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REVIEW

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Physiopathology of peri-implant diseases

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Abstract

Background: Peri-implant health is characterized by the absence of clinical signs of soft tissue inflammation. Peri-implant diseases are initiated by the presence of bacterial biofilms and share a similar etiology as that involved in the onset of periodontal diseases.

Purpose: To summarize available evidence on the physiopathology of peri-implant diseases with emphasis on similarities and differences with periodontal diseases.

Materials and Methods: Evidence on the biologic mechanisms involved in the pathogenesis of peri-implant mucositis and peri-implantitis were explored in the recent scientific literature.

Results: Findings of studies in animals and in humans indicate that experimental peri-implant mucositis leads to a larger inflammatory connective tissue infiltrate and to a higher frequency of bleeding sites around implants compared with teeth. Tissue destruction at experimental peri-implantitis sites is more pronounced 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 physiopathologic point of view.

Conclusions: Diagnosis of peri-implant health requires a clinical examination to confirm absence of peri-implant soft tissue inflammation. In order to make a correct diagnosis and select the appropriate therapeutic steps to manage peri-implant diseases, knowledge of their pathogenetic mechanisms is required.

KEYWORDS
bone, histological analysis, inflammation, peri-implant lesions, peri-implantitis

SUMMARY BOX

What is known

- Peri-implant diseases are inflammatory conditions initiated by bacterial biofilms
- Peri-implant mucositis is a reversible inflammatory disease
- Untreated peri-implantitis leads to implant loss

What this study adds

- A new classification of peri-implant diseases and conditions

- New insights on the comparison between the pathogenesis of periodontitis and peri-implantitis

1 | INTRODUCTION

Following completion of osseointegration and soft-tissue healing after implant placement,[1] peri-implant diseases are initiated by the presence of similar etiologic factors as those characterizing the onset of periodontal diseases.[2] As recently summarized by Larsson et al.,[3] environmental, genetic, and epigenetic factors also contribute to patient's susceptibility to periodontal diseases.[4] Very limited evidence, however, is available on how these factors affect the pathogenesis of peri-implant diseases.

Although human periodontal and peri-implant lesions share similarities with respect to etiology and clinical characteristics, analysis of tissue biopsies from patients affected by severe periodontitis and peri-implantitis indicate that they represent distinct entities from a histopathological point of view.[5] In addition, comparative gene expression analyses of soft tissue biopsies harvested around teeth and implants indicated that periodontitis and peri-implantitis lesions represent two distinct entities from a functional point of view.[6,7]

It was the aim of the present review to summarize and compare, starting from peri-implant health, similarities and differences between periodontal diseases (i.e., gingivitis and periodontitis) with their counterparts around dental implants (i.e., peri-implant mucositis and peri-implantitis) with emphasis on their physiopathologic mechanisms.

1.1 | Classification and definitions of peri-implant health and diseases

The 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions introduced new disease and case definitions for peri-implant health, peri-implant mucositis and peri-implantitis.[8] After the World Workshop of 1999, this was the first time that peri-implant diseases and conditions were addressed as part of the World Workshop Classification.

1.2 | Peri-implant health

Healthy soft tissues around an osseointegrated dental implant are termed peri-implant mucosa and are composed of a layer of connective tissue covered by either keratinized or non-keratinized epithelium.

Under healthy conditions, clusters of inflammatory cells may be observed in the connective tissue lateral to the epithelium. The apico-coronal dimension of the peri-implant mucosa amounts to 3–4 mm of which approximately 2 mm are epithelium facing the implant surface. The three-dimensional characteristics of the peri-implant mucosa, however, may vary depending on factors such as the depth of implant placement and the soft-tissue phenotype. The predominant part of the endosseous component of the implant is in direct contact with mineralized bone, while the remaining implant surface faces bone marrow, fibrous tissue, and vascular structures. From a clinical point of view, peri-implant health is characterized by the absence of signs of inflammation such as erythema, swelling, bleeding on probing (BoP), and suppuration (Figure 1A–C).[9]

1.3 | Peri-implant mucositis

Peri-implant mucositis is defined as an inflammatory lesion in the soft tissues around an osseointegrated implant in the absence of loss of supporting bone or continuing marginal bone loss.[10] Peri-implant mucositis is initiated by bacterial biofilms disrupting the host/parasite homeostasis at the implant-mucosa interface and results in an inflammatory lesion in the supracrestal mucosal compartment.[10] The main clinical characteristic of peri-implant mucositis is bleeding on probing (BoP).[10] Suppuration following probing may also be observed (Figures 2–4).

