

Microenvironmental Succession and Host Immune Responses in Peri-Implantitis

Xiaonan Qi^{1*}

¹School of Arts and Sciences, The State University of New Jersey, New Brunswick, United States of America

Abstract. Peri-implantitis (PI) is a prevalent complication following dental implant therapy, characterized by progressive bone resorption, peri-implant tissue destruction, and potential implant failure. Its management poses substantial challenges for long-term oral health. Current diagnostic and therapeutic approaches mainly depend on clinical examination and imaging techniques, which often detect the disease only after progression. Moreover, treatment methods frequently lack long-term stability, highlighting the need for early biomarkers and mechanistic insights. Recent studies demonstrate that plaque biofilms undergo a microbial succession, shifting from early facultative anaerobes to late strict anaerobes, while extracellular polysaccharides and proteases contribute to the stability of the pathogenic community. In parallel, dysregulation of the IL-23/Th17 axis and macrophage M1/M2 polarization amplify local immune imbalance and chronic inflammation. Bone resorption is further accelerated by disruption of the RANKL/OPG pathway and matrix metalloproteinase-mediated extracellular matrix degradation. Emerging biomarkers in peri-implant crevicular fluid, such as IL-17, RANKL/OPG, and MMP-8, together with imaging modalities including CBCT, hold promise for early diagnosis and risk prediction. This review aims to elucidate the interplay between biofilm succession, host immunity, and bone metabolism in PI, while evaluating potential biomarkers and diagnostic strategies for clinical application.

1 Introduction

In recent decades, implant restoration has gradually become a common treatment for partial and complete tooth loss, significantly improving patients' chewing function and quality of life. However, with the increasing prevalence of dental implant applications, its associated complication, especially peri-implantitis, have become a growing concern. Peri-implantitis refers to the inflammation and destruction of soft and hard tissues around implants. It is a persistent, irreversible inflammatory disease with common clinical manifestations including marginal bone resorption, loss of bone integration, deepening of peri-implant periodontal pockets, and purulent exudate [1]. Studies have shown that peri-implantitis (PI) affects approximately 5% to 37% of implants and 11% to 53% of patients, posing a huge challenge to clinical treatment [2]. The pathogenesis of peri-implantitis (PI) is believed to be like that of periodontitis, caused by environmental exposure, host susceptibility, and the presence of bacterial biofilms [3]. In the early stages, biofilms are dominated by facultative anaerobes. As the bacteria mature, strict anaerobic pathogens (such as *Porphyromonas gingivalis* and *Prevotella intermedia*) gradually accumulate. The secretion of exopolysaccharides and proteases promotes bacterial colonization and stabilizes the biofilm, a process that forms a vicious cycle because it not only provides an immune escape barrier for pathogens but also

continuously stimulates the host to produce inflammatory mediators.

The host's immune inflammatory response is a key driver of PI progression, among which the Th17/IL-23 axis and macrophage M1/M2 polarization play a crucial role. The Th17 cell-mediated immune response is highly dependent on the proinflammatory cytokine IL-23 secreted by dendritic cells. This signalling pathway is often referred to as the IL-23/Th17 axis [4]. At the same time, macrophages polarize in response to environmental signals. M1 macrophages are mainly involved in bacterial-induced proinflammatory responses, while M2 macrophages play a role in inflammation resolution and tissue repair. Studies have shown that M1 macrophages are significantly increased in PI lesions [2]. Bone metabolism imbalance is another core mechanism of PI pathogenesis. The RANKL/OPG system regulates bone resorption by regulating osteoclast differentiation; the Wnt/ β -catenin signalling pathway plays a role in osteoblast proliferation and differentiation; and the MMP/TIMP system mediates the decomposition and remodelling of the extracellular matrix. Recent studies have found that these three molecular networks are intertwined and interact with each other in the PI microenvironment, jointly shaping the dynamic balance between bone resorption and regeneration in the lesion [5]. This review aims to provide an overview of the microbial biofilm succession in PI and its interactions with immune response and bone metabolism, and to explore the potential clinical

* Corresponding author: xiaonan.qi@rutgers.edu

applications of biomarkers such as IL-17 and RANKL/OPG in the early diagnosis and risk assessment of this disease.

