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PERI-IMPLANTITIS (I DARBY, SECTION EDITOR)

Etiology of Peri-Implantitis

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Abstract

Purpose of Review Peri-implant diseases represent the biological complications associated with implant therapy. They are defined as inflammatory responses of the peri-implant soft tissues with or without progressive loss of marginal bone. The term peri-implantitis is used when the bone loss extends beyond initial bone remodeling after loading. Knowledge of the etiology and case definitions of peri-implant diseases are used to evaluate the impact of peri-implant diseases on the long-term survival and maintenance of dental implants. The present review summarizes the current knowledge about case definitions and contemporary understanding of the etiopathogenesis of peri-implant diseases.

Recent Findings Recent studies have evaluated the instigation of peri-implant mucositis and its natural deterioration to peri-implantitis. Animal models, similar to the ones used for showcasing biofilm-induced periodontal disease, have been utilized to understand the inflammatory response of supporting soft and hard tissue around dental implants. In addition, similarities have been drawn regarding the microbial composition around diseased natural teeth and implants.

Summary A better insight of the pattern of disease progression and understanding of the host response to the increased inflammatory overload provides a foundation on which future research studies can focus on host-microbial interactions and therapies that could lead to more favorable outcomes in prevention and treatment of peri-implant diseases.

Keywords Oral implants · Pathogenesis · Peri-implantitis · Review

Introduction

The term peri-implantitis was first appeared in the French literature in 1965 and described as a biofilm associated biological complications [1]. That was well before the term resurfaced again in the seminal work of Mombelli in 1987 where the term peri-implantitis was described as a site-specific infectious disease with many features common to periodontitis [2]. Over the past three decades, multiple definitions describing peri-implant diseases appeared in the implant literature with several proposals for treatment strategies of varied extents. The lack of uniformity in defining peri-implant diseases, from a clinical perspective, seems to result from the use of different threshold measures to assess bone loss and the lack of defined follow-up periods among the different studies.

Despite the ambiguity of definition, peri-implant disease has been recognized as the most common complication associated with dental implant therapy [3]. The frequency of occurrence of peri-implant diseases was summarized in a systematic review [4•] where 63.4% of patients and 30.7% of individual implants encountered peri-implant mucositis, while the frequency of peri-implantitis was in 18.8% of the patients and in 9.6% of the individual implants. With these numbers in mind and considering the staggering number of dental implants placed worldwide, the need to understand the multifaceted etiology of peri-implant disease, its case definition, and characteristics cannot be overemphasized. It is only through this process of understanding that the true impact of peri-implant disease on the individual dental implant performance and on the implant therapy in continuum can be estimated and effective treatment strategies can be instituted. In the present review, the current literature on the case definitions and etiopathogenesis of peri-implant mucositis and peri-implantitis was summarized.

This article is part of the Topical Collection *on Peri-implantitis*

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Evolution of Case Definitions

Since 1993, several world forums have described the etiology, pathogenesis, and progression of peri-implant diseases. A clinical scenario devoid of mucosal inflammation and erythema of soft tissues surrounding dental implants is regarded as a state of heath. The clinical presentation of both peri-implant mucositis and peri-implantitis was first discussed at the First European Workshop on Periodontology [5]. The case definitions have since evolved through deliberations at various workshops. The discussions were based on emerging evidences on the prevalence, manifestations, and treatment outcomes of different management strategies. In 2008, the definitions adopted by the Sixth European Workshop on Periodontology [6] were based on a review paper by Zitzmann and coworkers [7]. Peri-implant mucositis was defined as the presence of bleeding on probing and inflammation of peri-implant tissues without signs of supporting bone loss, while peri-implantitis included the loss of supporting bone. The Seventh European Workshop on Periodontology referred to the presence of bleeding on probing as the key feature of peri-implant mucositis [8]. Recently, the World Workshop on the classification of periodontal and peri-implant diseases, in 2017, confirmed the case definitions proposed by the Sixth and Seventh European Workshops on Periodontology [7, 8] but referred to the progressive bone loss as the one that exceeds initial bone remodeling during healing [9•].