1.4 | Peri-implantitis

Peri-implantitis is defined as a pathological condition induced by bacterial biofilms and occurs in the tissues surrounding an osseointegrated implant. It is characterized by bleeding on probing (BoP) and/or suppuration together with progressive loss of supporting bone (Figure 5A–N).[11] The accumulation of bacterial biofilms on implant and abutment surfaces has been documented to be involved in the development of experimental peri-implantitis in animal models.[12–15]

2 | EXPERIMENTAL GINGIVITIS VS. EXPERIMENTAL PERI-IMPLANT MUCOSITIS

2.1 | Animal studies

Analysis of biopsies from healthy supracrestal connective tissue compartments revealed qualitative and quantitative differences with respect to collagen fibers orientation, density of collagen fibers and fibroblasts as well as vascular structures between the gingiva and the peri-implant mucosa.[16,17]

The transition from peri-implant health to peri-implant mucositis has been investigated using preclinical animal models of

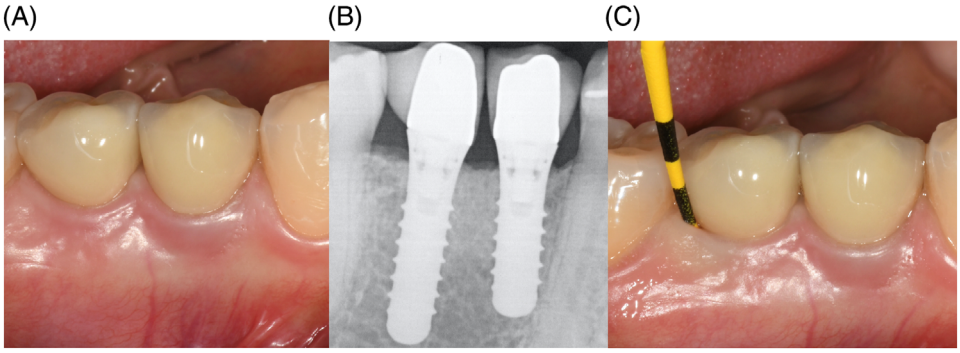

FIGURE 1 (A–C) Healthy clinical and radiographic peri-implant tissue conditions. Absence of signs of inflammation including absence of bleeding on probing (BoP) can be observed.

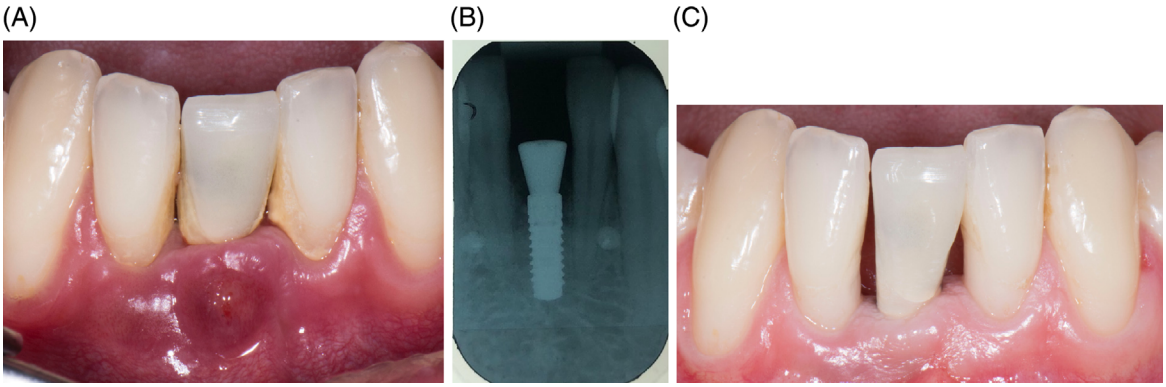

FIGURE 2 (A–C) Acute signs of inflamed peri-implant soft tissues in the presence of bacterial biofilms and calculus without marginal bone loss (i.e., peri-implant mucositis). Clinical appearance 3 months following non-surgical treatment and prosthesis modification.

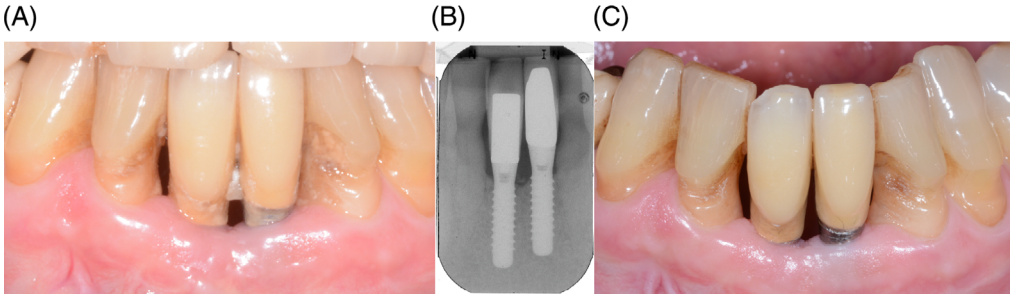

FIGURE 3 (A–C) Inflamed peri-implant soft tissues in the presence of bacterial biofilms without marginal bone loss (i.e., peri-implant mucositis). Clinical appereance 12 months following mechanical non-surgical therapy and prosthesis modification.

experimentally induced peri-implant mucositis.[18–20] Comparisons of histopathological similarities and differences between experimentally induced gingivitis and peri-implant mucositis have been summarized by Lang and co-workers.[21]

Although a comparable host response to a 21-day experimental biofilm accumulation was observed between gingiva and peri-implant mucosa,[18] the apical extension and the size of the inflammatory lesion were larger in the peri-implant mucosa compared with those in the gingiva when bacterial biofilms were allowed to form under experimental conditions up to 9 months.[19,20] These outcomes indicated a stronger host response in the peri-implant mucosa to a long-standing biofilm challenge around implants compared with that around teeth.