2 Microbial Succession of Peri-Implant Biofilms

PI is caused by the accumulation of biofilm in the peri-implant tissue, leading to inflammation of the surrounding mucosa and, subsequently, loss of supporting bone. PI is associated with a variety of bacteria, including *Streptococcus salivarius*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythiae*, *Prevotella intermedia*, and *Porphyromonas gingivalis* [6]. Among them, *Porphyromonas gingivalis* and *Tannerella forsythiae* have relatively large colonies. In healthy peri-implant tissue, the microbial community is usually dominated by cocci, with a relatively low proportion of anaerobic and aerobic bacteria, and a low detection rate of Gram-negative bacteria and pathogenic bacteria. However, small numbers of anaerobic Gram-negative rods may still be detected around some implants. Compared with healthy conditions, the subgingival microbiota at diseased sites undergoes notably compositional shifts, including an overall increase in bacterial load, elevated proportions of *Prevotella intermedia*, *Fusobacterium*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*, along with a decrease in cocci, and a significant rise in motile organisms and spirochetes [7].

Streptococcus species act as pioneer colonizers in biofilm formation. They adhere to tooth surfaces via extracellular polysaccharides synthesized by glucosyltransferases, thereby facilitating the attachment of other microorganisms. They produce lactic acid to regulate local pH and release antimicrobial substances such as hydrogen peroxide, which inhibit cariogenic and periodontopathogenic bacteria. In addition, *Streptococcus* interacts with the host immune system, enhancing mucosal barrier integrity and preventing excessive inflammatory activation. *Actinomyces* works with *Streptococcus* synergistically to promote the maturation of biofilms. It generates acidic metabolites that can be utilized by other microorganisms by degrading complex carbohydrates. While contributing to ecological balance under healthy conditions, its overgrowth may lead to root caries or chronic periodontitis. The stable ecological environment of the gingival sulcus can be disrupted by host-related or microbial shifts. The proliferation of *P. gingivalis* alters the nutritional environment at the site of colonization, disrupting the symbiotic balance between the microbiota and the host. It also promotes the growth of *Tannerella forsythia*, further exacerbating inflammation and tissue destruction. *T. forsythia*, together with *P. gingivalis* and *Treponema denticola*, forms the “red complex,” which colonizes periodontal pockets under anaerobic conditions and contributes to periodontal tissue breakdown. The multispecies biofilm they form is resistant to immune responses and antimicrobial therapy. Moreover, *T. forsythia* can stimulate immune cells by secreting proteases and cell wall lipopolysaccharides

(LPS), inducing the release of inflammatory cytokines such as IL-1, IL-6, and TNF- α , thereby exacerbating inflammation. During active phases of periodontitis, its interactions with *P. gingivalis* become more frequent, further aggravating tissue destruction [8].

3 IL-23/Th17 axis–Driven Inflammatory Cascades and Macrophage Polarization

Pro-inflammatory cytokines can activate the IL-23/IL-17 axis, leading to peri-implant bone resorption. In PI lesions, the colonizing microbiota typically includes anaerobic Gram-positive rods, anaerobic Gram-negative bacteria, and Gram-positive cocci. Among these, lipopolysaccharides (LPS) from the outer membrane of Gram-negative bacteria form complexes with proteins and are transferred to Toll-like receptor 4 (TLR4), enabling antigen-presenting cells (APCs) to recognize LPS and activate downstream signalling pathways.

Activated APCs present antigens to CD4⁺ T cells, promoting their differentiation into effector subsets such as Th1, Th2, Th17 cells, and regulatory T cells (Treg). Th17 cells secrete IL-17, a pro-inflammatory cytokine that recruits macrophages and neutrophils, thereby amplifying the inflammatory response. IL-23, a key cytokine for promoting Th17 proliferation, is secreted by dendritic cells and macrophages upon recognition of pathogen-associated or damage-associated molecular patterns. Binding of IL-23 to its receptor (IL-23R) on Th17 cells initiates intracellular signalling cascades, ultimately driving transcription factor activation, Th17 differentiation, and IL-17 production.

