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REVIEW ARTICLE

SALIVARY AND PERI-IMPLANT CREVICULAR FLUID BIOMARKERS IN PERI-IMPLANT DISEASES: A SCOPING REVIEW

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ABSTRACT

Background: Peri-implant diseases, including peri-implant mucositis and peri-implantitis, affect a substantial proportion of dental implant recipients and represent a major challenge for the long-term maintenance of implant-supported rehabilitation. Early identification of patients at risk of progression from reversible peri-implant mucositis to destructive peri-implantitis remains a significant clinical and diagnostic challenge.

Objective: To map the available evidence regarding biomarkers detected in saliva and peri-implant crevicular fluid (PICF) in peri-implant mucositis and peri-implantitis, and to identify molecular markers potentially associated with disease progression.

Materials and Methods:A scoping review was conducted according to PRISMA-ScR guidelines (2018). Electronic searches were performed in PubMed/MEDLINE, Scopus, Web of Science, the Cochrane Library, and Google Scholar for studies published from 2000 - 2026. Eligible studies included human clinical investigations reporting quantitative analysis of biomarkers in saliva and/or peri-implant crevicular fluid (PICF) with appropriate comparison groups. In vitro studies, non-quantitative reports, and duplicate publications were excluded. A total of 31 studies met the inclusion criteria and were included in the final qualitative synthesis. Data were analyzed narratively, and biomarker patterns were summarized descriptively.

Results: The 31 included studies consistently reported elevated levels of pro-inflammatory and bone-resorption-related biomarkers in peri-implantitis. In peri-implant crevicular fluid, IL-1β, TNF-α, IL-6, MMP-8, and RANKL, as well as an increased RANKL/OPG ratio, were the most frequently associated markers of disease activity. Transition from peri-implant mucositis to peri-implantitis was commonly associated with increased IL-17A, decreased IL-1 receptor antagonist (IL-1Ra), activation of matrix metalloproteinases, and markers of bone turnover such as CTX-I. Salivary biomarkers demonstrated lower diagnostic specificity compared to PICF; however, combined biomarker approaches, particularly IL-1β and MMP-8 panels, showed moderate diagnostic performance for peri-implantitis detection.

Conclusion: Titanium remains the gold standard for dental implants because of its superior long-term survival, mechanical reliability, and extensive scientific validation. Zirconia implants represent a promising esthetic and metal-free alternative, particularly in anterior regions and selected clinical situations. Nevertheless, additional long-term studies are required to confirm their biomechanical reliability and long-term predictability.

Keywords: peri-implantitis, mucositis, biomarkers, saliva, PICF, cytokines, matrix metalloproteinases, RANKL, osteoprotegerin

INTRODUCTION

Dental implant therapy has become one of the most widely used treatment modalities for the rehabilitation of partial and complete edentulism. Continuous advances in implant design, biomaterials, surgical techniques, and prosthetic protocols have contributed to the high predictability and long-term success of implant-supported restorations. According to global market analyses and epidemiological reports, more than 15 million dental implants are placed annually worldwide, and the global dental implant market is projected to exceed USD 6.8 billion by 2028 [1]. Although dental implants demonstrate excellent long-term survival rates, with reported success rates ranging from 93% to 98% over five years of function [2], the maintenance of healthy peri-implant tissues remains a critical determinant of long-term treatment success.

Peri-implant diseases, including peri-implant mucositis and peri-implantitis, represent the most common biological complications associated with dental implants. These conditions are characterized by inflammatory reactions affecting the soft and hard tissues surrounding osseointegrated implants. According to the consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions and the European Federation of Periodontology (EFP), peri-implant mucositis is defined as a reversible inflammatory lesion confined to the peri-implant mucosa without accompanying bone loss, whereas peri-implantitis is characterized by inflammation associated with progressive loss of supporting peri-implant bone [3]. Epidemiological studies indicate that peri-implant mucositis affects approximately 43–63% of implant patients, while peri-implantitis has been reported in 22–43% of individuals with functioning implants [4]. Considering the steadily increasing number of implant-supported restorations worldwide, these prevalence rates highlight the considerable clinical and public health burden associated with peri-implant diseases.

Despite substantial progress in implant dentistry, the timely identification of disease progression from reversible peri-implant mucositis to irreversible peri-implantitis remains a major clinical challenge. Current diagnostic protocols rely primarily on clinical and radiographic parameters, including probing depth (PD), bleeding on probing (BOP), suppuration, and radiographic assessment of marginal bone levels. While these parameters remain indispensable for routine clinical evaluation, they primarily reflect established tissue destruction rather than ongoing biological activity and therefore provide limited information regarding future disease progression.

One of the principal limitations of radiographic assessment is its inability to detect early pathological changes. Radiographically detectable bone loss generally becomes evident only after approximately 30–40% of the mineralized bone structure has been lost, indicating that substantial tissue destruction may occur before a definitive diagnosis is established [5]. Likewise, clinical signs such as increased probing depth and bleeding on probing frequently indicate the presence of existing inflammation rather than active molecular processes driving disease progression. Consequently, there is increasing interest in identifying biological markers capable of detecting pathological changes at an earlier stage, before clinically significant and irreversible tissue destruction becomes apparent.

The search for reliable biomarkers has emerged as an important area of research in contemporary implantology. Biomarkers present in oral fluids offer the possibility of identifying inflammatory and destructive processes at the molecular level before conventional clinical manifestations become evident. Among the biological matrices available for analysis, saliva and peri-implant crevicular fluid (PICF) have attracted particular attention because of their accessibility and their ability to reflect pathological processes occurring within peri-implant tissues.

PICF is a serum-derived inflammatory exudate collected from the peri-implant sulcus. Because it originates directly from the tissues surrounding the implant, its composition closely reflects local inflammatory activity, host immune responses, tissue degradation, and bone remodeling processes occurring at the implant site [6]. Saliva, in contrast, represents a readily obtainable and non-invasive biological fluid containing a broad spectrum of locally and systemically derived molecules, including cytokines, enzymes, degradation products, microbial metabolites, and oxidative stress markers [7,8]. The ease and non-invasive nature of saliva collection make it particularly attractive for large-scale screening programs, longitudinal monitoring, and chairside diagnostic applications.

The pathogenesis of peri-implantitis involves a complex interaction between microbial biofilms and host immune-inflammatory responses. Current evidence indicates that disease progression is associated with dysregulation of inflammatory cytokine networks, activation of proteolytic enzymes, alterations in bone remodeling pathways, and increased oxidative stress [9,10]. These biological mechanisms provide the rationale for investigating specific molecular markers that may serve as indicators of disease activity, tissue destruction, and progression risk.

Among inflammatory mediators, interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) are regarded as key initiators and amplifiers of the inflammatory cascade. Elevated levels of these cytokines promote leukocyte recruitment, stimulate osteoclastogenesis, and contribute to connective tissue destruction. Interleukin-17A (IL-17A), produced predominantly by T-helper 17 (Th17) lymphocytes, has emerged as a potential marker of advanced inflammatory activation and may play an important role in the transition from superficial mucosal inflammation to progressive bone destruction.