The size and composition of inflammatory infiltrates in the peri-implant mucosa were also investigated for implant systems with different macro- and microtopography characteristics (e.g., ITI Dental Implant System, Astra Tech Dental Implant System, and Brånemark System) over a period of 5 months of biofilm formation under experimental conditions in dogs.[22] Comparable inflammatory infiltrates in terms of size and composition around the three implant brands were observed, suggesting that the host response to the biofilm accumulation was not linked the implant systems usedp.[22]

2.2 | Studies in humans

The effects of biofilm accumulation on the development of experimental peri-implant mucositis have also been investigated in humans.[23–29]

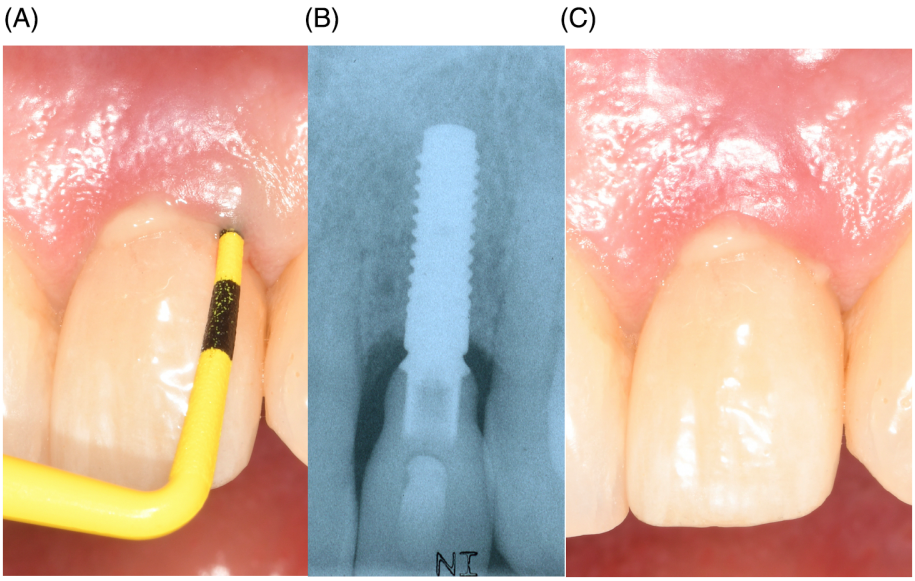

FIGURE 4 (A–C) Peri-implant mucositis characterized by 6 mm peri-implant probing depth in conjunction with suppuration following probing.

Collectively, the results of these studies indicated that a pre-experimental phase under optimal oral hygiene practices yielded healthy peri-implant conditions. Following this phase, subjects refrained from oral hygiene practices for 21 days. At the end of this period of biofilm accumulation under experimental conditions, an inflammatory response in the peri-implant mucosa was observed in all studies, indicating a true cause-effect relationship.[23–29]

A true cause-effect relationship between biofilm accumulation under experimental conditions and development of peri-implant mucositis, however, should also include the proof of reversibility to pre-experimental levels of mucosal health.

Outcomes of a study by Salvi et al.[25] indicated that clinical signs of experimental peri-implant mucositis were significantly less reduced compared with those of experimental gingivitis and were still present following 21 days of reinstituted self-performed biofilm control. This suggests that clinical resolution of experimental peri-implant mucositis in humans may take longer than 21 days of healing.[25]

Resolution of experimental peri-implant mucositis, however, was achieved at the biochemical level of the host response, as documented by the decrease to pre-experimental concentrations of biomarkers in the crevicular fluid.[25]

Results from an experimental peri-implant mucositis study in subjects aged ≥70 years indicated that all clinical parameters returned to pre-experimental levels after 21 days of reinstituted oral hygiene practices, suggesting reversibility of experimental mucositis in elderly subjects.[23]

The effects of the insertion depth of tissue level implants on the resolution of experimen-tal mucositis were investigated in humans.[27] Resolution of experimental mucositis was delayed and of smaller magnitude during the first 21 days of reinstituted oral hygiene practices at implants with a mucosal tunnel depth ≥3 mm compared with that at implants with a depth ≤1 mm.[27] Extraoral professional biofilm removal of screw-retained single-unit crowns was needed to revert peri-implant mucositis to pre-experimental levels at implants with a mucosal tunnel depth ≥3 mm.[27]

In summary, a cause-effect relationship between biofilm accumulation under experimental conditions and development of peri-implant mucositis has been demonstrated in humans. Moreover, findings from studies in humans indicate that resolution of the clinical signs of inflammation following experimental mucositis requires a healing period longer than 21 days[25] and is dependent on the implant insertion depth and presence or absence of keratinized mucosa.[27,30,31]