Etiopathogenesis of Peri-Implant Mucositis

The degradation of healthy soft tissues around dental implants leading to mucositis has been attributed to the presence and accretion of microbial biofilms around osseointegrated implants. This etiological factor pertaining to establishing mucosal inflammation has been investigated and confirmed in various animal and human studies. The classical study of experimental gingivitis in man [10] formed the basis for experimental peri-implant mucositis studies in man which evaluated the association between biofilm and peri-implant mucositis [11, 12]. The known methodology in these experiments involved asking patients to stop any oral home care regimen for a period of 3 weeks followed by reinstitution of optimum oral health. Clinical data, including periodontal indices and probing depths, were collected around osseointegrated dental implants prior and after the period of undisturbed plaque formation. In addition, soft tissue biopsies were harvested, and microbial composition around dental implants and natural teeth was evaluated. The clinical data revealed visible cardinal signs of mucosal inflammation (i.e., redness, bleeding, and swelling) at the time of abolishing oral home care. Increased levels of T and B cells were noticed in the inflammatory infiltrate at dental implants and natural teeth with no significant difference in the microbial composition. The experimental studies in man also showed similar patterns of disease initiation around dental implants and natural teeth and confirmed the direct cause and effect relationship between biofilm accumulation and peri-implant mucositis [11, 12].

The inflammatory soft tissue reactions to plaque formation have also been evaluated around relatively new implant materials. In a recent prospective cohort study, clinical, microbiological, and host-derived factors were assessed in experimental mucositis around natural teeth and titanium and zirconia implants [13, 14]. The authors examined the pro-inflammatory parameters such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin 1b (IL-1b). The deepest probing site around each unit (implant and tooth) was selected to evaluate the inflammatory response. The immunological response to biofilm-induced mucosal inflammation was evaluated by examining the compositional changes in the mucosal/gingival crevicular fluid. Any changes associated with inflammation were transient, and levels of different markers revert back to baseline upon resolution of inflammation.

Several animal studies confirmed the alteration of peri-implant mucosa following biofilm accumulation with migration of leukocytes through the sulcular and junctional epithelium, formation of inflammatory infiltrate, and increased proportions of T and B cells in the adjacent connective tissue around dental implants and natural teeth [15, 16]. It is worth noting that despite similarities in inflammatory response, the apical extent of inflammatory infiltrate at dental implants was more pronounced compared with the one observed at natural teeth.

Etiopathogenesis of Peri-Implantitis

The known differences and similarities in the anatomy of surrounding supporting tissues around teeth and implants have influenced the host response to infection and consequently natural history, pathogenesis, and clinical appearance of periodontitis and peri-implantitis. One of the fundamental differences is the lack of periodontal fibers and cementum at implant surface. In contrast, natural teeth's supporting structure is mainly made of complex network of collagen fiber that support gingival tissue and connect teeth to teeth and alveolar bone. A series of experimental studies using a dog model demonstrated that collagen fibers are not inserted into the implant surface but rather run parallel to it [15, 17, 18]. However, the mean dimensions of the junctional epithelium and supra-crestal connective tissue were similar to the ones reported around natural teeth [19].

The pathogenesis of periodontitis has been described by Page and Schroeder [20], and many of its immunohistochemical features have been explored. The comparison of clinical, radiographic, microbiological, and histological features of periodontitis and peri-implantitis remain the mainstream of

many studies investigating the pathogenesis of peri-implantitis. Analyzing human autopsy material and animal experiments forms the basis of our current understanding of the pathogenesis of peri-implantitis.

Animal Studies

Several animal studies [18, 21–24, 25, 26, 27•, 28–31] showed more pronounced clinical and radiographic signs of tissue destruction around dental implants compared with natural teeth (Table 1). The most commonly used methodology is the placement of cotton or silk ligatures around the neck of the implant in dogs, monkeys, and mini-pigs along with undisturbed plaque buildup to induce peri-implant tissue breakdown in an attempt to mimic a natural peri-implantitis lesion.