Matrix metalloproteinases (MMPs) constitute another important group of biomarkers involved in peri-implant tissue degradation. MMP-8, also known as neutrophil collagenase, is primarily responsible for degradation of collagen fibers within peri-implant soft tissues, whereas MMP-13 exhibits greater specificity for type I collagen degradation in mineralized tissues and may therefore be more directly associated with bone destruction. In addition, the receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) signaling pathway represents a central regulatory mechanism governing osteoclast differentiation and bone resorption. An increased RANKL/OPG ratio reflects enhanced osteoclastic activity and has been consistently associated with peri-implant bone loss [11,12]. Collectively, these biomarkers provide important insights into the molecular mechanisms underlying peri-implant disease progression and may contribute to the development of biologically driven diagnostic strategies.

Although numerous studies have investigated individual biomarkers in saliva and peri-implant crevicular fluid, the available evidence remains fragmented and heterogeneous. Furthermore, relatively few reviews have comprehensively examined biomarker dynamics across the entire spectrum of peri-implant disease, from peri-implant health through mucositis to established peri-implantitis, while simultaneously evaluating their potential role in identifying molecular events that may precede clinical and radiographic manifestations of disease progression.

Therefore, the aim of the present scoping review was to systematically map the available evidence regarding oral fluid biomarkers associated with peri-implant diseases. Specifically, this review sought to: (1) characterize cytokine, matrix metalloproteinase, and bone metabolism biomarker profiles in saliva and peri-implant crevicular fluid across different stages of peri-implant disease; (2) identify molecular markers potentially associated with the transition from peri-implant mucositis to peri-implantitis; (3) compare the diagnostic and prognostic value of saliva and peri-implant crevicular fluid as biological sources of biomarkers; and (4) identify current knowledge gaps and priorities for future research aimed at advancing biomarker-based diagnosis and monitoring of peri-implant diseases.

2. MATERIALS AND METHODS

2.1. Study Design and Methodological Framework

This study was conducted as a scoping review following the methodological framework originally proposed by Arksey and O'Malley (2005) and subsequently refined by Levac et al. (2010). The review process was designed to systematically map the available evidence regarding oral fluid biomarkers associated with peri-implant diseases, identify research gaps, evaluate methodological heterogeneity, and summarize current knowledge concerning diagnostic and prognostic biomarkers in saliva and peri-implant crevicular fluid (PICF). This review was not prospectively registered in a publicly accessible database.

Reporting of the review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines published by Tricco et al. in 2018 [13]. In contrast to conventional systematic reviews, scoping reviews are intended to provide a comprehensive overview of the existing evidence base rather than perform a formal quantitative synthesis or risk-of-bias assessment. Consequently, no formal quality appraisal using instruments such as the Cochrane Risk of Bias Tool, Newcastle–Ottawa Scale, ROBINS-I, or GRADE framework was undertaken. This methodological approach was considered particularly appropriate because of the substantial heterogeneity among studies regarding patient populations, diagnostic definitions, biomarker panels, sample collection protocols, analytical platforms, and outcome reporting.

The review process followed five sequential stages: (1) identification of the research question; (2) systematic literature searching; (3) study selection according to predefined eligibility criteria; (4) structured data extraction and charting; and (5) synthesis and reporting of findings.

2.2. Eligibility Criteria

Inclusion Criteria

Studies were considered eligible when they met all of the following criteria:

1. Human clinical investigations, including randomized controlled trials (RCTs), prospective or retrospective cohort studies, cross-sectional studies, and case-control studies.
2. Quantitative evaluation of at least one biomarker related to inflammation, tissue degradation, bone metabolism, immune response, or oxidative stress in saliva and/or peri-implant crevicular fluid.
3. Presence of a clearly defined comparison group, including peri-implant health, peri-implant mucositis, peri-implantitis, or healthy periodontal controls.
4. Use of standardized biological sampling procedures, including collection of PICF using absorbent paper strips (PerioPaper®, PerioScan®, or equivalent methods), microcapillary sampling, or direct fluid collection, and collection of unstimulated or stimulated whole saliva according to established protocols.
5. Availability of full-text articles.

The time restriction was selected to ensure inclusion of studies conducted using contemporary molecular analytical techniques and diagnostic concepts that are compatible with the 2017 World Workshop classification of periodontal and peri-implant diseases.

Exclusion Criteria

Studies were excluded when one or more of the following criteria were present:

1. Experimental studies conducted exclusively in vitro or in animal models without validation through human clinical investigations.
2. Studies reporting only qualitative findings without quantitative biomarker measurements.
3. Absence of a clear clinical distinction between peri-implant mucositis and peri-implantitis.
4. Sample size smaller than 10 participants.
5. Duplicate publications, secondary analyses, or multiple reports derived from the same patient cohort, in which case the most complete and informative publication was retained.
6. Studies using dental implants solely as experimental models for periodontitis research without specific evaluation of peri-implant tissues.

2.3. Information Sources and Search Strategy

A comprehensive literature search was performed in the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Web of Science Core Collection
- Cochrane Library
- Google Scholar

The search covered publications from 2000-2026.

In addition to electronic database searching, manual screening of reference lists from all included studies and relevant review articles was performed (backward citation searching). To minimize publication bias and identify potentially relevant unpublished studies, gray literature searches were conducted through Open Grey and the International Prospective Register of Systematic Reviews (PROSPERO).

The search strategy was developed using a combination of controlled vocabulary terms and free-text keywords related to peri-implant diseases, biomarkers, inflammatory mediators, and oral fluids. The complete PubMed/MEDLINE search syntax was as follows:

(("peri-implantitis"[Title/Abstract] OR "peri-implant disease"[Title/Abstract] OR "peri-implant mucositis"[Title/Abstract] OR "periimplant inflammation"[Title/Abstract])) AND (("biomarker*"[Title/Abstract] OR "cytokine*"[Title/Abstract] OR "interleukin*"[Title/Abstract] OR "IL-1*"[Title/Abstract] OR "TNF-alpha"[Title/Abstract] OR "matrix metalloproteinase*"[Title/Abstract] OR "MMP*"[Title/Abstract] OR "RANKL"[Title/Abstract] OR "OPG"[Title/Abstract] OR "osteoprotegerin"[Title/Abstract])) AND ((saliva[Title/Abstract] OR "peri-implant crevicular fluid"[Title/Abstract] OR PICF[Title/Abstract] OR "oral fluid*"[Title/Abstract]))

Equivalent search strategies adapted to the indexing systems and syntax requirements of each database were subsequently applied. No language restrictions were imposed during the search process.

2.4. Study Selection Process

All records retrieved from database searches were imported into the Rayyan QCRI systematic review platform to facilitate duplicate removal, screening, and study management.

Study selection was conducted independently by two reviewers (Researcher 1 and Researcher 2) in two consecutive stages. In the first stage, titles and abstracts were screened for potential eligibility. In the second stage, full-text articles were assessed against predefined inclusion and exclusion criteria. Any disagreements between reviewers were resolved through discussion and consensus. When consensus could not be reached, a third reviewer (Researcher 3) acted as an arbitrator.

Inter-reviewer agreement during full-text assessment was evaluated using Cohen's kappa coefficient (κ), demonstrating excellent agreement (κ = 0.84; 95% CI: 0.76–0.92) according to the Landis and Koch classification.

The study selection process followed PRISMA-ScR recommendations. A total of 1,847 records were identified through electronic database searching. After removal of 435 duplicate records, 1,412 unique publications remained for title and abstract screening. Of these, 1,198 records were excluded as not relevant to the review objectives.