Although experimentally induced peri-implant mucositis may be reversible, early diagnosis and management of naturally occurring mucositis is clinically relevant. This is corroborated by findings indicating that pre-existing mucositis in conjunction with lack of compliance with maintenance care was associated with a higher incidence of peri-implantitis over 5 years.[32] Subjects compliant with a yearly maintenance care program displayed a 5-year incidence of peri-implantitis of 18.0% whereas a 43.9% peri-implantitis incidence was observed in subjects non-compliant with maintenance care.[32]

2.3 | Analysis of tissue biopsies in humans

Biopsies from gingiva and peri-implant mucosa characterized by clinical health or inflammation were collected to investigate the expression of vascular cell adhesion molecules and the cellular composition in the connective tissue.[33–38] 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. Based on the fact that the studies cited above are characterized by a cross-sectional design, information on the temporal exposure of implants in the oral cavity was lacking. This, in turn, suggests that, depending on the exposure of implants to the bacterial challenge, both qualitative and quantitative changes in the

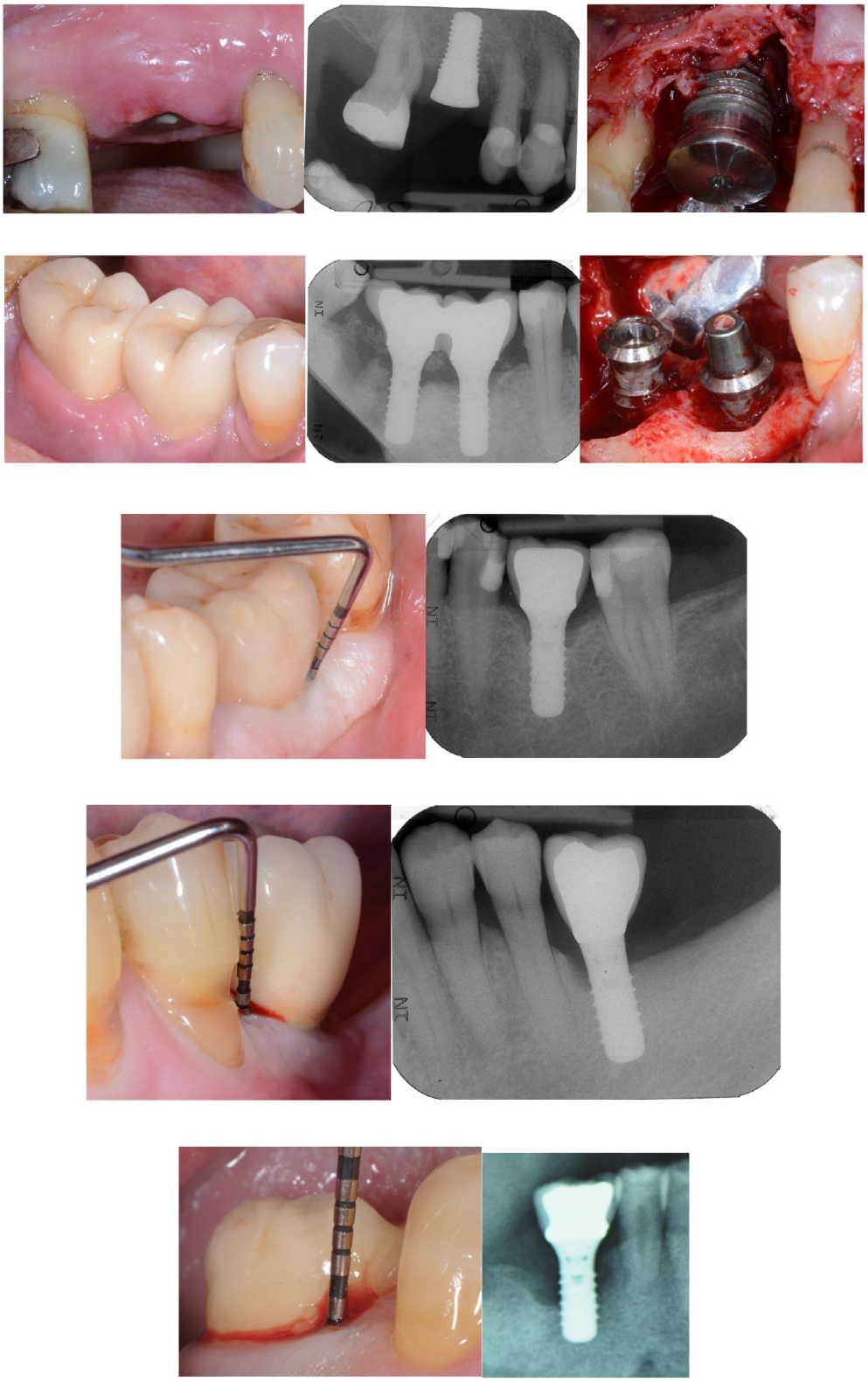

FIGURE 5 (A–N) Clinical and radiographic scenarios of peri-implantitis (i.e., increased peri-implant probing depth, BoP and/or suppuration and peri-implant marginal bone loss).

composition of the inflammatory infiltrate may be observed (Figure 6A, B).