In a dog model in which ligatures were applied to implants and teeth, Lindhe and colleagues [18] showed that the infiltrated connective tissue extended to peri-implant bone level, while the advanced lesions of periodontitis are guarded by a band of non-infiltrated connective tissue. The parallelly directed collagen fibers to implant surface may allow greater expansion of the inflammatory infiltrate [18]. Histological findings showed a more pronounced bone loss around implants compared with teeth with increased number of osteoclasts on the bone crest [26, 28]. Moreover, the type of mucosa was investigated in a monkey model and showed a greater recession around implants with non-keratinized mucosa compared with those with keratinized tissue [30]. In both monkey and dog models, histological analysis also showed that occlusal orthodontic forces and lateral static load did not increase the bone loss in sites of peri-implantitis [24, 25].

To assess the progression of peri-implantitis, several studies [21, 22, 31, 32] used a spontaneous progression model of experimental peri-implantitis by removing the ligatures when 40% of supporting bone is lost and then allowing undisturbed plaque buildup. Continuous breakdown was noticed among the majority of implants with inflammatory infiltrate extending apical to the pocket epithelium and close to the bone crest. In addition, implants with rough surfaces had greater bone loss than smooth-surfaced implant [22]. In interpreting the findings of animal research, one must take into consideration that ligature-induced model of peri-implantitis causes severe and acute inflammatory reaction that does not truly resemble peri-implantitis lesion seen in humans which is chronic in nature.

Human Autopsy Studies

Human autopsy studies provide an opportunity to study the pathology of peri-implant diseases in humans [33–38] (Table 2). However, histological investigations of peri-implantitis in humans did not provide elaborated details as those reported in animal models. Ethical concerns of inducing and leaving peri-implantitis without treatment will always limit histological descriptions in humans. Nevertheless, the surrounding tissues of failing implants were histologically examined [33, 39]. The inflammatory infiltrate of peri-implantitis contained mostly plasma cells which resembled plasm cell lesion of periodontitis [33, 40]. In addition, the infiltrated connective tissues lacked collagen which was mostly replaced by increased vascularity and inflammatory cells [33]. Another resemblance to periodontitis lesion is the thin and ulcerated apical portion and thick marginal portion of pocket epithelium with rete pegs extending into the infiltrated connective tissues [33]. Inflammatory infiltrate in peri-implantitis sites had both B and T lymphocytes. In one study [34], T cells outnumbered the B cells, while an immunohistochemistry analysis showed a higher level of B lymphocytes than T lymphocytes in peri-implantitis lesions [36]. In addition, higher number of IL-1α and IL-6 positive cells and smaller number of cells positive for TNF-α were observed in peri-implantitis compared with periodontitis lesions [37].

Microbiology of Peri-Implant Diseases

The microbiology of peri-implant tissues bears resemblance to that associated with natural teeth. Plaque associated with healthy implant abutments consists predominately of gram-positive facultative cocci and rods [41]. Quirynen and colleagues [42] investigated the microbial composition of plaque around teeth and implant after initial exposure. A similarity in the microbial composition was shown. Likewise, implants with peri-implantitis lesions had over 50% of gram-negative anaerobes [2] and considerable amounts of periodontal pathogens including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Tannerella forsythia* [43], which resembles the microbial composition of periodontitis lesions.

Concluding Remarks

Experimental studies in man, human autopsy studies, and animal studies confirmed that the microbial biofilm is an initiator and sustainer of peri-implant diseases. While human autopsy studies provided direct information on peri-implantitis lesions, they are limited in that they do not permit us to obtain specimens at various levels of severity. On the other hand, the information gathered from animal studies allowed histological examination of the whole lesion including bone, but the findings may not truly represent the course of human peri-implant disease.