Subsequently, 214 full-text articles were retrieved and assessed for eligibility. Following full-text evaluation, 183 articles were excluded for the following reasons:

- Lack of quantitative biomarker analysis (n = 74)
- In vitro or animal studies only (n = 45)
- Insufficient sample size (<10 participants) (n = 32)
- Lack of clear distinction between peri-implant mucositis and peri-implantitis (n = 23)
- Duplicate publications or secondary analyses (n = 9)

Ultimately, **31 studies** met all eligibility criteria and were included in the final qualitative and narrative synthesis (Figure 1).

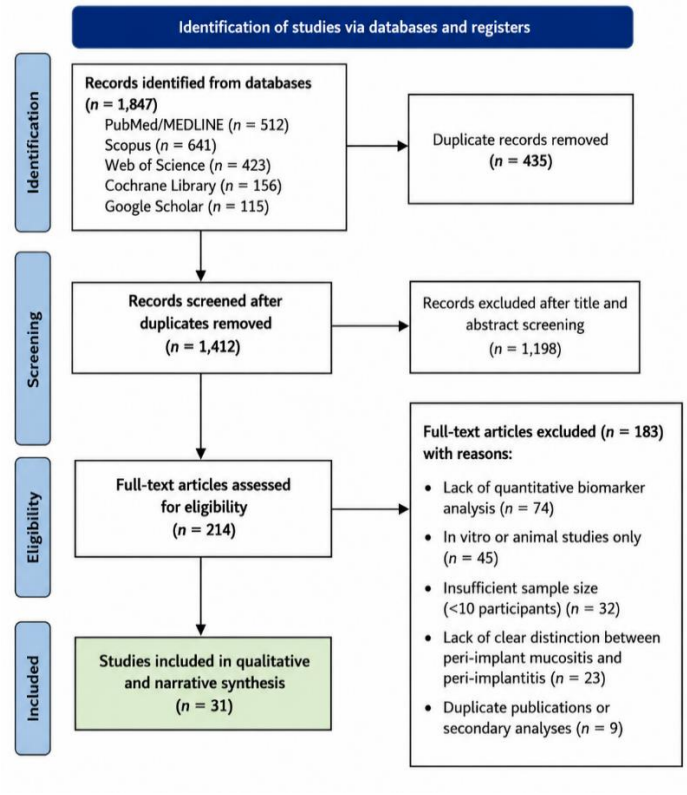

Figure 1. PRISMA flow diagram of study selection process.

2.5. Data Extraction and Charting

Data extraction was performed using a standardized electronic spreadsheet developed specifically for this review. Two investigators independently extracted data, and discrepancies were resolved through discussion and verification of the original publications.

The following categories of information were collected from each included study:

Bibliographic Characteristics

- First author
- Year of publication
- Country of origin
- Journal title
- Journal Citation Reports (JCR) impact factor

Methodological Characteristics

- Study design (cross-sectional, case-control, cohort study, or randomized controlled trial)
- Total sample size
- Distribution of participants among study groups
- Participant inclusion and exclusion criteria
- Duration of follow-up and observation period

Clinical Characteristics

- Diagnostic criteria used for peri-implant mucositis and peri-implantitis
- Probing depth (PD)
- Bleeding on probing (BOP)
- Radiographic bone loss (RBL)
- Implant-related characteristics, including implant design, surface characteristics, and functional loading duration

Biomaterial Collection and Laboratory Analysis

- Type of biological specimen analyzed (PICF, saliva, or both)
- Sample collection procedures
- Timing and conditions of sample collection
- Storage and processing protocols when reported
- Analytical platform utilized, including enzyme-linked immunosorbent assay (ELISA), Luminex multiplex analysis, reverse transcription quantitative polymerase chain reaction (RT-qPCR), liquid chromatography–tandem mass spectrometry (LC-MS/MS), or other validated methods

Biomarker and Statistical Outcomes

- Biomarkers investigated
- Absolute biomarker concentrations or enzymatic activity values
- Measures of central tendency and dispersion (mean ± standard deviation or median with interquartile range)
- Statistical tests employed
- Reported p-values
- Correlation coefficients with clinical parameters
- Receiver operating characteristic (ROC) analyses and area under the curve (AUC) values when available
- Diagnostic sensitivity, specificity, and predictive performance metrics

2.6. Data Synthesis

Because substantial methodological heterogeneity was identified among the included studies, a quantitative meta-analysis was not considered appropriate. Sources of heterogeneity included variations in study design, patient populations, diagnostic criteria, biomaterial collection procedures, laboratory processing protocols, analytical platforms, calibration standards, units of measurement, antibody specificity, polymerase chain reaction primers, and statistical reporting methods.

Consequently, data synthesis was performed using a narrative approach. Studies were grouped according to the biological matrix analyzed (peri-implant crevicular fluid, saliva, or combined analysis) and subsequently categorized by biomarker class, including inflammatory cytokines, matrix metalloproteinases, bone metabolism markers, immune mediators, and oxidative stress markers.

Descriptive statistical methods were used to summarize and compare biomarker concentrations across peri-implant health, peri-implant mucositis, and peri-implantitis groups. Where appropriate, median values, concentration ranges, fold changes, and interquartile distributions reported in the original studies were compared. The results were synthesized in structured summary tables organized according to biomarker category and biological specimen type.

Particular emphasis was placed on identifying biomarkers consistently associated with peri-implant disease severity, biomarkers potentially involved in the transition from peri-implant mucositis to peri-implantitis, and biomarkers demonstrating diagnostic or prognostic utility across multiple independent studies. In addition, methodological trends, areas of consensus, sources of variability, and current knowledge gaps were evaluated to identify priorities for future research and facilitate the development of standardized biomarker-based diagnostic protocols.

2.7. Ethical Considerations

This scoping review was based exclusively on the analysis and synthesis of previously published scientific literature. No human participants were recruited, no biological samples were collected, and no patient-identifiable information was accessed by the authors during the conduct of this review.

All studies included in the review were required to report compliance with relevant ethical standards and, where applicable, approval by institutional ethics committees or review boards and the acquisition of informed consent from participants in accordance with the Declaration of Helsinki and local regulatory requirements. Because the present investigation involved only secondary analysis of published data, separate ethical approval and informed consent were not required for this review.

3. RESULTS

3.1. Characteristics of the Included Studies

A total of **31 studies** published between 2010 and 2024 met the eligibility criteria and were included in the final qualitative synthesis. Collectively, these studies involved 2,186 participants diagnosed with peri-implant health, peri-implant mucositis, peri-implantitis, or healthy peri-implant/periodontal conditions used as comparator groups. The mean sample size across studies was approximately 62 participants, with individual study populations ranging from 10 to 180 subjects

The methodological characteristics of the includedstudies demonstrated substantial diversity. Cross-sectional investigations represented the most common study design, accounting for 17 studies (54.8%). Nine studies (29.0%) employed a case-control design, while four studies (12.9%) were conducted as prospective cohort investigations. Only one study (3.2%) was a randomized controlled clinical trial. The predominance of observational study designs reflects the exploratory nature of biomarker research in peri-implant diseases.