Hence, caution should be applied when interpreting differences in outcomes of comparative cross-sectional studies in humans.

Tissue biopsies harvested at implant and tooth sites from a clinically healthy situation and following 21 days of experimental biofilm accumulation indicated that in the connective tissue surrounding both implants and teeth an increased volume of T- and B-lymphocytes was

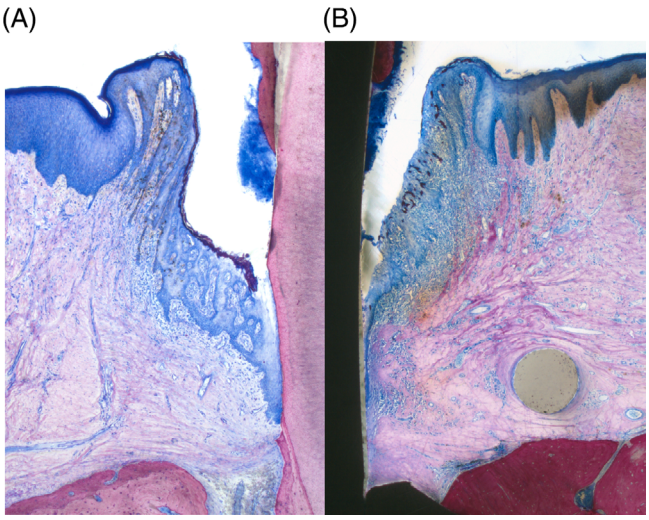

FIGURE 6 (A, B) Histological sections of a gingivitis lesion (A) and of a peri-implant mucositis lesion (B) in humans. (A) Inflammatory connective tissue infiltrate as a result of the host response to the bacterial challenge leading to gingivitis. Bacterial biofilm on the tooth surface: blue, on top of calculus deposits: red. (B) Inflammatory connective tissue infiltrate as a result of the host response to the bacterial challenge leading to peri-implant mucositis. Bacterial biofilm on the surface of the implant: blue, on top of calculus deposits: red (courtesy of Prof. Dr. Dieter D. Bosshardt, adapted from Reference 21).

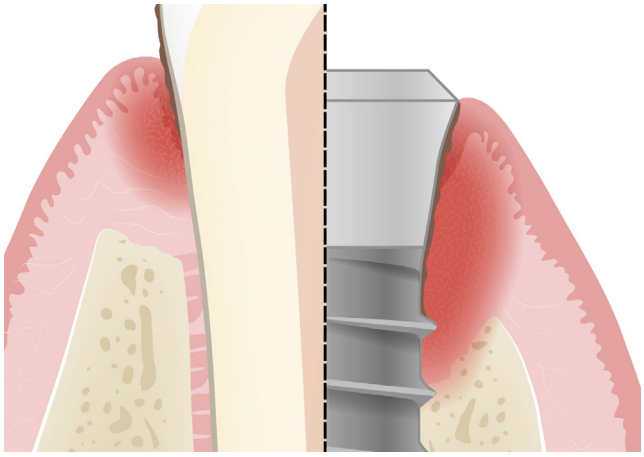

FIGURE 7 (A,B) Extension of the inflammatory connective tissue (ICT) infiltrate at tooth (A) and implant (B) sites in relation to the alveolar crest following ligature-induced experimental peri-implantitis in dogs. At tooth sites, the ICT was separated apically from the alveolar crest by a layer of supracrestal collagen fibers, whereas at implant sites the ICT reached the alveolar crest and extended into the bone marrow (adapted from Reference 14).

present.[26] The size of the inflammatory lesion and the number of selected immune cell populations, however, was not significantly different when comparing biopsies from peri-implant mucosa and gingiva.[26]

3 | COMPARATIVE EVALUATION OF PERIODONTITIS VS. PERI-IMPLANTITIS

3.1 | Animal studies

The ligature-induced experimental peri-implantitis model has been used to investigate the effects of biofilm accumulation around osseointegrated implants in animal models.[13,14,39,40] The histopathologic characteristics reported in these pre-clinical animal studies include the establishment of an inflammatory tissue infiltrate extending apical to the pocket epithelium and containing large numbers and densities of plasma cells.[39]

Moreover, the lesions are characterized by biofilm layers and suppuration adjacent and apical to the pocket epithelium. Marginal bone loss with crater-like defects surrounding the implant is observed in conjunction with the presence of osteoclasts suggesting active bone destruction.