Macrophages can polarize into two major types depending on environmental signals: M1 macrophages, which mediate bacteria-induced pro-inflammatory responses, and M2 macrophages, which facilitate inflammation resolution and tissue repair. Foreign body stimuli drive macrophages toward M1 polarization, resulting in the release of IL-1 β , IL-6, and TNF. These cytokines activate retinoic acid-related orphan receptor γ t (ROR γ t), initiating the differentiation of Th17 cells. At the same time, TNF and IL-1 β also enhance the production of IL-6, further promoting the differentiation of Th17 cells and the expression of IL-17, thereby exacerbating inflammation [9]. In contrast, during inflammation, M2 macrophages secrete IL-4, IL-10, IL-13, and TGF- β to balance the M1 response, regulate inflammation, and promote tissue repair and wound healing [2].

4 RANKL/OPG Imbalance and MMP-Mediated Mechanisms of Bone Resorption

Receptor activator of nuclear factor- κ B ligand (RANKL) and osteoprotegerin (OPG) are pivotal molecular determinants of bone metabolism, exerting opposing influences on osteoclast differentiation and function. RANKL is primarily secreted by osteoblasts,

fibroblasts, and activated T cells in a membrane-bound form, and upon binding to its receptor RANK on osteoclast precursors, initiates intracellular signalling cascades that drive osteoclastogenesis and sustain osteoclast survival. This ligand–receptor interaction constitutes the essential molecular axis underlying bone resorption. In contrast, OPG, a soluble decoy receptor released by osteoblasts, neutralizes RANKL by sequestering it away from RANK, thereby restricting osteoclast activation. Thus, the ratio of RANKL to OPG operates as a finely tuned rheostat that governs the equilibrium between bone resorption and formation [5].

In PI, this equilibrium tends to shift toward a resorptive state. Clinical analyses have frequently reported elevated RANKL concentrations and an increased RANKL/OPG ratio in peri-implant crevicular fluid compared to healthy controls, though the statistical significance varies across studies. This heterogeneity likely reflects differences in sampling protocols, patient characteristics, and stages of disease progression. Nevertheless, the recurring observation of an upward RANKL/OPG trend suggests that PI lesions are primed toward an osteoclast-dominant microenvironment, which predisposes affected sites to progressive marginal bone loss and implant destabilization.

Matrix metalloproteinases (MMPs) add a further layer of complexity to this pathogenic landscape. These zinc- and calcium-dependent proteolytic enzymes not only mediate physiological tissue remodelling but also participate directly in pathological extracellular matrix (ECM) degradation. Under healthy conditions, MMP activity is tightly counterbalanced by tissue inhibitors of metalloproteinases (TIMPs). In PI, this regulatory system becomes uncoupled, resulting in sustained MMP overexpression. MMP-8 and MMP-9, in particular, are consistently associated with active peri-implant tissue breakdown. Their heightened activity accelerates collagen fiber cleavage and laminin degradation, which undermines the structural cohesion of peri-implant connective tissues and facilitates lesion expansion [10].

Beyond structural degradation, MMPs exert a signalling role by modulating cytokine activity and generating bioactive ECM fragments. These fragments can act as endogenous danger signals, recruiting neutrophils and macrophages, and further enhancing secretion of IL-1 β , IL-6, and TNF- α . This feedback loop amplifies pro-inflammatory signalling, which in turn augments RANKL expression by immune and stromal cells, thereby reinforcing osteoclastogenic stimuli. In this way, the pathological synergy between heightened MMP activity and RANKL/OPG imbalance establishes a self-reinforcing molecular circuit that accelerates bone resorption and peri-implant tissue degradation.

The mechanistic convergence of RANKL-driven osteoclastogenesis and MMP-mediated matrix degradation illustrates how immune, stromal, and microbial signals intersect in PI pathogenesis. Rather than acting as isolated pathways, these molecular systems are dynamically integrated within the peri-implant microenvironment. Current evidence indicates that targeting either RANKL signalling or MMP activity alone may be insufficient, as their mutual reinforcement

sustains the chronicity of tissue destruction. Consequently, combinatorial strategies, for instance, local delivery of RANKL inhibitors together with selective MMP antagonists, are increasingly discussed as potential means to attenuate peri-implant bone loss. Equally important, the quantification of RANKL/OPG ratios and MMP activity in peri-implant crevicular fluid is emerging as a promising approach for identifying patients at risk of rapid disease progression.