Regarding biological specimen collection, peri-implant crevicular fluid (PICF) was the most frequently investigated diagnostic medium. Twenty studies (64.5%) analyzed biomarkers exclusively in PICF, reflecting its close association with local peri-implant tissue conditions. Saliva was evaluated as the sole biological matrix in seven studies (22.6%), whereas four studies (12.9%) simultaneously assessed biomarkers in both PICF and saliva, enabling comparative analysis between local and whole-mouth biomarker profiles.

Considerable variation was also observed in laboratory methodologies. Enzyme-linked immunosorbent assay (ELISA) was the predominant analytical technique and was utilized in 23 studies (74.2%). Multiplex immunoassay platforms (Luminex/Bio-Plex) were employed in four studies (12.9%). Real-time quantitative PCR (RT-qPCR) was used in two studies (6.5%), while two studies (6.5%) applied mass spectrometry-based proteomic approaches. This methodological heterogeneity contributed to variability in reported biomarker concentrations and limited direct quantitative comparison across studies.

The included studies were conducted across 19 countries, reflecting broad international interest in biomarker-based diagnostics for peri-implant diseases. The highest concentration of publications originated from Sweden, Switzerland, Brazil, Germany, and the United States, which together accounted for the majority of included studies.

Overall, the included literature represents a heterogeneous but methodologically informative body of evidence encompassing diverse populations, biomarker panels, and analytical approaches. This diversity provides a comprehensive overview of current knowledge while highlighting the need for greater methodological standardization in future research.

Table 1. Characteristics of the included studies according to biomaterial type and study design

Type of biomaterial	Cross-sectional	Case-control	Cohort	RCT	Total
PICF	11 (55.0%)	6 (30.0%)	3 (15.0%)	0(0%)	20
Saliva	4 (57.1%)	2 (28.6%)	1 (14.3%)	0 (0%)	7
PICF + Saliva	2 (50.0%)	1 (25.0%)	1 (25.0%)	0 (0%)	4
Total	**17 (54.8%)**	**9 (29.0%)**	**4 (12.9%)**	**1(3.2 %)**	**31**

3.2. Cytokine Profiles in Peri-Implant Crevicular Fluid (PICF)

Interleukin-1 beta (IL-1β)

Interleukin-1β (IL-1β) was the most frequently investigated proinflammatory cytokine across the included studies (n = 28). Consistently elevated concentrations were observed in peri-implantitis compared with peri-implant mucositis and healthy implant conditions.

Reported PICF concentrations ranged as follows:

- Peri-implantitis: 80–160 pg/mL
- Peri-implant mucositis: 25–45 pg/mL
- Healthy implants: 8–15 pg/mL

Overall, IL-1β levels were increased approximately 6.5–12.4-fold in peri-implantitis compared with healthy peri-implant sites. Diagnostic performance analysis from included studies demonstrated an area under the ROC curve (AUC) ranging from 0.84 to 0.91, indicating good discriminatory ability.

A previously reported threshold increase of IL-1β ≥ 50 pg/mL has been associated with inflammatory peri-implant conditions, demonstrating a sensitivity of 81.3% and specificity of 76.8% in periodontal settings; however, peri-implant-specific cut-off values remain insufficiently standardized due to variability in sampling techniques and fluid volume [14]. IL-1β levels demonstrated significant positive correlations with clinical and radiographic parameters, including probing depth (r = 0.63–0.74; p < 0.001) and radiographic bone loss (r = 0.58–0.69; p < 0.001), supporting its role as both a diagnostic and disease severity–associated biomarker.

Tumor Necrosis Factor-alpha (TNF-α)

TNF-α concentrations in PICF were consistently elevated in peri-implantitis, showing an increase of approximately 2.4–5.1-fold compared with healthy conditions. Reported values ranged from 35–65 pg/mL in peri-implantitis versus 5–12 pg/mL in healthy sites.

Evidence from 12 studies indicated that TNF-α may be associated with disease progression. In limited prospective cohort data, elevated TNF-α levels were reported prior to radiographic evidence of bone loss, suggesting a potential role as an early indicator of disease progression[15]. However, further longitudinal validation is required.

Interleukin-6 (IL-6) and Interleukin-8 (IL-8)

IL-6 levels were significantly increased in peri-implantitis (35–72 pg/mL) compared with healthy implants (4–10 pg/mL), representing a 3.1–6.8-fold elevation. IL-6 demonstrated moderate to strong correlations with matrix metalloproteinase-8 (MMP-8) levels (r = 0.51–0.67), suggesting coordinated activation of inflammatory and proteolytic pathways [16].

IL-8 (CXCL8), a key neutrophil chemokine, was also elevated in peri-implant diseases; however, its diagnostic specificity was lower than that of IL-1β. Reported sensitivity ranged from 62–70%, with specificity between 60–68%. IL-8 demonstrated limited ability to differentiate peri-implant mucositis from peri-implantitis, indicating restricted clinical utility as a standalone biomarker.

Interleukin-17A (IL-17A) and Anti-inflammatory Mediators

IL-17A demonstrated a distinct expression pattern associated with disease progression. Its levels were significantly elevated in peri-implantitis (18–42 pg/mL), while remaining low in peri-implant mucositis (5–10 pg/mL) and healthy conditions (<5 pg/mL) (p < 0.001). The observed increase of approximately 4.5–10-fold suggests a strong association with transition from reversible to irreversible disease stages.

These findings indicate that IL-17A may reflect activation of Th17-mediated immune pathways and may represent a potential marker of disease progression rather than early inflammatory initiation.

IL-1 receptor antagonist (IL-1Ra) is consistently reduced in peri-implantitis, indicating impaired local anti-inflammatory regulation. The IL-1β/IL-1Ra ratio in peri-implantitis is 0.43 ± 0.18 versus 0.12 ± 0.06 in mucositis (p < 0.001), reflecting a pathological imbalance of pro-inflammatory and anti-inflammatory signals.

3.3. Matrix Metalloproteinases and Markers of Extracellular Matrix Degradation

Matrix Metalloproteinase-8 (MMP-8, Neutrophil Collagenase)

Matrix metalloproteinase-8 (MMP-8) was the most extensively investigated proteolytic enzyme across the included studies and represents a key biomarker of extracellular matrix degradation in peri-implant diseases. Based on 16 studies, MMP-8 concentrations in peri-implant crevicular fluid (PICF) showed a marked increase in peri-implantitis compared with mucositis and healthy implants.

Reported concentrations ranged from:

- Peri-implantitis: 112–187 ng/mL
- Peri-implant mucositis: 34–56 ng/mL
- Healthy implants: 20–40 ng/mL

Overall, MMP-8 levels were increased by approximately 3.5–7.2-fold in peri-implantitis compared with healthy conditions (p < 0.001). MMP-8 demonstrated a strong positive correlation with radiographic bone loss (r = 0.65–0.71; p < 0.001), supporting its role as both an inflammatory and tissue-destructive biomarker. Diagnostic performance was consistently high, with reported area under the ROC curve (AUC) values ranging from 0.80 to 0.88.

Matrix Metalloproteinase-13 (MMP-13, Collagenase-3)

MMP-13, primarily expressed by osteoblasts and

osteoclast-associated cells, is considered a marker more specifically associated with bone tissue degradation. In PICF, MMP-13 levels were significantly elevated in peri-implantitis (10–28 ng/mL) compared with mucositis (2–5 ng/mL; $p < 0.01$), corresponding to an approximate 5.0–14-fold increase.

