

Peri-implantitis Vol 2. (Etiology - Microbiology)

1. **AK** Salvi GE, Cosgarea R, Sculean A. Prevalence and Mechanisms of Peri-implant Diseases. J Dent Res. 2017 Jan;96(1):31-37.
 2. **TV** Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. J Periodontol. 2018 Jun;89 Suppl 1:S267-S290.
 3. **DL** Belibasakis GN, Manoil D. Microbial Community-Driven Etiopathogenesis of Peri-Implantitis. J Dent Res. 2021 Jan;100(1):21-28.
 4. **CM** Shi Y, Tong Z, Zhang Y, Si M, He F. Microbial profiles of peri-implant mucositis and peri-implantitis: Submucosal microbial dysbiosis correlates with disease severity. Clin Oral Implants Res. 2022 Feb;33(2):172-183.
 5. **VX** Lafaurie GI, Sabogal MA, Castillo DM, Rincón MV, Gómez LA, Lesmes YA, Chambrone L. Microbiome and Microbial Biofilm Profiles of Peri-Implantitis: A Systematic Review. J Periodontol. 2017 Oct;88(10):1066-1089.
 6. **RH** Wang HL, Garaicoa-Pazmino C, Collins A, Ong HS, Chudri R, Giannobile WV. Protein biomarkers and microbial profiles in peri-implantitis. Clin Oral Implants Res. 2016 Sep;27(9):1129-36.
 7. **NL** Kensara A, Hefni E, Williams MA, Saito H, Mongodin E, Masri R. Microbiological Profile and Human Immune Response Associated with Peri-Implantitis: A Systematic Review. J Prosthodont. 2021 Mar;30(3):210-234.
 8. **MS** Kotsakis GA, Olmedo DG. Peri-implantitis is not periodontitis: Scientific discoveries shed light on microbiome-biomaterial interactions that may determine disease phenotype. Periodontol 2000. 2021 Jun;86(1):231-240.
 9. **AK** Ivanovski S, Bartold PM, Huang YS. The role of foreign body response in peri-implantitis: What is the evidence? Periodontol 2000. 2022 Oct;90(1):176-185.
 10. **TV** Albrektsson T, Tengvall P, Amengual L, Coli P, Kotsakis GA, Cochran D. Osteoimmune regulation underlies oral implant osseointegration and its perturbation. Front Immunol. 2023 Jan 24;13:1056914.
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Topic: peri-implant diseases

Authors: Salvi GE, Cosgarea R, Sculean A.

Title: Prevalence and Mechanisms of Peri-implant Diseases

Source: J Dent Res. 2017 Jan;96(1):31-37

DOI: 10.1177/0022034516667484

Reviewer: Amber Kreko

Type: review

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

Purpose: To summarize the evidence on the prevalence of peri-implant diseases and their similarities and differences with periodontal diseases with a focus on their pathogenic mechanisms.

Discussion:

Prevalence of Peri-implant diseases

- Derks and Tomasi – peri-implant mucositis 43% and peri-implantitis 22%. Other studies stated variable prevalence numbers
- Different case definitions – one study had a threshold of 5mm bone loss and only reported 1% peri-implantitis prevalence and another study has a 0.4mm bone loss threshold and reported 47% prevalence.

Pathogenesis of Gingivitis vs peri-implant mucositis

- Animal studies –

- o studies on dogs and monkeys were compared with histopathologic findings of experimental gingivitis.
- o Apical extension and size of inflammatory infiltrate were more pronounced in peri-implant mucosa – stronger host response to bacterial challenge in soft tissues adjacent to implants compared with teeth
- o Similar inflammatory lesions in terms of extension and composition around 3 different systems – so not system specific
- o Deeper penetration of probe in tissues around implants with mild and severe mucositis compared to teeth with gingivitis
- Human studies –
 - o After 3wk of biofilm accumulation, more bleeding around implants than teeth but after 3 wk of reinstituted plaque control, absence of bleeding was not found so resolution may require greater than 3 weeks or may not be achieved
 - o Costa – 5 year incidence of peri-implantitis of 18% in patients with maintenance and 43.9% in the group without

Pathogenesis of Periodontitis vs Peri-implantitis

- Human studies
 - o Peri-implantitis contains a greater proportion of B cells and neutrophils.
 - o Area of inflammatory connective tissue at implant sites is twice as large when compared with a tooth site.
 - o Peri-implantitis has more aggressive character and may progress more rapidly when compared to periodontitis.

Conclusions:

- Prevalence of peri-implant diseases – controversial prevalences reported; different case definitions influence extent and severity of peri-implant diseases
- Peri-implant mucositis – Plaque accumulation around implants yields a stronger inflammatory response compared to natural teeth; early diagnosis and management should be implemented to prevent onset of peri-implantitis
- Peri-implantitis – tissue at peri-implantitis sites is faster and more extensive than at periodontitis sites; peri-implantitis and periodontitis has distinct entities from a histopathologic point of view

Topic: Peri-implantitis

Authors: Schwarz F, Derks J, Monje A, Wang HL

Title: Peri-implantitis

Source: J Periodontol. 2018 Jun;89 Suppl 1:S267-S290

DOI:10.1002/JPER.16-0350

Reviewer: Tam Vu

Type: Review

Keywords: diagnosis, peri-implantitis, mucositis, inflammation, bone loss

Purpose: review of peri-implantitis for 2017 World Workshop on Classification of Periodontal and Peri-Implant Diseases and Conditions

Discussion:

Current definition of peri-implantitis

- Peri-implantitis: a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and progressive loss of supporting bone
 - o Soft tissue inflammation detected by BOP
 - o Progressive bone loss identified via radiographs