Table 1 Characteristics of the experimental animal studies

	Animal model	Number of animals	Number of implants/teeth	Implant system	Methodology	Assessment methods	Concluding remarks
Lindhe et al. 1992	Dog	5	10/10	Brånemark system, Nobelpharma AB, Göteborg, Sweden	Ligatures placed 6 months after abutment connection Undisturbed plaque formation Ligatures removed after 6 weeks	Clinical and radiographic assessment Histometric and morphometric analyses	More pronounced tissue breakdown and larger soft tissue lesion at implant sites Inflammatory infiltrate extended to bone marrow at implant sites
Schou et al. 1993	Monkey	8	16/16	Titanium-coated cylindric polycarbonate implants	Ligatures placed 3 months after abutment connection Undisturbed plaque formation Ligatures removed after 7 weeks	Histological analysis	Increased number of lymphocytes and susceptibility for bone loss around implants compared with teeth
Warrer et al. 1995	Monkey	4	30	ITI hollow-cylinder implants with TPS coating (Straumann AG, Waldenburg, Switzerland)	Ligature placed after 9 months of implant placement and undisturbed plaque formation	Clinical examination Histometric analysis	More recession and attachment loss at ligated implants without keratinized tissue
Marinello et al. 1995	Dog	5	20	Brånemark system, Nobelpharma AB, Göteborg, Sweden	Ligatures placed 6 months after abutment connection Ligatures removed after 4–6 weeks Undisturbed plaque formation for additional 1–3 months	Clinical examination Histometric and morphometric analyses	After 1 month: Inflammatory infiltrate extended to bone crest After 3 months: Inflammatory infiltrate is encapsulated by fibrous connective tissue
Hurzeler et al. 1998	Monkey	5	20	ITI implants with turned and SLA surfaces (Straumann AG, Waldenburg, Switzerland)	Ligatures placed for 4 months and replaced once every 4 weeks Orthodontic devices were used to apply excessive occlusal load for 4 months	Histological analyses	Inflammatory infiltrate extended to bone crest Occlusal load did not increase the amount of bone loss
Gotfredsen et al. 2002	Dog	5	20	ITI implants with turned and SLA surfaces (Straumann AG, Waldenburg, Switzerland)	Ligatures placed for 4 months After ligature removal Activation of expansion screws for 3 months	Radiographic examination Histological analyses	Inflammatory infiltrate extended to bone crest Static lateral load did not increase the amount of bone loss
Schou et al. 2002	Monkey	4	8/8	Implants with machined surface (Astra Tech, Dentsply Implants, Mölndal, Sweden)	Ligatures placed after 3 months of implant placement Ligatures were fixed by orthodontic elastics at implants for 7 months and at teeth for 4 months Ligatures were replaced or placed more apically once every 4 weeks	Histological analyses	Inflammatory infiltrate extended to bone crest with ulceration at implant sites Osteoclasts at implants and teeth
Zitzmann et al. 2004	Dog	5	22	Brånemark system, Nobelpharma AB, Göteborg, Sweden	Ligatures placed after 5 months of abutment connection Ligatures placed for 2 months	Radiographic examination Histological analyses	Calculus and ulceration Inflammatory infiltrate extended to bone Inflammatory infiltrate is composed mostly of plasma cells,

Table 1 (continued)

	Animal model	Number of animals	Number of implants/teeth	Implant system	Methodology	Assessment methods	Concluding remarks
					Undisturbed plaque formation for additional 12 months		polymorphonuclear neutrophils, lymphocytes, macrophages, and few fibroblasts and collagen
Berglundh et al. 2007	Dog	5	30	Implants with SLA and polished surfaces (Straumann AG, Basel, Switzerland)	Ligatures placed for 4 months and replaced once every 2 weeks Undisturbed plaque formation for additional 5 months	Radiographic examination Histological analyses	Inflammatory infiltrate extended to bone with ulcerated epithelium Inflammatory infiltrate is composed mostly of plasma cells, polymorphonuclear neutrophils, lymphocytes, macrophages, and no fibroblasts or collagen
Albouy et al. 2009	Dog	6	64	Implants with turned surface (Biomet 3i, Palm Beach Gardens, Florida, USA) Implants with TiOblast surface (Astra Tech, Dentsply Implants, Mölndal, Sweden) Implants with SLA surface (Straumann AG, Basel, Switzerland) Implants with TiUnite surface (Nobel Biocare AB, Göteborg, Sweden)	Ligatures placed for 3 months and replaced once every 3 weeks Undisturbed plaque formation for additional 6 months	Histological analyses	Inflammatory infiltrate extended to bone with ulcerated epithelium Inflammatory infiltrate is composed mostly of plasma cells, polymorphonuclear neutrophils, lymphocytes, and macrophages Inflammatory infiltrate close to the bone: Numerous osteoclasts Crater-like bony defects
Fickl et al. 2015	Dog	5	50	Biomet 3i implants, Palm Beach Gardens, Florida, USA Straumann bone level implants (Straumann AG, Basel, Switzerland) Nobel Replace Tapered implants, Nobel Biocare AB, Göteborg, Sweden	Ligatures placed after 2 months of implant placement Additional ligatures were placed over the old ones every 2 weeks for 8 weeks Ligatures removed after 10 weeks Undisturbed plaque formation	Clinical and radiographic assessment	Higher probing depths and more pronounced bone loss at Nobel Replace tapered implants compared with the other two implant systems
Roehling et al. 2019	Dog	5	40	SLA titanium and zirconia implants (Straumann AG, Basel, Switzerland)	Ligatures placed after 4 weeks of functional loading and removed after 8 weeks Undisturbed plaque formation for additional 16 weeks	Clinical and radiographic assessment	Less inflammation and bone loss at zirconia implants compare to titanium implants