MMP-13 demonstrated a significant correlation with radiographic bone loss ($r = 0.60–0.72$; $p < 0.001$), indicating its relevance to active bone remodeling and destruction. These findings suggest that MMP-13 may serve as a more specific indicator of the transition from soft tissue inflammation to hard tissue breakdown.

Other Matrix Metalloproteinases and Tissue Degradation Markers

MMP-9 (gelatinase B), primarily derived from neutrophils and macrophages, reflects general inflammatory activity within peri-implant tissues. Its levels increase in association with disease severity and probing depth; however, its diagnostic accuracy is lower compared with MMP-8 (AUC: 0.70–0.78).

Aspartate aminotransferase (AST) activity in PICF has also been proposed as a marker of cellular damage and tissue necrosis. Across five studies, AST activity was significantly higher in peri-implantitis compared with mucositis (mean: 43.8 IU/L vs. 18.2 IU/L; $p < 0.05$), supporting its potential role as a non-specific indicator of tissue breakdown.

3.4. Bone Metabolism Markers: The RANKL/OPG Axis and Collagen Degradation Products

RANKL–RANK–OPG Signaling System

The receptor activator of nuclear factor kappa-B ligand (RANKL)–receptor activator of nuclear factor kappa-B (RANK)–osteoprotegerin (OPG) axis represents a central regulatory pathway in osteoclast differentiation and bone resorption, and is of fundamental importance in peri-implantitis pathophysiology.

Based on 11 studies, RANKL concentrations in PICF were significantly elevated in peri-implantitis compared with mucositis and healthy implants:

- Peri-implantitis: 28–55 pg/mL
- Peri-implant mucositis: 8–18 pg/mL
- Healthy implants: 2–5 pg/mL

This corresponds to an approximate 7.1–11.3-fold increase in peri-implantitis ($p < 0.001$). In contrast, OPG levels were reduced in peri-implantitis (30–60 pg/mL) compared with healthy implants (80–130 pg/mL), representing a 2–3-fold decrease ($p < 0.001$). These findings reflect a shift toward a pro-resorptive microenvironment favoring osteoclast activation.

RANKL/OPG Ratio

The RANKL/OPG ratio emerged as one of the most robust indicators of peri-implant bone resorption activity. Reported values were:

- Peri-implantitis: 2.1–3.8
- Mucositis: 0.6–0.9
- Healthy implants: 0.2–0.4

The ratio was increased approximately 10-fold in peri-implantitis compared with healthy conditions ($p < 0.001$). Diagnostic performance was excellent, with reported AUC values ranging from 0.87 to 0.93.

In limited longitudinal studies, elevated RANKL/OPG ratios were associated with subsequent radiographic bone loss, suggesting potential utility as a predictive marker of disease progression [18,19].

Osteocalcin and Osteopontin

Osteocalcin, a marker of osteoblastic activity and bone formation, was consistently reduced in PICF during active peri-implantitis, reflecting suppression of bone formation processes in favor of resorption-dominated remodeling.

Osteopontin (SPP1), in contrast, was elevated in peri-implantitis and demonstrated a positive correlation with inflammatory severity ($r = 0.61$; $p < 0.01$). This supports its role as a marker associated with osteoclast activation and bone resorption activity.

Collagen Type I C-terminal Telopeptide (CTX-I)

CTX-I, a specific degradation product of type I collagen, represents a direct marker of osteoclastic bone resorption. In PICF, CTX-I levels were significantly increased in active peri-implantitis (4–12 ng/mL) compared with stable peri-implantitis (1–2.5 ng/mL) and mucositis (<1 ng/mL; $p < 0.001$).

These findings indicate that CTX-I may be particularly useful for monitoring disease activity and evaluating treatment response in peri-implant inflammatory conditions

Table 2. Key PICF biomarkers: concentrations and diagnostic value

Biomarker	Norm	Mucositis	Peri-implantitis	Frequency ↑	Relationship with bone loss
IL-1β	8-15 pg/ml	25-45	80-160 pg/ml	6,5-12,4×	r = 0,58-0,69
TNF-α	5-12 pg/ml	16-28	35-65 pg/ml	2,4-5,1×	r = 0,48-0,62
IL-6	4-10 pg/ml	15-25	35-72 pg/ml	3,1-6,8×	r = 0,51-0,64
IL-8	25-50 pg/ml	70-120	140-280 pg/ml	2,8-5,6×	r = 0,39-0,55
IL-17A	< 5 pg/ml	5-10	18-42 pg/ml	4,5-10,0×	r = 0,55-0,67
MMP-8	20-40 ng/ml	35-56	112-187 ng/ml	3,5-7,2×	r = 0,65-0,71
MMP-13	< 2 ng/ml	2-5	10-28 ng/ml	5,0-14×	r = 0,60-0,72
RANKL	2-5 pg/ml	8-18	28-55 pg/ml	7,1-11,3×	r = 0,67-0,78
OPG	80-130 pg/ml	65-100	30-60 pg/ml	↓ 2-3×	r = -0,55 - -0,68
RANKL/OPG	0,2-0,4	0,6-0,9	2,1-3,8	≈ 10×	r = 0,72-0,81
CTX-I	< 1 ng/ml	1-2,5	4-12 ng/ml	4,5-12×	r = 0,63-0,74

Note: M - mean values; SD - standard deviation; Me - median; IQR - interquartile range; CI - confidence interval; AUC - area under the ROC curve.

3.5. Salivary Biomarkers in Peri-Implant Diseases

Saliva represents an alternative and clinically attractive biological matrix for the assessment of peri-implant diseases due to its non-invasive collection, cost-effectiveness, and suitability for repeated longitudinal monitoring. These characteristics make saliva particularly valuable for large-scale screening and population-based diagnostic approaches. However, compared with peri-implant crevicular fluid (PICF), saliva is a less site-specific diagnostic fluid, as it reflects a mixture of secretions originating from major and minor salivary glands, gingival crevicular fluid, and other oral and systemic sources. This dilution effect reduces its specificity for localized peri-implant inflammatory processes.

Cytokines and Proteolytic Enzymes in Saliva

Salivary interleukin-1β (IL-1β) is consistently elevated in peri-implantitis, showing approximately a 2.3–4.1-fold increase compared with healthy conditions (healthy range: 5–8 pg/mL; peri-implantitis: 15–30 pg/mL). Salivary IL-1β levels demonstrate a moderate-to-strong correlation with PICF concentrations (r = 0.58–0.72), suggesting that salivary cytokine levels partly reflect local peri-implant inflammatory activity. However, diagnostic specificity remains limited due to contributions from other oral inflammatory sources and systemic influences.

Matrix metalloproteinase-8 (MMP-8) is one of the most consistently elevated salivary biomarkers in peri-implantitis. Reported median concentrations are significantly higher in peri-implantitis (68.4 ng/mL) compared with peri-implant mucositis (28.7 ng/mL; $p < 0.01$). The clinical applicability of salivary MMP-8 has been strengthened by commercially available point-of-care diagnostic systems such as PerioSafe® and OraLyzer®, which have demonstrated diagnostic potential in implant patients across several clinical studies [20].

Matrix metalloproteinase-9 (MMP-9) is also elevated in peri-implant disease; however, its diagnostic performance is limited by high biological variability and lower specificity compared with MMP-8. Neutrophil elastase (NE), another marker of neutrophil activation, is increased in peri-implantitis and correlates with the severity of clinical inflammation, reflecting active innate immune response within the oral cavity [21].