5 Biomarkers and Risk Assessment for Early Diagnosis

Biomarker detection is increasingly explored as a means of improving the early diagnosis of PI. PICF, collected non-invasively from the peri-implant sulcus, directly reflects the molecular events occurring at the implant–tissue interface and thus provides a suitable medium for analysis. Parameters measured in PICF can indicate shifts in bone metabolism, inflammatory signalling, and tissue remodelling before overt clinical changes become evident [11].

Among bone-related indicators, RANKL and its soluble form (sRANKL) have been repeatedly evaluated. Several studies reported higher sRANKL levels in PISF from PI patients, whereas others did not observe meaningful differences compared with healthy controls. OPG, the natural antagonist of RANKL, has also been detected in PICF; one study found it present in nearly 80% of samples and closely associated with bleeding on probing (BOP). Such variability likely reflects differences in sampling methods, patient cohorts, and disease stages rather than the irrelevance of the markers themselves. These findings suggest that the RANKL/OPG ratio may capture an underlying tendency toward bone resorption in PI, but the reliability of this measure requires confirmation in standardized, longitudinal studies [12].

MMP-8 has likewise attracted attention as a potential biochemical marker. Elevated levels have been documented in some PISF samples from PI patients, supporting its role as a readout of active collagen breakdown. However, other investigations failed to replicate this association, raising questions about its diagnostic consistency. Because MMP-8 participates in both ECM degradation and inflammatory amplification, its concentration may fluctuate depending on the stage of lesion activity, which complicates its interpretation as a stand-alone marker.

Biochemical assays alone are insufficient for clinical decision-making, and imaging modalities complement this gap. CBCT, for example, offers three-dimensional assessment of bone morphology around implants without the distortion inherent in conventional radiography. It allows visualization of horizontal and vertical bone loss patterns, as well as defect morphology. Yet bone loss rarely develops independently of mucosal inflammation, underscoring the need to interpret CBCT findings in conjunction with soft tissue parameters and biochemical markers [13, 14].

To systematize risk prediction, structured scoring tools such as the PIRA model have been proposed. PIRA

integrates eight parameters, history of periodontitis, BOP, bone-to-implant length ratio, diabetes, smoking, plaque-positive sites, residual pockets ≥ 5 mm, and implant functional time, into a weighted index. By summing these scores, patients can be stratified into risk categories. This structured approach provides a quantitative framework that aligns clinical, behavioural, and systemic factors, enabling tailored maintenance schedules and preventive interventions for those most susceptible to PI.

Overall, evidence from PICF biomarkers, imaging, and structured risk indices indicates that no single parameter is sufficient to capture the complex biology of PI. Instead, combining molecular signatures such as the RANKL/OPG ratio and MMP-8 with CBCT evaluation and validated risk scores may create a more precise diagnostic toolkit. Progress in this direction will depend on harmonizing sampling protocols, validating candidate markers across diverse populations, and integrating biochemical and imaging data into clinically usable models that genuinely improve early detection and risk stratification in implant dentistry.

6 Conclusion

The onset and progression of PI involve coordinated shifts in microbial ecology, immune signalling, and bone remodelling pathways. Early biofilms dominated by facultative anaerobes are gradually supplanted by strict anaerobic taxa such as *P. gingivalis* and *T. forsythia*. These organisms secrete extracellular polysaccharides and proteases that consolidate the biofilm structure, alter nutrient availability, and generate an environment favouring persistent inflammation. On the host side, activation of the IL-23/Th17 axis and polarization of macrophages toward an M1 phenotype amplify cytokine release and neutrophil recruitment, thereby maintaining chronic inflammation at the peri-implant interface. Concurrently, an elevated RANKL/OPG ratio and excessive MMP activity accelerate osteoclast differentiation and matrix degradation, directly contributing to marginal bone resorption and peri-implant tissue loss.

Recent work has turned to molecular markers in PICF, such as IL-17, RANKL/OPG ratios, and MMP-8, together with CBCT imaging, to capture early alterations in disease activity. These approaches suggest that combining molecular readouts with high-resolution bone morphology can improve detection before overt clinical breakdown occurs. Yet evidence remains fragmented: variations in sampling techniques, cohort size, and disease definitions have produced inconsistent results, limiting clinical applicability. Moving forward, longitudinal studies with harmonized protocols and cross-centre validation are needed to determine which markers most reliably predict progression. Integrating these data into risk-stratification models could shift PI management from delayed intervention to earlier, individualized prevention strategies.

