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Biomarkers in Peri-Implant Crevicular Fluid: Insights into Diagnosis and Prognosis of Peri-Implant Diseases.

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ABSTRACT

Background:

Peri-implant diseases, including peri-implant mucositis and peri-implantitis, present substantial challenges in the field of dental implantology. Biomarkers found in peri-implant crevicular fluid (PICF) have shown promise as tools for early detection, prognosis, and monitoring of these conditions.

Objective:

This review seeks to assess the existing evidence on PICF biomarkers and their potential role in diagnosing and managing peri-implant diseases.

Methods:
A detailed search of PubMed was conducted to identify articles published between 2010 and 2024. From an initial pool of 134 studies, 50 were reviewed for relevance, and 14 met the inclusion criteria, focusing on PICF biomarkers for detecting and predicting peri-implant disease progression.

Results:
The studies reviewed identified various PICF biomarker categories, such as inflammatory markers (e.g., IL-1β, TNF-α), markers of bone remodeling (e.g., RANKL, OPG), oxidative stress markers (e.g., malondialdehyde), and emerging biomarkers (e.g., SIRT1). These biomarkers demonstrated varying degrees of sensitivity and specificity, with fluctuations in their levels reflecting disease activity and treatment response. Such findings highlight their potential in tailoring patient care.

Conclusion:
PICF biomarkers offer valuable insights into the underlying mechanisms, diagnosis, and prognosis of peri-implant diseases. While advancements have been made, further large-scale, longitudinal research is needed to validate these biomarkers and enable their routine application in clinical practice.

Keywords: peri-implant diseases, peri-implant crevicular fluid, biomarkers, diagnosis, prognosis, peri-implantitis

INTRODUCTION

Biomarkers are essential tools in identifying, diagnosing, and monitoring periodontal and peri-implant conditions. Recent research underscores the potential of peri-implant crevicular fluid (PICF) as a medium for detecting biomarkers that can distinguish between peri-implant health and disease. Among these, matrix metalloproteinases (MMPs)—including MMP-8, MMP-9, and MMP-13—have garnered attention for their involvement in tissue breakdown and inflammatory responses. Elevated MMP levels in PICF are associated with the progression of peri-implantitis and other periodontal diseases **(Luchian et al., 2022**(1)**; Alassy et al., 2019)** (2)

Additionally, biomarkers such as soluble ST2, RANKL, OPG, and calprotectin have been proposed for diagnosing peri-implant conditions, including peri-implant mucositis and peri-implantitis **(Hentenaar et al., 2021**(3)**; Zani et al., 2016)** (4)**.** Inflammatory mediators like IL-1β and PGE2 have also been widely studied, with their elevated levels linked to bone loss and the inflammatory processes around dental implants **(Sakamoto et al., 2018**(5)**; Duarte et al., 2016**) (6)**.** These cytokines have shown potential as both diagnostic and prognostic indicators for peri-implant health.

The ability to monitor these biomarker levels in PICF offers the possibility of detecting peri-implantitis before clinical symptoms become evident **(Moaven et al., 2022**(7)**; Faot et al., 2015)** (8). This non-invasive approach is particularly relevant given the rising prevalence of peri-implant diseases, especially in high-risk populations.

This review aims to explore the clinical utility of PICF biomarkers in diagnosing peri-implant diseases and predicting treatment outcomes, emphasizing their role in enhancing diagnostic accuracy, guiding early interventions, and monitoring disease progression.

MATERIAL AND METHODS

Study Design

This narrative review was undertaken to explore the current understanding of biomarkers present in peri-implant crevicular fluid (PICF) and their potential clinical significance in diagnosing and predicting peri-implant diseases, including peri-implant mucositis and peri-implantitis. The objective was to compile and summarize key findings from published research on specific biomarkers associated with these conditions.

Literature Search Strategy

A comprehensive search of the PubMed database was conducted to identify relevant studies published between 2010 and 2024. Search terms included "peri-implant crevicular fluid," "biomarkers," "peri-implantitis," "peri-implant mucositis," "diagnosis," and "prognosis." Articles were screened for their relevance to the topic, with an emphasis on studies that investigated specific biomarkers in PICF and their relationship to peri-implant diseases.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Research focusing on biomarkers in PICF related to peri-implant diseases (peri-implant mucositis and peri-implantitis).
2. Articles published from 2010 to 2024.
3. Full-text studies available in English.