The features described above are substantially different from those occurring around teeth undergoing ligature-induced experimental periodontitis.[14] In that study, the interposition of an intact layer of supracrestal connective tissue fibers was observed between the apical extension of the inflammatory infiltrate and the bone crest[14] (Figure 7A, B). The histopathological analysis of another study in dogs[12] indicated that experimental peri-implantitis lesions contained inflammatory infiltrates that were (i) larger, (ii) extended closer to the bone crest, and (iii) harbored larger proportions of neutrophils and osteoclasts compared with those observed in experimentally induced periodontitis lesions.[12]

In the absence of therapy including biofilm removal, spontaneous progression of experimentally induced peri-implantitis was reported around the majority of implants over a 1-year period.[40] Ligature-induced experimental peri-implantitis was documented until approximately 40% of the height of the surrounding bone was lost. Following ligature removal, biofilm accumulation was allowed to continue for another 12 months. During this additional 12-month period, several implants were lost while the majority of the remaining implants displayed various amounts of bone loss. Inflammatory lesions extending apically to the pocket epithelium were observed in the peri-implant soft tissue and a destructive inflammatory process characterized the majority of implant sites (Figure 8A, B).[40]

In addition, spontaneous progression of experimental peri-implantitis is influenced by implant surface characteristics, with more pronounced tissue breakdown at implants with modified (i.e., moderately rough) surfaces compared with non-modified (i.e., turned) surfaces.[12,41]

3.2 | Analysis of tissue biopsies in humans

Histopathological and functional characteristics of sites with periodontitis and peri-implantitis have been reported in humans.[5,42,43–45]

An immunohistochemical analysis and comparison of soft tissue biopsies from patients diagnosed with peri-implant mucositis and peri-

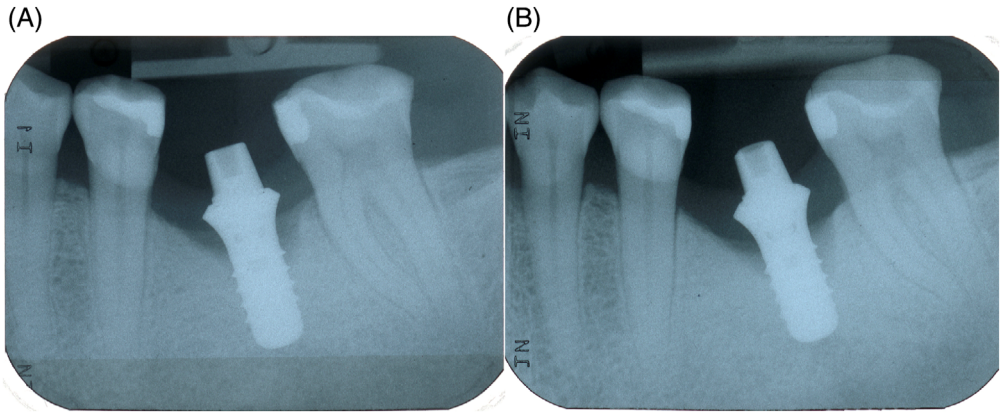

FIGURE 8 (A, B) Radiographic evidence of progressive peri-implant marginal bone loss in the absence of treatment 18 months following diagnosis of peri-implantitis.

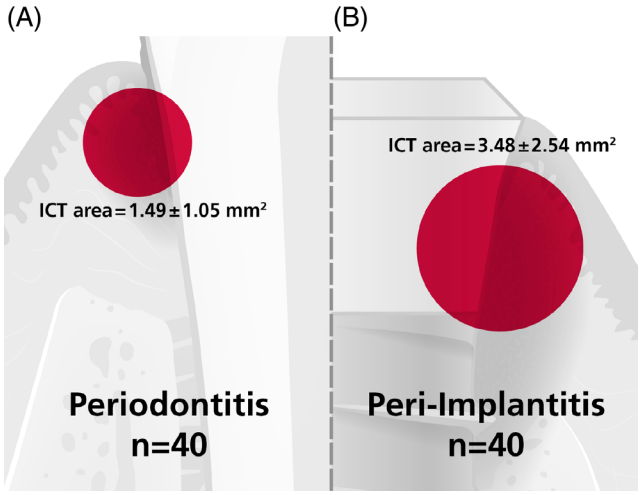

FIGURE 9 (A, B) Different sizes of the inflammatory connective tissue (ICT) area comparing 40 tissue biopsies around human teeth with periodontitis (A) with 40 tissue biopsies around implants in humans with peri-implantitis (B). The area of the ICT at implant sites was more than twice as large (i.e., 3.48 vs. 1.49 mm^2) when compared with that at tooth sites (adapted from Reference 5).

implantitis was reported by Gualini and Berglundh.[45] In that study it was observed that peri-implantitis lesions contained significantly larger proportions of B-cells and neutrophils compared with mucositis lesions indicating that peri-implantitis and mucositis differed with respect to the size of the lesion and to a specific immune cell profile.[45]

Although periodontitis and peri-implantitis in humans share common etiologic factors and clinical features,[2] comparative analyses of soft tissue biopsies around teeth and implants revealed substantial histopathological differences. Compared with periodontitis lesions, peri-implantitis lesions (i) displayed a larger size of the inflammatory infiltrate, (ii) contained a higher number and density of plasma cells, macrophages and neutrophils, (iii) extended apically of the pocket epithelium, and (iv) were not encapsulated by healthy connective tissue fibers (Figure 9A, B).[5]