References

1. Smeets R, Henningsen A, Jung O, et al. Definition, etiology, prevention and treatment of peri-implantitis: a review. *Head Face Med.* **10**, 34 (2014). <https://doi.org/10.1186/1746-160X-10-34>
2. Li Y, Li X, Guo D, et al. Immune dysregulation and macrophage polarization in peri-implantitis. *Front Bioeng Biotechnol.* **12**, 1291880 (2024). <https://doi.org/10.3389/fbioe.2024.1291880>
3. Alassy H, Parachuru P, Wolff L, et al. Peri-implantitis diagnosis and prognosis using biomarkers in peri-implant crevicular fluid: a narrative review. *Diagnostics (Basel).* **9**, 4 (2019). <https://doi.org/10.3390/diagnostics9040214>
4. Mardegan GP, Shibli JA, Roth LA, et al. Transforming growth factor- β , interleukin-17, and IL-23 gene expression profiles associated with human peri-implantitis. *Clin Oral Implants Res.* **28**, e10 (2017). <https://doi.org/10.1111/clr.12846>
5. Theodoridis C, Doukeridou C, Menexes G, et al. Comparison of RANKL and OPG levels in peri-implant crevicular fluid between healthy and diseased peri-implant tissues: a systematic review and meta-analysis. *Clin Oral Investig.* **26**, 823 (2022). <https://doi.org/10.1007/s00784-021-04061-w>
6. Alves CH, Russi KL, Rocha NC, et al. Host-microbiome interactions regarding peri-implantitis and dental implant loss. *J Transl Med.* **20**, 425 (2022). <https://doi.org/10.1186/s12967-022-03636-9>
7. Ata-Ali J, Candel-Marti ME, Flichy-Fernández AJ, et al. Peri-implantitis: associated microbiota and treatment. *Med Oral Patol Oral Cir Bucal.* **16**, e937 (2011). <https://doi.org/10.4317/medoral.17227>
8. Cui Z, Wang P, Gao W, et al. Microbial dysbiosis in periodontitis and peri-implantitis: pathogenesis, immune responses, and therapeutic. *Front Cell Infect Microbiol.* **15**, 1517154 (2025). <https://doi.org/10.3389/fcimb.2025.1517154>
9. Alarcón-Sánchez MA, Becerra-Ruiz JS, Rodríguez-Montaña R, et al. The role of interleukin-23 and interleukin-17 in peri-implant crevicular fluid of subjects with peri-implant disease: a systematic review. *J Clin Lab Anal.* **39**, e70071 (2025). <https://doi.org/10.1002/jcla.70071>
10. Jansson L, Lundmark A, Modin C, et al. Levels of matrix metalloproteinase-1 (MMP-1), MMP-2, MMP-3, osteopontin, pentraxin-3, and thymic stromal lymphopoietin in crevicular fluid samples from peri-implantitis, periodontitis, and healthy sites. *J Periodontal Res.* **60**, 473 (2025). <https://doi.org/10.1111/jre.13338>
11. Lumbikananda S, Srithanyarat SS, Mattheos N, et al. Oral fluid biomarkers for peri-implantitis: a scoping review. *Int Dent J.* **74**, 387 (2024). <https://doi.org/10.1016/j.identj.2023.11.005>
12. Sahrman P, Kühl S, Dagassan-Berndt D, et al. Radiographic assessment of the peri-implant site.

- Periodontol 2000. **95**, 70 (2024).
<https://doi.org/10.1111/prd.12577>
13. Algahtani FN, Hebbal M, Alqarni MM, et al. Prevalence of bone loss surrounding dental implants as detected in cone beam computed tomography: a cross-sectional study. PeerJ. **11**, e15770 (2023). <https://doi.org/10.7717/peerj.15770>
 14. Quirynen M, Tarce M, Siawasch M, et al. Peri-implantitis risk assessment (PIRA) Part 2: retrospective study and framework for an evidence-based prediction model for clinicians. Int J Oral Maxillofac Implants. **0**, 1 (2025).
<https://doi.org/10.11607/jomi.11211>