Conversion from peri-implant mucositis to peri-implantitis

- Plaque formation causes inflammation of peri-implant soft tissue

- Presence of inflammatory cell infiltrate into connective tissue
- Factors assoc w/conversion of mucositis to peri-implantitis in a retrospective study
 - “maintained” group: BOP at >50% of all sites, and PD $\geq$ 4 mm at >5% of sites were assoc w/peri-implantitis
 - “not maintained” group: PD, BOP, lack of regular mtx, presence of periodontitis
- Histopathologic and clinical conditions for conversion still not completely understood

Onset and pattern of dz progression

- Animal studies:
 - Plaque formation and breaking of mucosal seal to implant promotes submucosal bacterial biofilm formation → inflammatory cell infiltrates
 - Dz progression also influenced by implant surface characteristics, more pronounced in modified surfaces compared to non-modified
- Observational studies
 - Onset may be early
 - Bone loss is non-linear, accelerating, and increased variance over time

Characteristics of peri-implantitis

- Histopathologic: more neutrophil granulocytes and larger “proportions of B cells (CD19+), plasma cells and lymphocytes similarly to periodontitis
- Microbiologic and immunologic:
 - Higher counts of bacterial species, including *P. ging* and *T. forsythia*
 - Linked to more opportunistic pathogens (i.e. *Pseudomonas aeruginosa*, *S. aureus*, fungi, and virus)
 - Higher levels of IL-1 β and TNF- α (compared to health)
- Clinical:
 - Redness, edema, mucosal enlargement, BOP w/or w/out suppuration
 - Incr PD and radiographic bone loss
 - Periapical peri-implantitis → radiolucency w/ or w/out clinical signs

Risk factors/indicators for peri-implantitis

- Hx of periodontitis [strong evidence]
- Smoking [currently no conclusive evidence]
- Diabetes [inconclusive evidence]
- Poor plaque control/lack of regular maintenance [evident]

Areas of future research

- KM: absence of reduced KM negative affects peri-implant mucosal health
- Excess cement: biofilm formation and plaque retention
- Genetic factors [insufficient evidence]
- Systemic conditions
- Iatrogenic factors (i.e. restorative, malpositioned implant, bone augmentation)
- Occlusal overload [no evidence]
- Titanium particles [no evidence]

Conclusion:

1. Peri-implantitis is a pathological condition of tissues around dental implants – characterized by inflammation in the peri-implant connective tissue and progressive bone loss
2. Histopathologic and clinical conditions for conversion of mucositis to peri-implantitis is not completely understood
3. Onset of peri-implantitis may occur early, dz progression is a non-linear and accelerating pattern
4. Peri-implantitis
 - a. Presence of inflammation and PD compared to baseline
 - b. Larger inflammatory lesions (compared to periodontitis)
 - c. Surgical entry often reveals circumferential bone loss pattern
5. Evidence
 - a. Incr risk in pts: hx of chronic perio, poor plq control, no regular mtx, smoking, and diabetes

- b. Limited evidence: excess cement, lack of KM, implant position
- c. Crestal bone loss around implants in absence of clinical signs of inflammation is rare

Topic: Peri-Implantitis (Microbiology)

Authors: Belibasakis GN, Manoil D.

Title: Microbial Community-Driven Etiopathogenesis of Peri-Implantitis.

Source: J Dent Res. 2021 Jan;100(1):21-28

DOI: 10.1177/0022034520949851

Reviewer: Daeoo Lee

Type: Review

Keywords: Peri-Implantitis, microbiology, etiopathogenesis

Purpose: Assessment of the physiology and virulence of the microbial communities of the peri-implant to describe the etiopathogenic mechanisms and drivers of the disease.

Discussions:

- Clinical Definition and Epidemiology of Peri-Implant Infections
 - (Berglundh 2018)
 - ♣ Peri-implant mucositis include BOP or suppuration but no radiographic crestal bone loss beyond the initial remodeling. Peri-implantitis also includes further bone loss and increased probing pocket depth (PPD), compared to previous examinations
 - (Kordbacheh Changi 2019)
 - ♣ Approximately one-third of all patients and one-fifth of all implants will experience peri-implantitis
 - ♣ Primary risk factors: ill-fitting or ill-designed fixed and cement-retained restorations, as well as a history of periodontitis
 - (Kumar 2019)
 - ♣ Smoking is also an important risk factor that is shared with periodontitis, particularly in combination with poor oral hygiene
- Histological Particularities of Peri-Implant Sites
 - Whereas natural teeth are socketed into the alveolus via the periodontal ligament (PDL), osseointegrated implants are directly anchored to the bone.
 - ♣ The resulting lack of PDL limits the blood supply to suprapariosteal vessels, thereby restricting the amount of nutrients and immune cells that may extravasate to tackle the early stages of bacterial infection.
 - Fibers of the supracrestal connective tissues are positioned circumferentially around implants, not perpendicularly as into natural teeth.
 - ♣ This anatomical-functional organization reduces the physical barrier against bacterial invasion into the submucosa and places peri-implant tissues in an “open wound” conformation.
- Ecological Characteristics of the Peri-Implant Niche
 - (Edgerton 1996)
 - ♣ Titanium pellicles formed in vitro were shown to comprise proline-rich proteins, secretory IgA, α amylase, and high molecular weight mucins, yet lacked low molecular weight mucins and cystatins as commonly detected on enamel
 - (Belibasakis 2015)
 - ♣ Bacterial colonization within 30 min after implant insertion and further evolves toward the establishment of organized biofilm communities in the peri-implant crevice in the next 2 wk.
 - (Payne 2017)
 - ♣ In the early months following implant insertion, peri-implant biofilms were shown to display only a few differences in their taxonomic composition, yet harbored a less diverse microbiota than that of neighboring teeth.