In addition, peri-implantitis lesions displayed higher densities of vascular structures in the non-infiltrated compared with the infiltrated connective tissue compartment, suggesting that host immune cells need to cover a longer distance to target the bacterial challenge.[5]

4 | PERI-IMPLANT DISEASES IN HUMANS

4.1 | Influence of titanium wear particles and implant surface topography

Findings of an in vitro study indicated that fibroblasts from the peri-implant granulation tissue challenged with both a *Porphyromonas gingivalis* infection and TiO_2 particles significantly enhanced the inflammatory response as measured by TNF-α secretion.[46] Presently, although titanium wear particles from implant surfaces have been detected in hard and soft peri-implant tissues, there is insufficient evidence to show a cause-effect relationship between the presence of titanium particles and peri-implant diseases.[47]

Evidence for the influence of implant surface topography (i.e., micro and macro design) on the incidence of peri-implant diseases in humans is still limited.[48–51]

Findings of an experimental study in 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.[49,52] Moreover, outcomes of a clinical study including three different 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 years.[48]

Based on the hypothesis that surface modification may yield enhanced soft tissue adhesion to transmucosal titanium implant necks, thereby reducing the incidence of peri-implant diseases, a randomized controlled trial evaluated and compared clinical and radiographic changes at tissue level implants with either a machined or a modified transmucosal neck surface.[51] The outcomes of that study indicated that tissue level implants with a hydrophilic sand-blasted and acid-etched transmucosal neck failed to yield clinical and radiographic benefits compared with implants with a machined neck up to 3 years.[51]

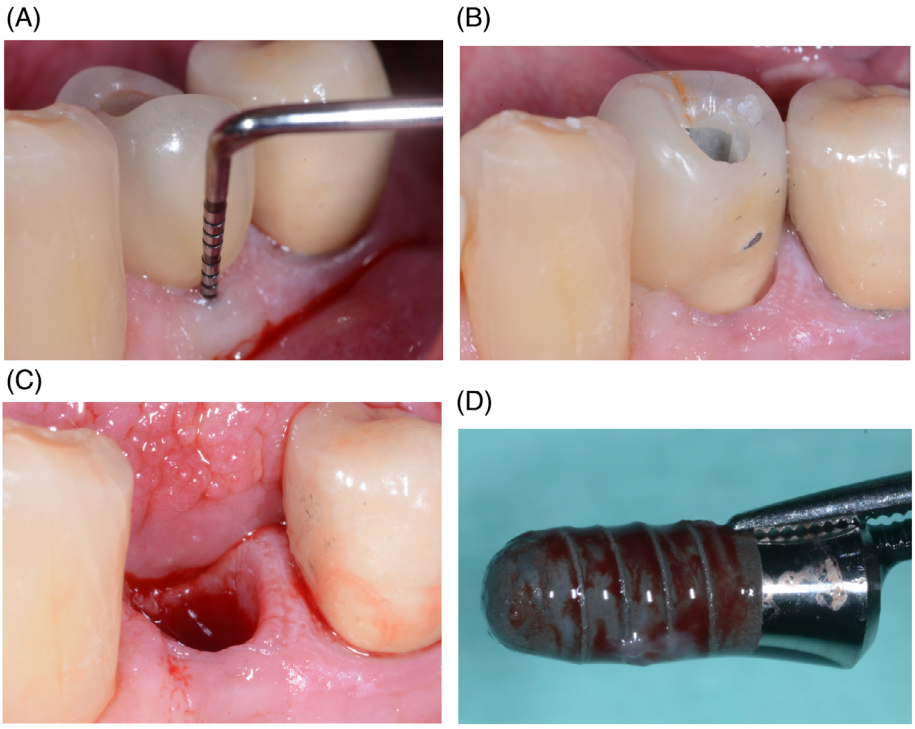

FIGURE 10 (A–D) Implant 34 with peri-implant probing depth of 7 mm on the buccal aspect. The patient reported increased mobility of the screw-retained crown placed 12 years before. After crown removal, loss of osseointegration and mobility of the implant were detected. Consequently, the implant was removed. The etiology of such aseptic loosening is still unknown.

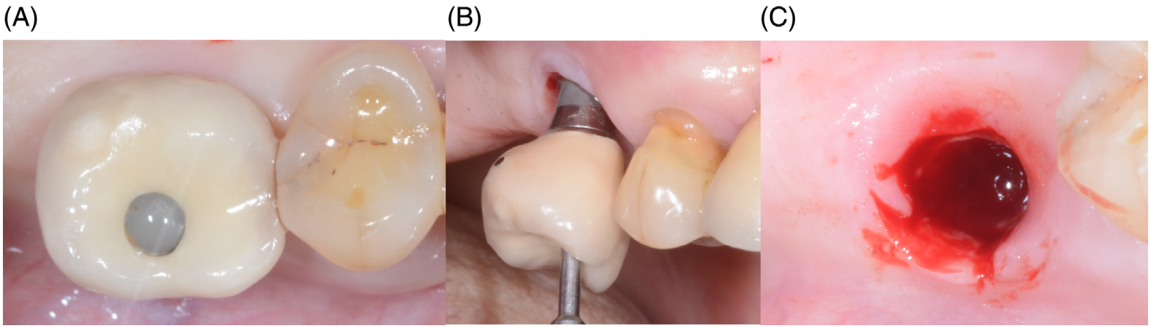

FIGURE 11 (A–C) Implant 16 without clinical signs of inflammation (i.e BoP and suppuration). The patient reported increased mobility of the screw-retained crown placed 5 years before.