ITI, international team for implantology; TPS, titanium plasma-spray; SLA, sandblasted large grit acid-etched

Table 2 Characteristics of human autopsy studies

	Number of participants	Number of implants/teeth	Case definition of peri-implantitis or failing implants	Implant system	Methodology	Concluding remarks
Sanz et al. 1991	12	NR	BOP, PPD > 3 mm, marginal bone loss >3 mm	Brånemark system, Nobelpharma AB, Göteborg, Sweden	Two groups: With and without peri-implantitis Interdental soft tissue biopsy Microscopy, histometry, and transmission electron microscopy	Higher inflammatory infiltrate and plasma cells in the peri-implantitis sites than in the healthy group
Cornelini et al. 2001	15	20	BOP, suppuration, swelling, PPD > 5 mm, marginal bone loss at implants that had been placed for 1 year or more	ITI implants (Straumann AG, Waldenburg, Switzerland)	Immunohistochemical evaluation of vascular endothelial growth factor (VEGF) and microvessel density of keratinized gingiva surrounding healthy and failing implants	Cells of inflammatory infiltrate were positive for VEGF suggesting a role of VEGF in the progression of peri-implant disease
Gualini and Berglundh 2003	16	NR	BOP, suppuration, marginal bone loss at implants that had been in function for 5–11 years	Brånemark system, Nobelpharma AB, Göteborg, Sweden	Immunohistochemical analysis: CD3, CD4, CD8, CD19, and elastase markers	Large proportions of CD19 and elastase positive B-cells
Bullon et al. 2004	15	NR	BOP, swelling, PPD > 5 mm, marginal bone loss at implants that had been in function for several months	NR	Histological and immunohistochemical analysis Analysis of vascular proliferation by assessing the immunoreactivity for CD34, factor VIII, and vascular endothelial growth factor Apoptosis analyzed by bcl2 and p53	T cells were the most dominant cells in peri-implantitis and aggressive periodontitis In sulcular junctional epithelium: Pronounced vascular proliferation at peri-implantitis sites
Berglundh et al. 2004	6	12	Suppuration, swelling and/or fistula formation, marginal bone loss at implants that had been in function for 4–21 years	Brånemark system, Nobelpharma AB, Göteborg, Sweden	Histometric and morphometric analysis	Inflammatory infiltrate extended apical to pocket epithelium and consisted mainly of plasma cells
Konttinen et al. 2006	20	10	Failing implants: Pain during mastication Implant mobility Vertical bone loss	NR	Histological and immunohistochemical analysis: TNF-α, IL-1 α, IL-6, PDGF-A, and TGF-α	Increased levels of TNF-α, IL-1 α, and IL-6 in peri-implantitis and periodontitis sites IL-1 α was the most common cytokine in peri-implantitis sites

NR, not reported; BOP, bleeding on probing; PPD, probing pocket depth; ITI, international team for implantology; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor alpha; IL-1 α, interleukin-1 alpha; IL-6, interleukin-6; PDGF-A, platelet-derived growth factor A; TGF-α, transforming growth factor alpha