- (HeitzMayfield 2015)
 - ♣ After biofilm formation, modifications in the microenvironment in turn cause dysbiotic shifts in the microbiota that exacerbate inflammatory progression and ultimately peri-implant health and implant functionality.
 - For instance, discontinuation of oral hygiene for a period of 3 wk was shown to increase the abundance of putative pathogens (*Tannerella*, *Prevotella*, *Fretibacterium*, or *Treponema* spp)
- Peri-implantitis is an endogenous mixed infection, occasionally implicating nontypical oral bacteria.
- Implant Surface as a Modifier of the Peri-Implant Niche
 - (Belibasakis 2015; Lauritano 2020), The implant surface structure and abutment interface may affect microbial colonization and disease progression
 - (Asensio 2019) Modification of its characteristics may enhance antimicrobial properties and clinical outcomes
 - Implant corrosion and negative effects of titanium ions/particles have been reported but where this is clinically significant has yet to be proven.
- Targeted Identification of PeriImplantitis–Associated Pathogens
 - (Persson and Renvert 2014)
 - ♣ Bacterial identification reveal similarities between peri-implant infections and gingivitis or chronic periodontitis. The only microbiological differences is that the infections may occasionally be dominated by pathogens most commonly isolated from implanted medical devices, such as *Peptostreptococcus* spp. or *Staphylococcus epidermidis* and *Staphylococcus aureus*.
 - Bacterial identification method relied on closed-ended molecular techniques, which entailed the preselection of a set of primers or probes and targeted bacterial identification toward specific taxa, often based on former knowledge derived from periodontitis.
 - ♣ “selection” bias, which technically precluded the identification of less studied or “unexpected” microbiota.
- Community-Based Microbial Pathogenesis of Peri-Implant Infections
 - Next-generation sequencing (NGS), that is, high-throughput DNA sequencing technologies, has become the method of choice for the taxonomic and functional characterization of the oral microbiota.
 - ♣ Bacterial identification relies on the sequencing of short amplicons (i.e., piece of DNA or RNA that is the source and/or product of amplification or replication events) from the 16S ribosomal RNA (16S rRNA) gene that are then assigned a taxonomic identity by comparison with databases.
 - ♣ The 16S rRNA gene comprises a combination of slowly evolving regions along with 9 fast-evolving (variable) regions, which differ among bacterial taxa and therefore become valuable targets for taxonomic assignment (Yarza et al. 2014).
 - (Maruyama et al. 2014)
 - ♣ Distinct bacterial communities between peri-implantitis and periodontitis have been observed
 - *Prevotella nigrescens* presenting at significantly higher abundance in peri-implantitis, whereas *Peptostreptococcaceae* sp. and *Desulfomicrobium orale* were significantly higher in periodontitis.
 - *Treponema* sp. HMT-257 was uniquely associated with the severity of peri-implantitis, correlating markedly with radiographic bone loss, PPD, and suppuration.
 - (Apatzidou 2017)
 - ♣ Healthy periodontal sites exhibited a more diverse microbiota and were associated with increased abundances of the genera *Actinobacillus* and *Streptococcus*. In contrast, *Prevotella* spp. and *Porphyromonas* spp. were most discriminative of peri-implantitis.

- o Peri-implant sites harbored a less diverse microbiota than periodontal sites in both health and disease. Yet, the peri-implant microbiota was shown to gradually gain complexity as the infection progressed toward peri-implant mucositis and peri-implantitis.

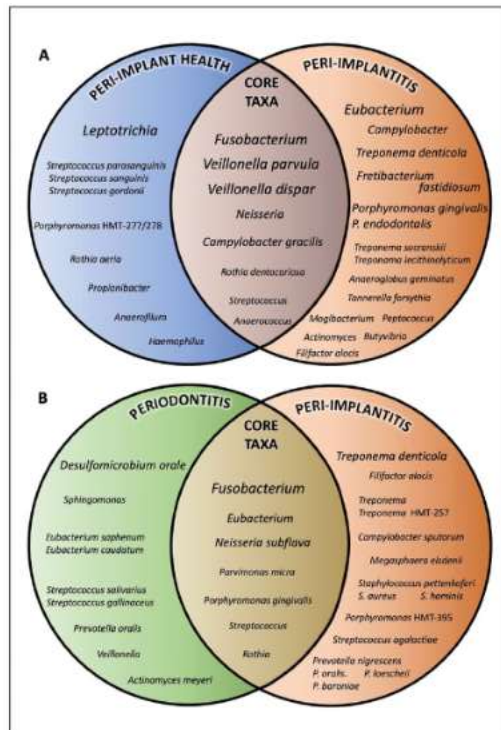


Figure 1. Model of characteristic and core microbiota associated with peri-implantitis. The Venn diagrams attempt a summative qualitative illustration of the characteristic taxa from the microbiota of healthy peri-implant, peri-implantitis, and periodontitis sites. Only taxa identified as significantly more abundant in each condition are represented, as reported in each individual study. **(A)** The microbiota from healthy implants and peri-implantitis are illustrated based on Kumar et al. (2012), Tsigarida et al. (2015), Zheng et al. (2015), Sanz-Martin et al. (2017), and Yu et al. (2019). **(B)** The microbiota from periodontitis and peri-implantitis sites are illustrated based on Kumar et al. (2012), Dabdoub et al. (2013), Maruyama et al. (2014), and Yu et al. (2019). Bacterial taxa are reported at the genus level or lower. The increase in font size depicts the frequency of identification among publications. Of note, criteria of taxonomic identification and statistical significance may vary among studies.

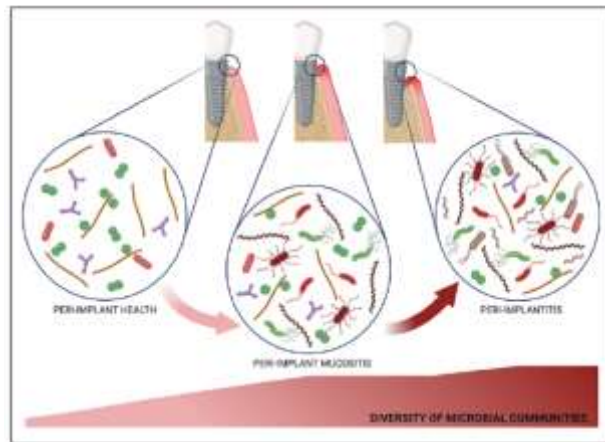


Figure 2. Diversity of submucosal microbial communities during the course of peri-implant infections. The scheme illustrates the increase in microbial diversity observed during the transition from peri-implant health to peri-implant mucositis and then to peri-implantitis. This figure was designed using the web interface BioRender.com.