Exclusion Criteria:

1. Studies not addressing PICF or biomarkers linked to peri-implant diseases.
2. Non-original works, such as editorials, reviews, or commentaries.
3. Publications not available in English or inaccessible in full text.

Study Selection and Data Extraction

From an initial pool of 134 articles identified through the search, abstracts were reviewed for relevance, and 50 articles were shortlisted for detailed evaluation. Of these, 14 articles met the inclusion criteria and were included in the final review. Data extracted from the selected studies included the types of biomarkers analyzed, methods of biomarker measurement in PICF, sensitivity and specificity of the biomarkers, and their significance in disease diagnosis and prognosis.

Biomarker Categories

The studies were grouped based on the biomarkers they examined:

1. **Inflammatory Markers:** These included cytokines and mediators, such as IL-1β and TNF-α, associated with inflammatory processes in peri-implant diseases.

2. **Bone Turnover Markers:** Markers like RANKL and OPG were studied for their role in bone remodeling and resorption around implants.
3. **Oxidative Stress Markers:** Indicators such as malondialdehyde were analyzed for their relationship to tissue damage and inflammation.
4. **Emerging Biomarkers:** Novel markers, including SIRT1 and soluble ST2, were investigated for their potential to detect early disease stages and monitor progression.

Methods for Biomarker Measurement

Various analytical techniques were employed in the reviewed studies to detect and measure biomarkers in PICF. These included enzyme-linked immunosorbent assay (ELISA), reverse transcription polymerase chain reaction (RT-PCR), immunohistochemistry, and mass spectrometry. The reliability and precision of these methods were assessed, and threshold levels indicative of significant biomarker presence were noted.

Statistical Analysis

Data from the selected studies were analyzed qualitatively. When available, information on sensitivity and specificity was included. The original studies' statistical approaches were considered to evaluate the robustness of their findings. A qualitative synthesis was conducted to assess the clinical utility of the biomarkers in diagnosing and managing peri-implant diseases.

RESULTS

The reviewed studies examined various biomarkers in peri-implant crevicular fluid (PICF) and their association with peri-implant health and disease. The focus was primarily on inflammatory markers, matrix metalloproteinases (MMPs), cytokines, bone metabolism indicators, and emerging biomarkers, emphasizing their diagnostic, prognostic, and therapeutic relevance. A total of 20 studies were analyzed, with findings categorized into key groups (Table 1).

Table 1 - Summary of Commonly Studied PICF Biomarkers in Peri-Implant Diseases

Author Name	Year	Biomarkers	Summary
Candel-Martí ME et al. (9)	2011	IL-6, IL-8, IL-10, IL- 12	Investigated interleukins in relation to peri-implant diseases.
Basegmez C et al. (11)	2012	PGE2, MMP-8	Assessed levels of prostaglandin E2 and MMP-8 in PICF.
Acharya A et al. (10)	2016	IL-1β	Studied salivary IL-1β and bacterial presence in peri-implantitis.
Duarte PM et al. (6)	2016	Cytokines	Analyzed cytokines to differentiate healthy and diseased implants.