Moreover, there are several similarities in the histopathological characteristics of peri-implantitis and periodontitis as demonstrated in human autopsy and animal studies. Nevertheless, differences do exist, namely, the extension of inflammatory infiltrate apical to pocket epithelium with relatively increased levels of neutrophil granulocytes and macrophages in peri-implantitis lesions. Moreover, peri-implantitis lesions differ in the structure of the granulation tissue compared with that observed in periodontitis lesions. Such differences have implications in treatment planning for peri-implant diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Levignac J. Periimplantation osteolysis- periimplantosis - periimplantitis. Rev Fr Odontostomatol. 1965;12(8):1251–60.
2. Mombelli A, van Oosten MA, Schurch E Jr, Land NP. The microbiota associated with successful or failing osseointegrated titanium implants. Oral Microbiol Immunol. 1987;2(4):145–51. https://doi.org/10.1111/j.1399-302x.1987.tb00298.x.
3. Renvert S, Persson GR, Pirih FQ, Camargo PM. Peri-implant health, peri-implant mucositis, and peri-implantitis: case definitions and diagnostic considerations. J Periodontol. 2018;89(Suppl 1):S304–S12. https://doi.org/10.1002/JPER.17-0588.
4.• Atieh MA, Alsabeeha NH, Faggion CM Jr, Duncan WJ. The frequency of peri-implant diseases: a systematic review and meta-analysis. J Periodontol. 2013;84(11):1586–98. https://doi.org/10.1902/jop.2012.120592 **This work determined the true prevalence of peri-implant disease to allow a well-informed consent and to develop rigid supportve maintenance programs for high-risk groups.**
5. Albrektsson T, Isidor F. Consensus report of session IV. In: Lang NP, Karring T, editors. Proceedings of the First European Workshop on Periodontology: Quintessence Publishing; 1994. p. 365–9.
6. Lindhe J, Meyle J, Group DoEWoP. Peri-implant diseases: consensus report of the sixth European workshop on periodontology. J Clin Periodontol. 2008;35(8 Suppl):282–5. https://doi.org/10.1111/j.1600-051X.2008.01283.x.
7. Zitzmann NU, Berglundh T. Definition and prevalence of peri-implant diseases. J Clin Periodontol. 2008;35(8 Suppl):286–91. https://doi.org/10.1111/j.1600-051X.2008.01274.x.
8. Lang NP, Berglundh T. Working Group 4 of Seventh European Workshop on P. Periimplant diseases: where are we now?–Consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol. 2011;38(Suppl 11):178–81. https://doi.org/10.1111/j.1600-051X.2010.01674.x.
9.• Berglundh T, Armitage G, Araujo MG, et al. Peri-implant diseases and conditions: consensus report of workgroup 4 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. J Periodontol. 2018;89(Suppl 1):S313–S8. https://doi.org/10.1002/JPER.17-0739 **This work determined the true prevalence of peri-implant disease to allow a well-informed consent and to develop rigid supportve maintenance programs for high-risk groups.**
10. Loe H, Theilade E, Jensen SB. Experimental gingivitis in man. J Periodontol. 1965;36:177–87. https://doi.org/10.1902/jop.1965.36.3.177.