- **Functionality-Based Microbial Pathogenicity of Peri-Implant Infections**
 - (Shiba 2016) Transcriptome (i.e., the full range of messenger RNA, or mRNA, molecules expressed by an organism) analysis to better understand functional aspects within microbial communities.
 - A differentially abundant microbial composition was confirmed between peri-implantitis and periodontitis sites.
 - ✦ Function-based assignment of messenger RNA (mRNA) sequences, especially focusing on putative virulence genes, identified similar functional profiles, suggesting that peri-implantitis and periodontitis are associated with similar virulence factors.
 - Peri-implant infections are ultimately driven by the microbial pathogenicity of the associated bacterial communities, whereas their functional and virulence profiles are poorly reflected in their taxonomic profiles.

Conclusions, Comments, and Perspectives by the authors:

- Peri-implant sites are distinct ecological niches, characterized by lower diversities than periodontal niches, yet harboring a differently abundant microbiota in both health and disease.
- These community surveys further indicated that health and disease situations were associated with compositional shifts within communities rather than the presence of specific pathogenic taxa.
- Could RNA-seq or NGS profiling of submucosal biofilms or saliva be adequate to identify incipient dysbiosis, thus alerting for intensified maintenance or initial treatment, prior to the magnified clinical signs of the disease?
- Could we preferentially target and block functional or metabolic pathways crucial to those taxa identified as differentially abundant in peri-implantitis or even at the earlier stage of peri-implant mucositis?

Topic: Dysbiosis in peri-implant diseases

Authors: Shi Y., Tong Z., Zhang Y., Si M., He F.

Title: Microbial profiles of peri-implant mucositis and peri-implantitis: Submucosal microbial dysbiosis correlates with disease severity

Source: Clin Oral Impl Res. 2022;33:172–183.

DOI: 10.1111/clr.13880

Reviewer: Cyrus J Mansouri

Type: Cross-sectional

Keywords: dysbiosis, high-throughput nucleotide sequencing, microbiota, mucositis, peri-implantitis

Purpose: Compare microbiological profiles of peri-implantitis (PI) and peri-implant mucositis (PM) and identify correlations between submucosal dysbiosis, the severity of clinical symptoms (PD, BOP, MBL), and other patient characteristics.

Material and methods: Patients with untreated peri-implant disease were recruited. The 2017 World Workshop definitions for PI and PM were used. All patients had baseline panoramic radiographs. Sites with PI were preferentially selected for patients exhibiting sites with both PI and PM.

Submucosal biofilm samples were obtained before clinical examination and after removing the supragingival plaque. Sterile paper points were used to collect samples at the deepest PD at diseased implants. PD measurement was obtained with a force ~0.25 N. BOP, suppuration, and plaque index were also obtained. Prosthetic/hardware complications were also recorded. Panoramic radiographs were used to estimate peri-implant bone level (MBL).

Total genomic DNA was isolated from the submucosal biofilm and DNA concentration and integrity were measured. PCR amplification of bacterial 16S rRNA genes was completed with primers and analyzed. Microbial richness, diversity, similarity, taxonomic differences between PM and PI were analyzed. Microbial dysbiosis index (MDI) was calculated to evaluate extent of submucosal dysbiosis.

Results: A total of 64 implant sites in 64 patients were analyzed (37 PI and 27 PM). Significant differences between PI and PM were found in patient's age, periodontal status, smoking status, MBL, max PD, mean PD, and BOP.

Operational taxonomic units were classified into 12 phyla, 21 classes, 35 orders, 69 families, 94 genera, and 210 species. Microbial richness and diversity in PM sites were higher than PI sites.

Microbial colonies were rich in the following phyla:

Bacteroidetes (45.08% in PM, 42.89% in PI), Firmicutes (21.03% in PM, 19.44% in PI), Proteobacteria (11.16% in PM, 10.41% in PI), Fusobacteria (11.12% in PM, 14.7% in PI) and Spirochetes (8.38% in PM, 9.68% in PI), and the genera Porphyromonas (17.04% in PM, 16.54% in PI), Fusobacterium (9.78% in PM, 12.39% in PI), Treponema (8.37% in PM, 9.59% in PI) and Prevotella (7.43% in PM, 7.04% in PI).

Core microbiomes in taxa were Porphyromonas, Fusobacterium, Treponema, Prevotella and Campylobacter. Alloprevotella was part of the PM core, while Filifactor comprised the PI core. The abundances of Oribacterium, Staphylococcus and Ralstonia were significantly higher in PM, whereas the abundances of Holdemanella and Cardiobacterium were significantly higher in PI.

- Majority are anaerobic Gram-negative taxa
- a decrease in species richness from PM to PI was found, although the difference was not statistically significant.

A significant association was found between microbial dysbiosis index and MBL. No other clinical measures were found to be correlated with MDI.

Conclusion: The microbial richness, diversity and distribution between PM and PI were quite similar, largely sharing the same core microbiome. Increased MBL was significantly associated with MDI.

Topic: Microbiology of Peri-implantitis

Author: Lafaurie GI, Sabogal MA, Castillo DM, Rincón MV, Gómez LA, Lesmes YA, Chambrone L.

Title: Microbiome and Microbial Biofilm Profiles of Peri-Implantitis: A Systematic Review.

Source: J Periodontol. 2017 Oct;88(10):1066-1089.

DOI: 10.1902/jop.2017.170123.

