Figure 4. Difference in the size of the inflammatory connective tissue (ICT) infiltrate of 40 human biopsies of teeth with chronic periodontitis and 40 human biopsies of implants with peri-implantitis. The area of the ICT at the implant sites was more than twice as large when compared with that at the tooth sites (adapted from Carcuac and Berglundh 2014).

Peri-implantitis

- Tissue destruction at experimental peri-implantitis sites is faster and more extensive than that at experimental periodontitis sites.
- Lack of treatment of experimental peri-implantitis leads to progression of tissue destruction.
- Despite similarities in etiology and clinical features, human periodontitis and peri-implantitis lesions represent distinct entities from a histopathologic point of view.
- Given a more aggressive pattern of tissue destruction than that of periodontitis, patients diagnosed with peri-implantitis should be treated without delay.

Author Contributions

G.E. Salvi, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; R. Cosgarea, contributed to conception, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; A. Sculean, contributed to conception and design, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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