11. Pontoriero R, Tonelli MP, Carnevale G, Mombelli A, Nyman SR, Lang NP. Experimentally induced peri-implant mucositis. A clinical study in humans. Clin Oral Implants Res. 1994;5(4):254–9. https://doi.org/10.1034/j.1600-0501.1994.050409.x.
12. Zitzmann NU, Berglundh T, Marinello CP, Lindhe J. Experimental peri-implant mucositis in man. J Clin Periodontol. 2001;28(6):517–23. https://doi.org/10.1034/j.1600-051x.2001.028006517.x.
13. Clever K, Schlegel KA, Kniha H, Conrads G, Rink L, Modabber A, et al. Experimental peri-implant mucositis around titanium and zirconia implants in comparison to a natural tooth: part 1-host-derived immunological parameters. Int J Oral Maxillofac Surg. 2019;48(4):554–9. https://doi.org/10.1016/j.ijom.2018.10.018.
14. Clever K, Schlegel KA, Kniha H, Conrads G, Rink L, Modabber A, et al. Experimental peri-implant mucositis around titanium and zirconia implants in comparison to a natural tooth: part 2-clinical and microbiological parameters. Int J Oral Maxillofac Surg. 2019;48(4):560–5. https://doi.org/10.1016/j.ijom.2018.10.017.
15. Berglundh T, Lindhe J, Marinello C, Ericsson I, Liljenberg B. Soft tissue reaction to de novo plaque formation on implants and teeth. An experimental study in the dog. Clin Oral Implants Res. 1992;3(1):1–8. https://doi.org/10.1034/j.1600-0501.1992.030101.x.
16. Ericsson I, Berglundh T, Marinello C, Liljenberg B, Lindhe J. Long-standing plaque and gingivitis at implants and teeth in the dog. Clin Oral Implants Res. 1992;3(3):99–103. https://doi.org/10.1034/j.1600-0501.1992.030301.x.
17. Berglundh T, Lindhe J, Ericsson I, Marinello CP, Liljenberg B, Thomsen P. The soft tissue barrier at implants and teeth. Clin Oral Implants Res. 1991;2(2):81–90. https://doi.org/10.1034/j.1600-0501.1991.020206.x.
18. Lindhe J, Berglundh T, Ericsson I, Liljenberg B, Marinello C. Experimental breakdown of peri-implant and periodontal tissues. A study in the beagle dog. Clin Oral Implants Res. 1992;3(1):9–16. https://doi.org/10.1034/j.1600-0501.1992.030102.x.
19. Gargiulo AW, Wentz FM, Orban B. Dimensions and relations of dentogingival junction in humans. J Periodontol. 1961;32:261–7.
20. Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal disease. A summary of current work. Lab Investig. 1976;34(3):235–49.
21. Albouy JP, Abrahamsson I, Persson LG, Berglundh T. Spontaneous progression of ligatured induced peri-implantitis at implants with different surface characteristics. An experimental study in dogs II: histological observations. Clin Oral Implants Res. 2009;20(4):366–71. https://doi.org/10.1111/j.1600-0501.2008.01645.x.
22. Berglundh T, Gotfredsen K, Zitzmann NU, Lang NP, Lindhe J. Spontaneous progression of ligature induced peri-implantitis at implants with different surface roughness: an experimental study in dogs. Clin Oral Implants Res. 2007;18(5):655–61. https://doi.org/10.1111/j.1600-0501.2007.01397.x.
23. Fickl S, Kebschull M, Calvo-Guirado JL, Hurzeler M, Zuhr O. Experimental peri-Implantitis around different types of implants -