Type: Systematic Review

Reviewer: Veronica Xia

Keywords: peri-implantitis, periodontitis, health, microbiology

Purpose:

- Describe microbiologic profiles of peri-implantitis, periodontitis, and healthy implants

Materials and Methods:

- Electronic search/inclusion and exclusion criteria applied

Results:

- 26 studies included

Microbial differences of peri-implantitis vs healthy

- 8 studies found red complex more in peri-implantitis
 - P ging most frequent (33.3%)
- 9 studies found orange complex more in peri-implantitis
 - P intermedia most frequency (42.8%)
- 7 studies failed to find differences
- Greater difference
 - P intermedia
 - Healthy 6.6-23% VS peri-implantitis 25-66%
 - NSSD in Pging/Tforsythia
 - Staph aureus
 - Healthy 0-19.1% VS peri-implantitis 0-43.4%
 - Gram neg
 - Healthy 6-13% VS peri-implantitis 10-65%

Difference in microbial biofilms in peri-implantitis vs perio

- 4 studies
- Similar microbial compositions
- Enteric rods, Pseudomonas aeruginosa, Staph a, candida albicans more frequent in peri-implantitis (may be associated with implant failure)

Comparison of peri-implantitis and perio using sequencing methods

- Parvimonas micra, F nucleatum, P intermedia in higher proportions in peri-implantitis
- Colonization by asaccharolytic anaerobic gram positive rods (AAGPR) and anaerobic gram neg rods (OGNR)
- Peri-implantitis sites showed more diversity than periodontitis sites
 - More peptococcus, mycoplasma, campylobacter
 - Primarily gram negative

Conclusion:

- Healthy and peri-implantitis implants are colonized by periodontopathic microorganisms
- Peri-implantitis implants:
 - Higher frequency of red complex (P ging), orange complex (P intermedia/P nigrescens)
 - Colonization by asaccharolytic anaerobic gram positive rods (AAGPR) and anaerobic gram neg rods (OGNR)
 - Sites showed more diversity than periodontitis sites (more gram neg)
 - Important to use anti-infectious protocols to treat disease
- Differences in results from conventional biofilm collection and microbiome sequencing (can include non-cultivable bacteria)

Topic: Peri-implantitis Biomarkers

Author: Wang HL, et al.

Title: . Protein biomarkers and microbial profiles in peri-implantitis

Source: Clin Oral Implants Res. 2016 Sep;27(9):1129-36

DOI: 10.1111/clr.12708

Reviewer: Ryan Higgins

Type: Cross-sectional study

Keywords: dental implant microbiology, peri-implant crevicular fluid, peri-implant disease, salivary diagnostics

Purpose: To investigate the peri-implant crevicular fluid (PICF) biomarkers and microbial profiles of implants with either healthy peri-implant tissue or peri-implantitis to assess real-time disease activity

Materials and Methods: 68 patients included → 34 patients with at least one healthy implant (control) and 34 with at least one peri-implantitis implant

- Total DNA content and qPCR analysis for periodontal bacteria (*Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*) obtained from subg plaque samples (mesio-buccal aspect of the healthy implant site and deepest implant site of the disease implant)
 - o PCIF analysis for IL-1B, VEGF, MMP-8, TIMP-2, and OPG were performed

Results:

- The mean concentration of IL-1b (44.6 vs. 135.8 pg/ml; $P < 0.001$), TIMP-2 (5488.3 vs. 9771.8 pg/ml; $P = 0.001$), VEGF (59.1 vs. 129.0 pg/ml; $P = 0.012$), and OPG (66.5 vs. 111.7 pg/ml; $P = 0.050$) was increased in the peri-implantitis patients
 - o Mean expression of MP-8 did not reveal a meaningful difference between groups
- NSSD in total bacterial DNA of selected microorganisms though there was a 3x increase in selected microorganisms present in peri-implantitis samples
- *T. denticola* combined with IL-1B, VEGF, and TIMP-2 PICF levels can enhance the ability to diagnose

Conclusions:

- From the results there are increased levels of selected PICF-derived biomarkers of periodontal tissue inflammation, matrix degradation/regulation, and alveolar bone turnover/resorption that could have potential to be predictors of peri-implant diseases

Topic: Immune response and Peri-implantitis

Authors: Kensara, A et al.

Title: Microbiological Profile and Human Immune Response Associated with Peri-Implantitis: A Systematic Review

Source: Journal of Prosthodontics 30 (2021) 210–234

DOI: 10.1111/jopr.13270

Reviewer: Nicolas Lobo

Type: Systematic review

Keywords: Peri-implantitis; dental implant; microbial; microbiota; immune response.

Purpose: to analyze the literature relating to the microbiological and human immune response associated with peri-implantitis in comparison to healthy implants

Materials and Methods: The study focused on clinical studies examining peri-implantitis in comparison to healthy dental implants. The review included only studies that used endosseous dental implants and focused on analyzing microbiological profiles or immune responses related to these implants.

Results: 20 studies focused on the microbiological profiles of endosseous dental implants, and 19 focused on the human immune response, with 2 studies investigating gene polymorphisms. Key findings for microbiological profiles revealed that peri-implantitis sites had more complex and diverse bacterial communities compared to healthy implants, *Asaccharolytic anaerobic Gram-positive rods (AAGPRs)*, and obligate anaerobic Gram negative rods (OGNRs) with higher counts of specific pathogens like *P. gingivalis* and *P. intermedia*. Some studies used PCR and 16S rRNA sequencing, showing that bacterial diversity and composition differed significantly between healthy and diseased implants. For immune

response studies, pro-inflammatory markers such as IL-1 β , IL-6, IL-17 and TNF- α were consistently higher in peri-implantitis sites. Bone-cell modulators like RANK, RANKL; Extra-celular enzymes like Cathepsin – K, MMP 2-9 were also elevated in peri-implantitis, while anti-inflammatory markers like IL-10 were more common in healthy implants. There was no clear correlation between gene polymorphisms and peri-implantitis pathogenesis.