Oxidative Stress-Related Biomarkers in Saliva

Salivary oxidative stress markers demonstrate a characteristic imbalance in peri-implant diseases. Uric acid levels are reduced in peri-implantitis, reflecting its consumption as part of antioxidant defense mechanisms. In contrast, malondialdehyde (MDA), a marker of lipid peroxidation, is significantly elevated, indicating increased oxidative damage to cellular membranes [22].

Similarly, 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, is significantly increased in patients with peri-implantitis compared with individuals with healthy implants ($p < 0.05$). These findings collectively indicate enhanced reactive oxygen species (ROS) production and systemic oxidative imbalance associated with peri-implant inflammatory processes.

Bone Metabolism Markers and Acute Phase Proteins in Saliva

Salivary osteopontin is elevated in peri-implantitis and has been shown to correlate positively with clinical parameters of disease severity. In the study by Lee et al. (2023), osteopontin levels demonstrated a significant correlation with probing depth around implants ($r = 0.59$; $p < 0.01$), suggesting its involvement in active inflammatory bone remodeling processes.

Lactoferrin, a neutrophil-derived antimicrobial glycoprotein, is also increased in saliva in peri-implantitis. Its elevation reflects sustained neutrophil activation and prolonged inflammatory activity within the oral environment, further supporting its role as a marker of chronic peri-implant inflammation [23].

Overall, while salivary biomarkers demonstrate consistent trends reflecting peri-implant inflammatory activity, their diagnostic specificity remains lower than that of PICF-based biomarkers. Nevertheless, salivary multi-marker panels, particularly those combining inflammatory and proteolytic markers, may provide valuable non-invasive tools for screening and monitoring peri-implant disease progression.

Salivary biomarkers show a progressive increase from peri-implant mucositis to peri-implantitis, with IL-1β and MMP-8 demonstrating the highest diagnostic accuracy and combined biomarker panels providing superior performance (Table 3).

Table 3. Salivary biomarkers in peri-implant diseases and their diagnostic performance

Biomarker	Peri-implant mucositis	**Peri-implantitis**	**Diagnostic value**	Sensitivity / Specificity (%)
IL-1β	Mild increase (↑)	Moderate–marked increase (↑↑)	Moderate	71-78 / 65-72
MMP-8	Mild increase (↑)	Marked increase (↑↑)	Moderate	68-75 / 67-74

Biomarker	Peri-implant mucositis	**Peri-implantitis**	**Diagnostic value**	Sensitivity / Specificity (%)
MMP-9	Minimal increase (↑)	Moderate increase (↑)	low	54-62 / 58-65
IL-6	Minimal increase (↑)	Moderate increase (↑)	Moderate	62-70/ 60-68
Neutrophil elastase	Mild increase (↑)	Marked increase (↑↑)	Moderate	65-72 / 63-70
Osteopontin	Minimal increase (↑)	Moderate increase (↑)	Moderate	60-67/ 58-66
Malondialdehyde (MDA)	Minimal increase (↑)	Moderate increase (↑)	low	55-63/ 52-60
IL-1β + MMP-8 combination	-	Marked increase (↑↑)	Good (highest performance)	73-78/ 70-76
Lactoferrin	Minimal increase (↑)	Moderate increase (↑)	low	52-60/ 50-58

3.6. Comparative Analysis of the Diagnostic Value of PICF and Saliva

A direct comparison between peri-implant crevicular fluid (PICF) and saliva was reported in 8 studies included in this review. Across all comparative investigations, PICF consistently demonstrated superior diagnostic performance in distinguishing peri-implant health, mucositis, and peri-implantitis when compared with salivary biomarkers.

For interleukin-1β (IL-1β), the area under the receiver operating characteristic curve (AUC) in PICF ranged from 0.84 to 0.91, whereas salivary IL-1β demonstrated lower diagnostic accuracy, with AUC values ranging from 0.67 to 0.76 [24]. These findings confirm the higher site-specific diagnostic value of PICF in peri-implant inflammatory conditions.

Nevertheless, several studies highlighted that saliva retains independent diagnostic potential when analyzed using standardized collection protocols and multi-marker approaches. In particular, a salivary biomarker panel comprising IL-1β, MMP-8, IL-6, and osteopontin demonstrated an AUC of 0.82 for the diagnosis of peri-implantitis in the study by Sánchez-Jiménez et al. (2023), indicating performance comparable to single-marker PICF-based assays [25].

The diagnostic advantage of PICF was most pronounced for markers directly associated with bone remodeling and resorption, including RANKL, OPG, and CTX-I, which were either absent or present at significantly lower and less reliable concentrations in saliva. In contrast, saliva provided a broader representation of the systemic and generalized inflammatory response, as well as oxidative stress and antioxidant status, reflecting its mixed biological origin.

Overall, PICF demonstrates higher specificity for local peri-implant tissue destruction, whereas saliva offers advantages for non-invasive screening and systemic inflammatory profiling. Therefore, the two biological fluids should be considered complementary rather than competing diagnostic matrices.

3.7. Molecular Markers of the Transition from Mucositis to Peri-Implantitis

The identification of molecular events associated with the transition from reversible peri-implant mucositis to irreversible peri-implantitis represents a central objective of this review. Based on data from 11 prospective and longitudinal studies, a stepwise molecular progression model can be proposed.

Stage 1: Early Peri-Implant Mucositis (Reversible Phase)

In the early inflammatory phase, the molecular profile is dominated by early pro-inflammatory cytokines, primarily interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), produced mainly by activated macrophages and innate immune cells in response to microbial biofilm accumulation. At this stage, bone metabolism remains largely balanced, and the RANKL/OPG ratio remains below 1.0, indicating predominance of osteoprotective signaling.

Matrix metalloproteinase-8 (MMP-8) is moderately elevated, reflecting early extracellular matrix degradation confined to peri-implant soft tissues without evidence of bone involvement. This phase remains clinically reversible with effective plaque control and inflammation management.

Transition Phase: Molecular Switch to Peri-Implantitis

The transition to peri-implantitis is associated with activation of the IL-17A-mediated Th17 immune pathway. Differentiation of naïve T cells into Th17 cells leads to increased expression of RANKL by osteoblasts and stromal cells, resulting in a shift in bone metabolism toward osteoclastogenesis. At this point, the RANKL/OPG ratio exceeds 1.0, marking a critical threshold for net bone resorption.

Concurrently, MMP-13 becomes detectable in peri-implant crevicular fluid, indicating active degradation of type I bone collagen. A reduction in interleukin-1 receptor antagonist (IL-1Ra) is also observed, reflecting depletion of endogenous anti-inflammatory regulatory mechanisms. These combined changes suggest the initiation of irreversible bone tissue damage, which may precede radiographic detection.

Stage 2: Advanced Peri-Implantitis (Irreversible Phase)

Advanced peri-implantitis is characterized by a pronounced and sustained upregulation of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6, and IL-8), extensive activation of matrix metalloproteinases (particularly MMP-8 and MMP-13), and a persistently elevated RANKL/OPG ratio (typically >> 2.0), indicating dominant osteoclastogenic activity.

The appearance of collagen degradation products such as C-terminal telopeptide of type I collagen (CTX-I), together with decreased osteocalcin levels, confirms active bone resorption and suppression of osteoblastic activity. At this stage, structural bone loss becomes radiographically evident and is generally considered irreversible, often requiring surgical and regenerative therapeutic approaches.