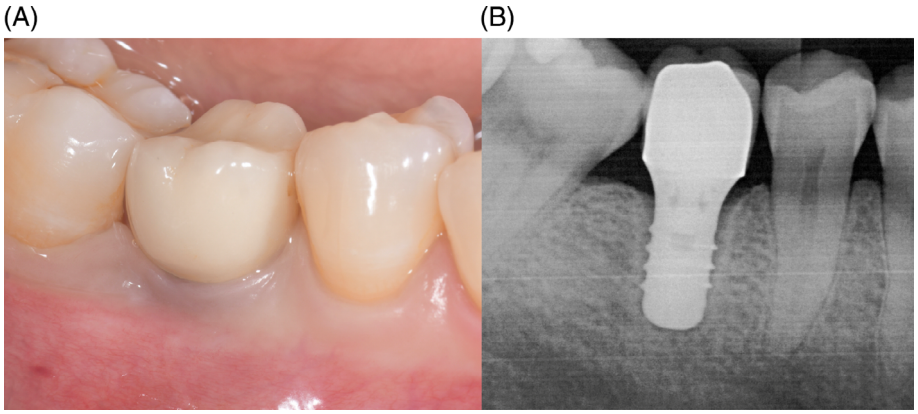

FIGURE 12 (A, B) Implant 46 with complete loss of osseointegration and mobility after 17 years in function. A radiolucent line between implant surface and alveolar bone is visible. Absence of signs of soft tissue inflammation (i.e., BoP and suppuration) and of marginal bone loss preclude from the diagnosis of peri-implantitis. The etiology of such aseptic loosening is presently unknown.

4.2 | Alternative hypotheses for the cause of peri-implantitis

Alternative hypotheses including excessive occlusal load[53–56] and foreign-body reaction have been proposed to explain breakdown of peri-implant tissues and loss of osseointegration. Although excessive occlusal load may result in mechanical/technical complications, implant fracture or complete loss of osseointegration, evidence for excessive occlusal load and marginal bone loss is lacking. On the contrary, findings from experimental studies in animals indicated that in the absence of peri-implant soft-tissue inflammation excessive occlusal load failed to induce peri-implant marginal bone loss.[53–56]

Biological and technical complications in 21 patients with 25 single implants supporting single-unit crowns with cantilever extension were reported in a retrospective cohort study with a follow-up of at least 10 years.[58] The outcomes indicated that implants supporting single-unit crowns with cantilever extension in posterior areas of maxilla and mandible yielded a 100% survival rate and were not diagnosed with peri-implantitis after a mean function time of 13.6 years.[58]

In conclusion, outcomes from experimental peri-implantitis models and from long-term clinical studies failed to demonstrate a detrimental effect of excessive occlusal load on peri-implant marginal bone levels in the absence of soft tissue inflammation (Figures 10–12).

5 | CONCLUSION

Although human periodontal and peri-implant diseases share similarities with respect to etiology and clinical features, they represent distinct entities from a histopathological point of view. In order to make a correct diagnosis and select the appropriate treatment strategy, knowledge of the pathogenetic mechanisms of peri-implant diseases is required.

Diagnosis of peri-implant health requires a clinical examination to confirm absence of peri-implant soft tissue inflammation.

Outcomes of pre-clinical studies in animals and in humans indicate that accumulation of bacterial biofilms under experimental conditions leads to a larger size of the inflammatory infiltrate in the connective tissue and to a higher frequency of bleeding sites around implants compared with teeth. Despite the proof of principle that experimentally induced mucositis may be reversible in humans, early diagnosis and management of naturally occurring peri-implant mucositis is recommended.

Compared with periodontitis lesions, peri-implantitis lesions in humans (i) display a larger size of the inflammatory infiltrate, (ii) contain a higher number and density of immune cells (iii) extend apically of the pocket epithelium, and (iv) are not encapsulated by healthy connective tissue fibers. Hence, based on these histopathologic features, diagnosis of peri-implantitis should be followed by treatment without delay in order to avoid implant loss.

AUTHOR CONTRIBUTIONS

All authors equally contributed in the design and conception of this manuscript. Giovanni E. Salvi and Andrea Roccuzzo drafted the manuscript and Alexandra Stähli, Jean-Claude Imber, and Anton Sculean critically revised the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interests with respect to this study. Andrea Roccuzzo was the recipient of a 3-year scholarship from the Clinical Research Foundation (CFR) for the Promotion of Oral Health, Brienz, Switzerland. Andrea Roccuzzo is the recipient of a 1-year scholarship from the International Team of Implantology (ITI). Jean-Claude Imber was the recipient of a 1-year scholarship from the Osteology Foundation.

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