Conclusions: Peri-implantitis is linked to complex microbiota. Fungi and viruses are more frequently found in peri-implantitis sites, potentially enhancing bacterial effects on tissues. The immune response is triggered, releasing pro-inflammatory cytokines along with bone remodeling mediators and proteolytic enzymes leading to pathogen overgrowth, local inflammation, and bone loss around implants.

Topic: Peri-implantitis

Authors: Kotsakis GA, et al.

Title: Peri-implantitis is not periodontitis: Scientific discoveries shed light on microbiome-biomaterial interactions that may determine disease phenotype

Source: Periodontol 2000. 2021 Jun;86(1):231-240.

DOI: 10.1111/prd.12372

Reviewer: Mahya Sabour

Type: Review

Keywords: dental implants, peri-implantitis, health, diagnosis, disease, microbiome

Purpose: Review on the microbiome-biomaterial interactions in peri-implantitis (PI).

Discussion:

- Peri-implantitis is not periodontitis: clinical observations:
 - Both are associated w/ biofilm, erythema, edema, and histological signs of leukocytic infiltration and pro-inflammatory signaling.
 - However, the pathogenesis of peri-implant diseases is not the same as periodontal disease, therefore tx protocols should be different.
 - Existing PI treatments only yield short-term benefits and disease recurrence could be up to 100% after 12 months - There is a need to revisit the pathogenesis of PI
- Peri-implantitis is dissimilar to periodontitis and a new model of infection is required:
 - Inflammation around implants leads to a rampant rate of bone loss even within 6m following initial placement – currently no explanation for this difference from bone loss in periodontitis
 - Different substrata (metal titanium vs. mineralized cementum/dentin) dictate the distinct type of bacterial accumulation
 - Titanium:
 - Develops a Ti oxide layer once exposed to fluid or air, making a boundary between the Ti and biological mediums which creates a passivation of the metal and determines the level of biocompatibility and biological response
 - The forces and bonds behind initial bacterial adhesion are different for Ti dioxide vs. mineralized organic hydroxyapatite.
 - Implants: Strep spp colonies as soon as there is exposure to the oral environment, followed by low levels of Actinomyces naeslundii, and coaggregation w/ Veillonella spp in early biofilms.
 - Teeth: colonized by Strep spp, followed by higher levels of Actinomyces naeslundii
 - Wettability properties and adsorption kinetics of microrough and hydrophilic implants differ from those of dentin, affecting pellicle organization.
 - BL: A core microbiome including early colonizers (Strep spp) and bridging organisms supporting complex biofilms (Fusobacterium spp) is present around both teeth and

implants, however these communities are shaped by different substrata. A new model for peri-implant infection is required for the distinct microbiome around implants.

– The peri-implant microbiota resists periodontal antibiotics regimens: a testament of unique functional signatures in peri-implant biofilms:

- 85% of pts share less than 8% of the species between implants & teeth.
- Peri-implant microbial communities are less diverse
- PI is resistant to antibiotic regimens used against periodontitis (beta-lactams)
- New model of infection in peri-implant tissues:
 - the low diversity peri-implant microbial community is dominated by Veillonella spp, and Neisseria spp (produce beta-lactamase enzymes) as well as gram+ bacteria: Strep mitis, Strep oralis (resistant to beta-lactam Abx)
 - red complex pathogens are not critical in peri-implant biofilms, however some might rarely be seen in lower abundance

– Findings of titanium particles in the tissues surrounding titanium dental implants:

- Some metal particles are released from the implant surface into the biological space as a result of corrosion and tribology (wear or friction) – the combination is called tribocorrosion.
 - Friction against bone during implant placement
 - Wear from micromovements between the implant connections
 - Wear from debridement at SPT
 - Corrosion from body fluids, bleaching agents, or fluorides
- Ti particles seen in peri-implant tissues could undergo tribocorrosion, leading to an inflammatory response – Cytology has shown Ti particles inside macrophages (higher numbers closer to the implant surface)

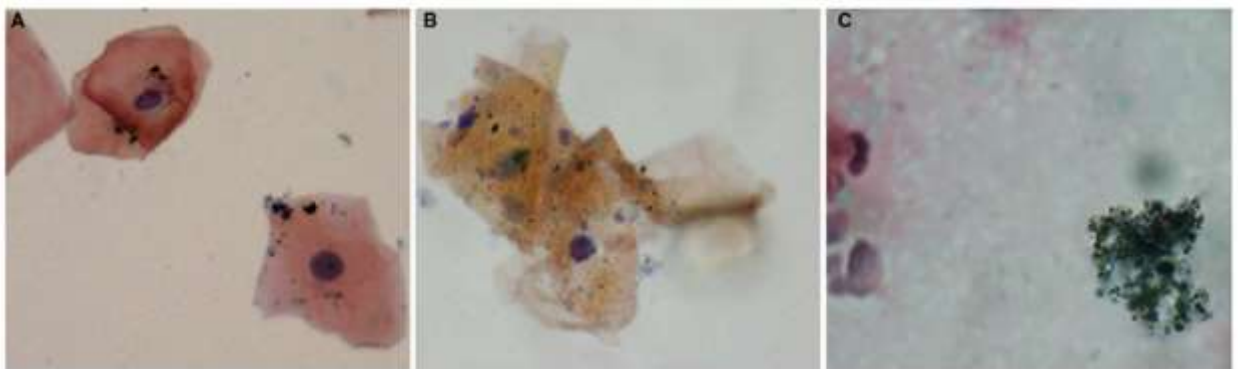


FIGURE 3 Cytologic smears of peri-implant mucosa from a patient without peri-implantitis. Particles can be seen inside epithelial cells (A and B) and outside cells (C). Papanicolau stain; original magnification $\times 400$ [Colour figure can be viewed at wileyonlinelibrary.com]