Table 4 summarizes the stepwise molecular changes of PICF biomarkers during peri-implant disease

progression, showing a transition from early cytokine-driven inflammation in mucositis to pronounced activation of proteolytic enzymes and dysregulated bone resorption pathways in peri-implantitis. Overall, the biomarker profile demonstrates a consistent shift toward a pro-inflammatory and pro-osteoclastic environment as disease severity increases.

Table 4. Molecular dynamics of PICF biomarkers during peri-implant disease progression

Biomarker	Healthy implant	Mucositis	Early peri-implantitis	Advanced peri-implantitis
IL-1β	–	+	++	+++
TNF-α	–	+	++	++
IL-6	–	+	++	+++
IL-17A	–	–/+	++	+++
IL-1Ra	+++	++	+	–/+
MMP-8	–	+	++	+++
MMP-13	–	–	+	+++
RANKL	–	+	++	+++
OPG	+++	++	+	–/+
RANKL/OPG	↓↓ (0,2-0,4)	↓ (0,6-0,9)	↑ (1,0-1,5)	↑↑↑ (2,1-3,8)
CTX-I	–	–	+	+++
Osteocalcin	++	++	+	–

Note: "-" - not determined/normal; "+" - slight increase; "++" - moderate increase; "+++" - marked increase; "↓↓" - marked decrease; "↑↑↑" - marked increase in the ratio.

4.1. Interpretation of Results in the Context of the Pathophysiology of Peri-Implantitis

The findings of this scoping review support a stepwise molecular model of peri-implant disease progression that shares similarities with, yet is mechanistically distinct from, classical periodontitis. In the initial phase, microbial biofilm formation on implant surfaces—predominantly composed of Gram-negative anaerobic species such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*—activates the innate immune system through pattern recognition receptors (PRRs) expressed on macrophages and dendritic cells. This interaction induces moderate secretion of pro-inflammatory cytokines, primarily IL-1β and TNF-α, by neutrophils and macrophages. Under physiological conditions, local regulatory mediators, including IL-1 receptor antagonist (IL-1Ra), osteoprotegerin (OPG), and transforming growth factor-β (TGF-β), maintain inflammatory homeostasis, thereby confining the process to reversible peri-implant mucositis [26].

With persistent biofilm accumulation and chronic antigenic stimulation, a progressive breakdown of local immunoregulatory mechanisms occurs. This stage is characterized by a reduction in IL-1Ra, resulting in an imbalance between pro- and anti-inflammatory signaling pathways. Concurrently, T-helper cell polarization shifts toward the Th17 phenotype under the influence of IL-6 and TNF-α, leading to increased production of IL-17A. IL-17A further amplifies inflammatory activity and enhances RANKL expression in osteoblasts and stromal cells, acting synergistically with IL-1β to promote osteoclastogenesis.

This shift in bone metabolism is reflected by an increased RANKL/OPG ratio, indicating a transition from physiological bone remodeling to net bone resorption. Similar molecular patterns have been reported in periodontal disease progression [27], and are corroborated by elevated CTX-I levels detected in peri-implant crevicular fluid (PICF) [12, 15].

In parallel, a coordinated activation of matrix metalloproteinases (MMPs) occurs. Neutrophil-derived MMP-8 is primarily responsible for degradation of collagen types I and II in peri-implant soft tissues, whereas MMP-13, produced by osteoblast-lineage cells, is more specifically associated with degradation of type I collagen within mineralized bone structures. This sequential activation of proteolytic enzymes provides a mechanistic explanation for the temporal progression of biomarker expression and supports the rationale for staged molecular diagnostics.

4.2. Comparison with Previous Studies

The present findings are generally consistent with previous systematic reviews while also extending current knowledge in several important aspects.

The results align with Faot et al. (2015), who identified IL-1β, TNF-α, and IL-6 as the most consistently elevated cytokines in peri-implant disease. However, comparatively fewer previous reviews have emphasized the role of IL-17A as a potential indicator of disease progression from mucositis to peri-implantitis [28].

Similarly, while Barros et al. (2016) reported that IL-1β ≥ 50 pg/mL provides acceptable diagnostic accuracy in periodontal disease (sensitivity 81.3%, specificity 76.8%) [14,] the present review confirms a comparable pattern in peri-implant tissues. However, standardized diagnostic thresholds for peri-implant conditions remain to be established due to methodological variability across studies [5, 24].

Importantly, this review highlights the diagnostic relevance of the RANKL/OPG ratio, which demonstrated higher reported diagnostic performance (AUC 0.87–0.93) compared with individual cytokines, suggesting its potential utility as a more stable marker of bone resorption activity.

4.3. Molecular Markers of the Transition from Mucositis to Peri-Implantitis

This review identifies a cluster of molecular markers associated with the transition from reversible mucositis to irreversible peri-implantitis based on longitudinal evidence.

Key transition-associated biomarkers include:

- Increased IL-17A (4.5–10-fold), reflecting Th17 pathway activation
- Decreased IL-1Ra, indicating reduced anti-inflammatory control
- Increased MMP-13, associated with bone matrix degradation
- Appearance of CTX-I, indicating active osteoclastic bone resorption

Notably, several prospective studies suggest that these molecular alterations may precede clinical and radiographic manifestations by approximately 3–6 months, highlighting their potential utility for early diagnostic and preventive strategies.

4.4. Clinical Utility of Salivary Biomarkers

Compared with PICF, saliva exhibits lower specificity for peri-implant disease diagnosis due to its mixed origin and dilution by glandular secretions. Nevertheless, salivary biomarkers may provide clinically relevant information when analyzed using standardized protocols and multimarker approaches.

For example, the study by Sánchez-Jiménez et al. (2023) demonstrated that a four-marker salivary panel (IL-1β, MMP-8, IL-6, osteopontin) achieved an AUC of 0.82, indicating moderate-to-good diagnostic performance [25]. These findings support the potential role of saliva as a non-invasive screening tool, particularly in population-based or preventive settings.

4.5. Clinical Applicability and Threshold Considerations

Although no formal meta-analysis was performed, multiple studies reported recurring biomarker ranges that may serve as preliminary reference points for clinical interpretation. However, these values should be

considered indicative rather than validated diagnostic thresholds.

Reported PICF thresholds associated with peri-implantitis include:

- IL-1β ≥ 50 pg/mL (risk indicator in selected cohorts)
- RANKL/OPG ≥ 1.2 (associated with onset of bone resorption)
- MMP-8 ≥ 80 ng/mL (active collagen degradation)
- IL-17A ≥ 12 pg/mL (transition phase marker)

For saliva:

- IL-1β ≥ 25 pg/mL (moderate inflammation)
- MMP-8 ≥ 50 ng/mL (increased progression risk)
- Combined IL-1β + MMP-8 panel: AUC 0.75–0.78

However, significant inter-study variability exists due to differences in sampling protocols, assay kits, calibration methods, and storage conditions, which limits direct comparability.

4.6. Standardization of Biomarker Assessment

A major limitation in biomarker research is methodological heterogeneity in sample collection and analysis.