Author Name	Year	Biomarkers	Summary
Janska E et al. (11)	2016	MMP-8	Linked MMP-8 levels with peri-implant sulcular fluid.
Al-Majid A et al. (12)	2018	MMP-8	Explored MMP-8 as an inflammation marker in peri-implantitis.
Alassiri S et al. (13)	2018	aMMP-8	Validated point-of-care tests for aMMP-8 in peri-implant diseases.
Sakamoto E et al. (5)	2018	Calprotectin, CTX-I	Investigated calprotectin and collagen breakdown markers in PICF.
Yakar N et al. (14)	2019	Sclerostin, TWEAK, RANKL, OPG	Evaluated biomarkers related to bone resorption in peri-implant tissues.
Ghassib I et al. (15)	2019	IL-1β, IL-6, TNF-α, MMP-8	Examined markers for peri-implant disease differentiation.
Jiang J et al. (16)	2021	SERPIN family proteins	Identified elevated SERPIN proteins in peri-implantitis.
Theodoridis C et al. (17)	2022	RANKL, OPG	Compared RANKL and OPG levels between healthy and diseased implants.
Wang Z (18)	2022	SIRT1	Studied SIRT1 in patients with peri-implant inflammation.
Luchian I et al. (1)	2022	MMP-8, MMP-9, MMP-13	Investigated MMPs' role in periodontal and peri-implant diseases.
Ozgur E et al. (19)	2023	Soluble ST2	Examined soluble ST2 levels in PICF and serum in peri-implant diseases.
AlMoharib HS et al. (20)	2023	MMP-8	Studied the connection between MMP-8 and peri-implantitis progression.
Saito Y et al. (21)	2024	Endothelin-1	Evaluated endothelin-1's diagnostic potential in peri-implantitis.
Xanthopoulou V et al. (22)	2024	aMMP-8, azurocidin	Explored aMMP-8 and azurocidin as diagnostic markers.
Önder YB et al. (23)	2024	Calprotectin, MMP-8	Investigated peri-implant phenotypes and related biomarkers.
Jansson L et al. (24)	2024	MMP-1, MMP-2, osteopontin	Analyzed several biomarkers for tissue health and inflammation.

Key Findings

1. **Inflammatory Biomarkers**

    - **IL-1β**: This cytokine was Widely studied for its correlation with tissue inflammation in peri-implantitis. **Sánchez-Fernández E et al. (2021)** (28) found that the levels of IL-1β in PICF were significantly elevated in peri-implantitis. **Acharya A et al. (2016)** (10) highlighted its potential as an early diagnostic marker.
    - **TNF-α**: Elevated TNF-α levels were associated with disease progression. **Ghassib I et al. (2019)** (15) found this marker reliable for distinguishing peri-implant disease.
    - **IL-6**: Frequently elevated in peri-implant diseases, supporting its utility for early diagnosis. **Candel-Martí ME et al. (2011)** (9).

2. **Matrix Metalloproteinases (MMPs)**

    - **MMP-8**: Identified as a key biomarker in tissue degradation. Studies consistently showed its elevation in diseased states. **Luchian I et al. (2022)** (1)**; Al-Majid A et al. (2018)** (12)
    - **MMP-9 & MMP-13**: Linked to tissue remodeling and destruction, particularly in advanced peri-implantitis. **Delucchi F et al. (2023)** (25).

3. **Bone Metabolism Markers**

    - **RANKL/OPG**: A critical ratio indicating bone resorption. Increased RANKL and reduced OPG were consistent indicators of peri-implantitis. **Yakar N et al. (2019)** (14); **Theodoridis C et al. (2022)** (17)
    - **Sclerostin & PGE2**: Emerging as markers of bone loss and inflammation, offering insights into disease severity. **Yakar N et al. (2019)** (14); **Pliavga V et al. (2023)** (26)**; Basegmez C et al. (2012)** (11); **Ali D et al. (2023)** (27).

4. **Novel Biomarkers**

    - **Soluble ST2, Calprotectin, and SERPIN Proteins**: Showed promise as diagnostic and prognostic tools for peri-implant diseases. **Ozgur E et al. (2023)** (19)**; Sakamoto E et al. (2018)** (5); **Jiang J et al. (2021)** (16).

5. **Diagnostic and Predictive Value**

    - Biomarkers such as IL-1β, MMP-8, and RANKL demonstrated strong diagnostic potential.
    - Prognostic markers like sclerostin and calprotectin may predict disease progression, particularly bone loss and inflammation. **Ali D et al. (2023)** (27).

This comprehensive evaluation of PICF biomarkers underscores their significant role in diagnosing and managing peri-implant diseases.

DISCUSSION

This review highlights the significant associations between peri-implant crevicular fluid (PICF) biomarkers and various peri-implant disease conditions, as evidenced by multiple studies. These biomarkers provide critical insights into the mechanisms underlying peri-implant diseases and hold promise for their use in clinical diagnosis, prognosis, and management.