- Controversial if the inflammation leads to corrosion or vice versa, but regardless of inflammation, particles will be released into the biological space
- BL: Tribocorrosion at the metal-tissue interface has significant importance in implantology as it could cause implant failure. Metal products in the adjacent tissues can migrate to more distant sites, beyond the peri-implant biological environment into other biological compartments.
- Findings of particles in the tissue surrounding ceramic dental implants:
 - Advantages of zirconia implants:
 - Eliminates the tribocorrosion phenomena, and only small amounts of inflammatory infiltrates are seen in the tissues.
 - Has low plaque affinity, good biocompatibility and ST integration, improved aesthetics (esp for thin biotypes) and good physical and mechanical properties.
 - Some metals, especially aluminum and zirconium are found in tissues adjacent to zirconia implants, but additional studies are required in this regard

- Ti particles elicit potent pro-inflammatory immune responses:
 - Metal particles act as foreign bodies and elicit an inflammatory reaction, leading to bone loss and peri-implant diseases
 - Particle size (micro vs. nano), concentration, composition, chemical reactivity, and host response all affect the local immune response
 - Particles ingested by macrophages stimulate cytokine release, leading to osteoclast activation and bone resorption. They could also suppress osteoblasts, reducing bone formation.
- BL: there is an association between tribocorrosion, Ti particles, and biological complications, however additional research is needed to better understand the role of the particles on peri-implant disease pathogenesis.
- Titanium dissolution products are microbiome community activists that shape microbiome structure and diversity:
 - Daubert et al: Ti particles have a strong influence in shaping peri-implant microbiome and the concentration of particles is inversely related to species richness. Microbiomes of diseased areas was similar to healthy sites with high titanium.
 - Veillonella spp are prominent peri-implant pathogens
 - A strong association is found between Ti particles and peri-implantitis. The particles may indirectly lead to the dysbiosis of the microbiome and recent studies have consistently reported an association between peri-implant disease and the presence of Ti particles

Conclusion:

- There is no completely inert metal and in situ degradation is inevitable.
- Metal tribocorrosion affects biofilm and has a direct (immune modulation) and indirect (microbiome perturbation) influence on peri-implant inflammation and failure
- Metal particles could migrate systemically in the serum and blood and deposit into target organs
- Aluminum and zirconium particles could be detected in peri-implant tissues around zirconia implants and further studies on this topic are required
- Tribocorrosion effects are not necessarily determining factors of the course of the implant, as not all pts have identical biological responses.
- De novo investigation of peri-implant biofilms regarding implant-related environmental factors is required to determine therapies critical for limiting the health burden from PI

Topic: foreign body response

Authors: Ivanovski S, Bartold PM, Huang YS

Title: The role of foreign body response in peri-implantitis: What is the evidence?

Source: Periodontol 2000. 2022 Oct;90(1):176-185

DOI: 10.1111/prd.12456

Reviewer: Amber Kreko

Type: Discussion

Keywords:

Purpose: To explore the evidence for a role of “foreign body reaction” in peri-implantitis by examining the influence that implant related factors may have in initiating or exacerbating the progressive crestal bone loss that is characteristic of peri-implantitis.

Discussion:

Foreign body reaction and osseointegration

- Foreign body response – a reaction composed of macrophages and foreign body giant cells is the end stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis, or biomaterial.
- Inflammatory reaction is elicited following surgical insertion of an implant. A prolonged inflammatory response can potentially trigger a foreign body response that leads to a lack of

integration of dental implants and resolution leads to repair via formation of bone at the implant interface.



FIGURE 1 Current understanding of the possible sequelae of dental implant placement into alveolar bone. During osseointegration, the initial inflammatory response is followed by timely resolution and pro-reparative processes leading to osseointegration and bone formation at the implant interface. The inability to resolve the initial inflammatory response leads to a chronic inflammatory state and fibrous encapsulation of the implant, which is characteristic of a foreign body response that leads to early implant failure. FBR: foreign body response

Foreign Body reaction and peri-implantitis

- Foreign body equilibrium theory for peri-implant bone loss is the presence of multinucleated cells around osseointegrated dental implants. There is no evidence that the presence of these multinucleated giant cells on a healthy, osseointegrated dental implant is a risk factor for peri-implantitis.
- There is clear evidence that poor plaque control leads to peri-implantitis.

Several non plaque related factors are not fully understood and could play a part in peri implantitis.

These include peri-implant keratinized mucosa, occlusal overload, titanium particles, bone compression necrosis, overheating, micromotion, and biocorrosion.

- Titanium particles are commonly detected in healthy and diseased peri-implant mucosa. There is a tendency for more titanium particles in close proximity to the implant surface and in specimens from diseased sites.
- Biocorrosion and tribocorrosion
 - o Biocorrosion – breakdown of titanium oxide layer leading to exposure of bare metal to active corrosion and release of titanium particles.
 - o Tribocorrosion – friction and wear in presence of corrosive body fluids.
 - o Some biological plausibility for a link between corrosion, the presence of titanium particles, and biological complications, but there is insufficient data to support a unidirectional role of titanium corrosion and metal particles in the pathogenesis of peri-implantitis

Conclusions:

- Titanium elicits an inflammatory response upon implantation but osseointegration represents a return to tissue homeostasis rather than a chronic inflammatory state.
- No evidence of a prominent role of a foreign body response to an osseointegrated implant in the pathogenesis of peri-implantitis.

- Lack of evidence for a unidirectional causative role of corrosion by-products and titanium particles as possible non-plaque related factors in the etiology of peri-implant disease.