For PICF, two main sampling approaches are used:

- Absorbent strips (Periopaper/PerioScan): standardized but prone to contamination and fluid dilution
- Microcapillary collection: more accurate but technically challenging and low-volume

For saliva, variability arises from:

- stimulated vs. unstimulated saliva
- whole saliva vs. gland-specific secretions
- circadian rhythm effects
- dietary and hydration status

Standardized protocols recommend morning collection (09:00–11:00), fasting state, oral rinse prior to sampling, and immediate freezing at −20 °C.

4.7. Multimarker and Systems Biology Approaches

No single biomarker demonstrates sufficient diagnostic accuracy for standalone clinical application. Therefore, multimarker panels combined with machine learning approaches represent a promising diagnostic strategy.

Distinct molecular subtypes of peri-implantitis have been proposed, including:

- IL-1β–dominant inflammatory phenotype
- Th17/RANKL-dominant osteoclastic phenotype
- MMP- and CTX-I–driven hyper-destructive phenotype

Metabolomic studies further indicate alterations in salivary composition, including increased putrescine and cadaverine, reduced arginine availability, and altered organic acid profiles, reflecting microbial and host metabolic dysregulation [29].

4.8. Limitations of the Review

Several limitations should be acknowledged.

First, significant heterogeneity in study design, populations, and analytical methods precluded quantitative meta-analysis. Second, the predominance of cross-sectional studies (50.7%) limits causal inference regarding biomarker dynamics over time. Third, insufficient reporting of implant-related variables (surface characteristics, loading duration, and prosthetic design) restricted subgroup analyses.

Fourth, publication bias may have led to overrepresentation of studies with positive findings. Fifth, patient-related factors such as smoking status, systemic diseases, and oral hygiene were inconsistently reported. Finally, this review focused exclusively on PICF and saliva, excluding serum and other potential biomatrices.

5.1. Diagnostic Superiority of PICF

Peri-implant crevicular fluid (PICF) represents a more biologically specific diagnostic medium for peri-implantitis compared with mixed saliva, as it directly reflects local inflammatory activity and bone remodeling processes at the peri-implant site. Among the investigated biomarkers, interleukin-1β (IL-1β), receptor activator of nuclear factor kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio, and matrix metalloproteinase-8 (MMP-8) demonstrated the highest diagnostic performance in PICF, with reported AUC values ranging from 0.84 to 0.91, 0.87 to 0.93, and 0.80 to 0.88, respectively.

5.2. Diagnostic Potential of Saliva

Saliva demonstrates clinically relevant diagnostic utility, particularly when used in combination within multimarker panels and under standardized collection protocols. The combined assessment of salivary IL-1β and MMP-8 yields a sensitivity of 73–78% and a specificity of 70–76% for peri-implantitis detection, supporting its potential application as a non-invasive screening tool in routine outpatient practice.

5.3. Molecular Indicators of Disease Progression

The transition from peri-implant mucositis to peri-implantitis is associated with a distinct molecular signature characterized by increased IL-17A expression (approximately 4.5–10-fold elevation) reflecting Th17-mediated immune activation, a marked reduction in IL-1 receptor antagonist (IL-1Ra), an elevated RANKL/OPG ratio exceeding 1.0, increased MMP-13 activity, and the emergence of CTX-I in PICF. These changes, reported in prospective studies, suggest a biologically plausible window for early therapeutic intervention prior to irreversible tissue destruction.

5.4. Recommendations for Future Research and Clinical Translation

To advance current findings toward clinically applicable diagnostic protocols, several key steps are required: (a) standardization of biomarker sampling methodologies, including control of circadian variation and procedural consistency; (b) large-scale, multicenter prospective validation studies to establish reliable diagnostic thresholds; (c) development and validation of commercially available multiplex biomarker assay systems; and (d) integration of biomarker-based diagnostics into established clinical guidelines, including those of the EFP and AAP.

5.5 Future Research Directions

Future investigations should focus on the development of advanced multimarker diagnostic models incorporating machine learning approaches to improve diagnostic accuracy and reproducibility. Longitudinal cohort studies with comprehensive clinical, radiographic, and molecular follow-up are essential to better characterize disease trajectories. Further research should also explore the interplay between systemic inflammatory status and local peri-implant biomarkers, particularly in patients with systemic conditions such as diabetes mellitus. Additionally, metabolomic and proteomic profiling may facilitate the identification of novel biomarkers and distinct molecular subtypes of peri-implantitis.

Practical Significance

The findings of this review provide a robust evidence-based foundation for the development of standardized biomarker-driven diagnostic strategies in implant dentistry. Such approaches have the potential to enable earlier identification of patients at risk for peri-implant disease before the onset of irreversible clinical and radiographic changes, thereby supporting timely preventive and minimally invasive therapeutic decision-making.

CONCLUSION

Current evidence indicates that peri-implant crevicular fluid provides greater diagnostic specificity than saliva for the assessment of peri-implant diseases. Biomarkers such as IL-1β, MMP-8, IL-17A, and the RANKL/OPG ratio appear to be closely associated with inflammatory activity and disease progression. However, heterogeneity among the 31 included studies limits direct comparability of findings. Future prospective studies with standardized sampling and analytical protocols are required to establish clinically applicable diagnostic thresholds and improve the translational value of biomarker-based diagnostics in implant dentistry.

Zirconia implants represent a promising metal-free alternative with favorable esthetic properties, soft tissue integration, and reduced bacterial adhesion [20,23,29,30]. These characteristics make zirconia particularly attractive in anterior esthetic regions and in patients seeking metal-free treatment solutions.

However, current evidence indicates greater variability in long-term survival and mechanical performance for zirconia implants compared with titanium systems [28,41,45,47]. Limitations related to brittleness, low-temperature degradation, prosthetic flexibility, and limited long-term evidence continue to restrict their universal application. Therefore, implant material selection should be based on evidence-based clinical decision-making integrating biomechanical, esthetic, prosthetic, anatomical, and patient-related factors. Continued advancements in ceramic biomaterials and implant technology may further improve the predictability and clinical applicability of zirconia implant systems in the future.

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Conflict of Interest

The author declare no conflict of interest.

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Ethical approval was not required as this is a narrative review of published literature.

Author Contributions

The following describes the individual contributions of each author to this manuscript:

1 Abdulaeva Salihat Abakarovna initiated the research, developed the concept and structure of the review, and oversaw the writing and approval of the text.

2 Akhmedova Asiyat Akhmedovna conducted a systematic search and selection of scientific publications and performed a critical analysis of the empirical data on the main focus of the review.

3 Lazaryan Maria Nikolaevna conducted an analytical comparison of various scientific approaches and theoretical models presented in the literature.

4 Gadzhiev Baza Gasanovich synthesized the data obtained and formulated general conclusions and practical recommendations based on the analyzed sources.

5.Asvarova Gulnara Abilovna provided expert review of the methodological aspects of the review and verified the logical coherence of the arguments.

6.Guseynova Salikhat Tagirovna conducted an analytical comparison of various scientific approaches and theoretical models presented in the literature.

7.Mirzekerimov Aivaz Meilanovich oversaw the editorial process and ensured that the text complied with the requirements of scientific style and publication format.

8.Omarov Murad Rashidovich conducted an analytical comparison of various scientific approaches and theoretical models presented in the literature.

9.Ordashev Khasan Alievich supervised the clinical case, provided expert consultation, and edited the final manuscript.

All authors reviewed and approved the final version of the manuscript.

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