a clinical and radiographic study in dogs. Clin Implant Dent Relat Res. 2015;17(Suppl 2):e661–9. https://doi.org/10.1111/cid.12303.

24. Gotfredsen K, Berglundh T, Lindhe J. Bone reactions at implants subjected to experimental peri-implantitis and static load. A study in the dog. J Clin Periodontol. 2002;29(2):144–51. https://doi.org/10.1034/j.1600-051x.2002.290209.x.
25. Hurzeler MB, Quinones CR, Kohal RJ, et al. Changes in peri-implant tissues subjected to orthodontic forces and ligature breakdown in monkeys. J Periodontol. 1998;69(3):396–404. https://doi.org/10.1902/jop.1998.69.3.396.
26. Marinello CP, Berglundh T, Ericsson I, Klinge B, Glantz PO, Lindhe J. Resolution of ligature-induced peri-implantitis lesions in the dog. J Clin Periodontol. 1995;22(6):475–9. https://doi.org/10.1111/j.1600-051x.1995.tb00180.x.
27.• Roehling S, Gahlert M, Janner S, Meng B, Woelfler H, Cochran DL. Ligature-induced peri-implant bone loss around loaded zirconia and titanium implants. Int J Oral Maxillofac Implants. 2019;34(2):357–65. https://doi.org/10.11607/jomi.7015 **This article presented an in-vivo account of the importance of surface characteristics that can have an effect on microbial aggregation around dental implants.**
28. Schou S, Holmstrup P, Reibel J, Juhl M, Hjorting-Hansen E, Kornman KS. Ligature-induced marginal inflammation around osseointegrated implants and ankylosed teeth: stereologic and histologic observations in cynomolgus monkeys (Macaca fascicularis). J Periodontol. 1993;64(6):529–37. https://doi.org/10.1902/jop.1993.64.6.529.
29. Schou S, Holmstrup P, Stoltze K, Hjorting-Hansen E, Fiehn NE, Skovgaard LT. Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. A histologic comparison in cynomolgus monkeys (Macaca fascicularis). Clin Oral Implants Res. 2002;13(2):113–26. https://doi.org/10.1034/j.1600-0501.2002.130201.x.
30. Warrer K, Buser D, Lang NP, Karring T. Plaque-induced peri-implantitis in the presence or absence of keratinized mucosa. An experimental study in monkeys. Clin Oral Implants Res. 1995;6(3):131–8. https://doi.org/10.1034/j.1600-0501.1995.060301.x.
31. Zitzmann NU, Berglundh T, Ericsson I, Lindhe J. Spontaneous progression of experimentally induced periimplantitis. J Clin Periodontol. 2004;31(10):845–9. https://doi.org/10.1111/j.1600-051X.2004.00567.x.
32. Albouy JP, Abrahamsson I, Persson LG, Berglundh T. Spontaneous progression of peri-implantitis at different types of implants. An experimental study in dogs. I: clinical and radiographic observations. Clin Oral Implants Res. 2008;19(10):997–1002. https://doi.org/10.1111/j.1600-0501.2008.01589.x.
33. Berglundh T, Gislason O, Lekholm U, Sennerby L, Lindhe J. Histopathological observations of human periimplantitis lesions. J Clin Periodontol. 2004;31(5):341–7. https://doi.org/10.1111/j.1600-051X.2004.00486.x.
34. Bullon P, Fioroni M, Goteri G, Rubini C, Battino M. Immunohistochemical analysis of soft tissues in implants with healthy and peri-implantitis condition, and aggressive periodontitis. Clin Oral Implants Res. 2004;15(5):553–9. https://doi.org/10.1111/j.1600-0501.2004.01072.x.
35. Cornelini R, Artese L, Rubini C, et al. Vascular endothelial growth factor and microvessel density around healthy and failing dental implants. Int J Oral Maxillofac Implants. 2001;16(3):389–93.
36. Gualini F, Berglundh T. Immunohistochemical characteristics of inflammatory lesions at implants. J Clin Periodontol. 2003;30(1):14–8. https://doi.org/10.1034/j.1600-051x.2003.300103.x.
37. Konttinen YT, Lappalainen R, Laine P, Kitti U, Santavirta S, Teronen O. Immunohistochemical evaluation of inflammatory mediators in failing implants. Int J Periodontics Restorative Dent. 2006;26(2):135–41.
38. Sanz M, Alandez J, Lazaro P, Calvo JL, Quirynen M, van Steenberghe D. Histo-pathologic characteristics of peri-implant soft tissues in Branemark implants with 2 distinct clinical and radiological patterns. Clin Oral Implants Res. 1991;2(3):128–34. https://doi.org/10.1034/j.1600-0501.1991.020305.x.
39. Esposito M, Thomsen P, Ericson LE, Sennerby L, Lekholm U. Histopathologic observations on late oral implant failures. Clin Implant Dent Relat Res. 2000;2(1):18–32. https://doi.org/10.1111/j.1708-8208.2000.tb00103.x.
40. Mackler BF, Frostad KB, Robertson PB, Levy BM. Immunoglobulin bearing lymphocytes and plasma cells in human periodontal disease. J Periodontal Res. 1977;12(1):37–45. https://doi.org/10.1111/j.1600-0765.1977.tb00107.x.
41. Lekholm U, Ericsson I, Adell R, Slots J. The condition of the soft tissues at tooth and fixture abutments supporting fixed bridges. A microbiological and histological study. J Clin Periodontol. 1986;13(6):558–62. https://doi.org/10.1111/j.1600-051x.1986.tb00847.x.
42. Quirynen M, Vogels R, Peeters W, van Steenberghe D, Naert I, Haffajee A. Dynamics of initial subgingival colonization of 'pristine' peri-implant pockets. Clin Oral Implants Res. 2006;17(1):25–37. https://doi.org/10.1111/j.1600-0501.2005.01194.x.
43. Hultin M, Gustafsson A, Hallstrom H, Johansson LA, Ekfeldt A, Klinge B. Microbiological findings and host response in patients with peri-implantitis. Clin Oral Implants Res. 2002;13(4):349–58. https://doi.org/10.1034/j.1600-0501.2002.130402.x.