Topic: Osteoimmunology

Authors: Albrektsson, T et al

Title: Osteoimmune regulation underlies oral implant osseointegration and its perturbation

Source: Frontiers in immunology vol. 13 1056914. 24 Jan. 2023

DOI: 10.3389/fimmu.2022.1056914

Reviewer: Tam Vu

Type: Review

Keywords: dental implants, osteoimmunology, immune reaction, inflammation, bone, osseointegration

Purpose: to review osteoimmunology of osseointegration and analyze bone/cell tissue response

Discussion:

Basics of osteoimmunology

- 3 types of bone cells: osteoblasts, osteoclasts, osteocytes
 - Osteoblasts:
 - ♣ bone growth,
 - ♣ originates from mesenchymal stem cell
 - ♣ produces OPG, which controls RANKL activity
 - Osteoclast:
 - ♣ bone resorption,
 - ♣ originates from monocyte-macrophage hematopoietic stem cells
 - Osteocytes: respond to mechanical stimuli and can induce osteoclastic/osteoblastic activity
- **Macrophages** play role in modulating osteogenesis → facilitates osteogenic cytokine release and formation of new bone tissue around implants
 - Recruit osteoprogenitor cells to build new peri-implant bone

Osteointegration and oral microbiology

- Oral bacteria is capable of producing mucosa and bone degrading peptides
 - Neutralized by B-cells, T-cells, and neutrophils
- Persistent inflammation impedes tissue repair and favors bacteria overgrowth
- Balanced inflammatory environment is critical for optimal bone regeneration

Perturbation of osteoimmune rxns

- Septic rxns:
 - Bacteria can be found within bone → recruits inflammatory bone resorbing cells and cause MBLoss
 - Host defense guard against bacterial actions and MBLoss
- Aseptic rxns:
 - Occlusal force – immune microenvironment that can stimulate conversion of monocytes into an activated state
 - ♣ Increased pressure → chronic hypoxia and inflammation → bone loss
 - On contrary, insufficient pressure also increase oxidant production → immune system stimulates macrophage and osteoclastic fxn more than osteoblastic activity → bone resorption
 - Other factors: implant design, clinical handling, pharmaceutical tx, disuse atrophy, old age

Stages of osseointegration failure

- Primary or early failure
 - Osseointegration never achieved, implant surrounded by connective tissue
 - Prolonged m1 polarization phase -- Increased M2 macrophages → pro-fibrotic

- ♣ Epithelial downgrowth seen with M1/M2 macrophage balance in mesenchymal epithelial transition
 - Low-grade inflammation → hypoxia
- Late implant failure
 - Overload, secondary corrosion, or both
 - Excessive MBLoss, implant mobility, and stratified connective tissue
 - Inflammatory M1 macrophages predominate in peri-implantitis cases
 - ♣ M1 exhibits incr production of pro-inflammatory cytokines, chemokines, and growth factors and decr phagocytic activity
 - ♣ M2 macrophages mediate particle uptake

Marginal bone loss from different perspectives

- Macrophage polarization and osteoimmunological mechanism of MBLoss (condition, not dz)
 - Prolonged inflammation → immunologically active microenvironment → tissue damage and bone resorption because pro-inflammatory cytokines negatively alters RANK/RANKL balance
 - Increase in M1/M2 ratio + high response of immune system against local signals may be key in pathogenesis of peri-implant bone loss
- Implant-abutment site and MBLoss
 - Placement and removal of abutment can prevent stable soft tissue attachment, cause corrosion, and increase bacterial access to interface
 - ♣ Absence of interface (tissue level implant) results in minimal cell infiltrate and no peak of inflammation at marginal bone level and minimal bone loss
 - Bacterial-induce inflammation + corrosion contribute to MBLoss

Peri-implant phenomena involved in osteoimmune regulation

- Implant “passivation” layer: composed of >98% titanium dioxide, it forms rapidly on the titanium surface under atmospheric conditions and protects against further passive oxidation of implant → contributes to long-term stability of implant in the tissues w/out further corrosion
 - During successful osseointegration, this layer thickens and improves bone anchorage
- Soft tissue inflammation and primary corrosion
 - Inflammation is host physiology – necessary to regulate tissue and organ fxn
 - Causes dz when deregulated → tissue destruction
 - Osseointegration is characterized by controlled immune/inflammatory response
- Implant passivation layer and secondary corrosion: chronic electrochemical oxidation of titanium leads to gradual destruction of passivation layer
 - Secondary corrosion: damage to passivation layer which results in accelerated titanium release (i.e. steel instruments to clean implant surface, leading to destructive corrosion)

Synergistic activation of pro-inflammatory pathways

- Macrophages and other innate immune system cells can respond to local environment
 - Inflammatory potential is multiplied due to synergistic activation of pro-inflammatory pathways
 - Titanium particles can cause immune rxn
 - ♣ Exposure to titanium dioxide nanoparticles can cause DNA damage
 - ♣ In bone and surround tissues, influx of immune and osteoclast cells can cause pro-inflammatory environment → lading to incr bone destruction and suppressed bone formation
 - In general, biomaterial implantation may allow opportunistic bacteria grow and cause dysregulated host response → leading to further invasion of bacteria into compromised tissues and contribute to susceptibility of dental implants to infx

Conclusion: Teeth are natural part of human bodies, while implants are foreign bodies with measurable immune reactions. Surgery to address marginal bone loss around implants have questionable clinical results. Many factors for marginal bone loss around implants Bacteria may be controlled by immune system, but bacteria will always be present.

1. Osseointegration is needed for oral implant fxn

2. Osseointegration is an osteoimmune defense rxn (more than simple bone repair process)
3. Bone-anchored implant integration = immunoinflammatory process (rather than inflammatory)
4. Osteoimmunological mechanisms of MBLoss is a condition, not a dz
5. Immune system is capable of causing MBLoss by controlling osteoblast/osteoclast
6. Bacteria may affect oral implants once immune rejection rxn has been initiated
 - a. Local bacterial rxn may occur adjacent to leakage from abutment connection, but not affect implant stability
7. Pt related factors: smoking, drugs, genetic disorders, surgical and prosthodontic techniques, local microbes, foreign bodies (cement), primary corrosion, implant fractures can cause MBLoss via immune system
 - a. Corrosion may negatively impact implant survival