1. **Inflammatory Biomarkers and Their Clinical Implications**

Elevated levels of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, are consistently reported in cases of peri-implantitis.

- **Clinical Importance**: Sánchez-Fernández E et al. (2021) observed a marked increase in IL-1β levels in PICF among peri-implantitis patients, with levels declining post-treatment, underscoring its value as both a diagnostic and therapeutic marker. Similarly, **Ghassib I et al. (2019)** (15) emphasized the diagnostic relevance of IL-1β and TNF-α in differentiating between peri-implant health and disease, highlighting their strong association with inflammation and tissue destruction.
- **Comparative Findings**: **Song L et al. (2022)** (29) supported these observations by showing that the interaction between microbial profiles and cytokine levels intensifies inflammatory responses in peri-implantitis cases.

2. **Matrix Metalloproteinases (MMPs): Indicators of Tissue Degradation**
Matrix metalloproteinases, especially MMP-8, are consistently elevated in peri-implant disease.

- **Research Evidence**: **Luchian I et al. (2022) (1)** reported higher MMP-8 levels in both periodontal and peri-implant diseases, reflecting its role in extracellular matrix breakdown and inflammation. Similarly, **Alassiri S et al. (2018)** (13) demonstrated the utility of point-of-care devices for measuring aMMP-8 levels, highlighting its diagnostic potential.
- **Therapeutic Implications**: **Janska E et al. (2016)** (30) identified a relationship between MMP-8 levels and the volume of peri-implant sulcular fluid, suggesting its potential in monitoring disease progression and therapeutic responses.

3. **Bone Metabolism Markers**

Bone remodeling markers, including RANKL, OPG, and sclerostin, are key indicators in peri-implant diseases.

- **Study Insights**: **Yakar N et al. (2019)** (14) identified an imbalance in RANKL/OPG ratios in peri-implantitis, with increased RANKL levels driving bone resorption. Similarly, **Saito Y et al. (2024)** (21) highlighted elevated endothelin-1 levels as a factor in peri-implant bone loss and vascular dysfunction.
- **Predictive Utility**: **Wohlfahrt JC et al. (2014)** (31) demonstrated that bone markers like CTX-I could predict surgical outcomes, underscoring their clinical relevance in decision-making.

4. **Emerging Biomarkers**

Novel biomarkers, including soluble ST2 and calprotectin, are emerging as promising tools for peri-implant disease evaluation.

- **Soluble ST2**: Research by **Ozgur E et al. (2023)** (19) revealed increased levels of soluble ST2 in peri-implantitis, suggesting its dual role in inflammation and tissue degradation.
- **Calprotectin**: **Sakamoto E et al. (2018)** (5) demonstrated that calprotectin effectively differentiates peri-implant diseases, highlighting its potential in diagnostic frameworks.

5. **Synthesis of Findings Across Studies**

The reviewed literature underscores the importance of standardized research approaches to enhance clinical applicability.

- **Integrated Analysis**: Combining molecular studies like **Chaparro A et al. (2022)** (32) with broader reviews such **Faot F et al. (2015)** (8) can facilitate the development of multi-biomarker diagnostic panels.
- **Stratified Insights**: **Gao X et al. (2018)** (33) **and Kaur A et al. (2017)** (34) emphasized the need for population-based analyses to account for variabilities arising from systemic health, geographic factors, and implant protocols.

6. **Challenges in Biomarker Utilization**

The application of PICF biomarkers in clinical settings faces several hurdles, including variability in biomarker expression and methodological inconsistencies.

- **Systemic Influences**: Studies like **Haque MIU et al. (2018) (35) and Moaven H et al. (2022) (7)** highlight the impact of systemic health conditions, smoking, and implant loading on biomarker levels, necessitating further investigation into disease-specific markers.
- **Standardization Issues**: **Alassy H et al. (2019) (2) and Al-Majid A et al. (2018) (12)** stressed the need for standardized methods to measure PICF biomarkers, as inconsistencies hinder their routine clinical adoption.

CONCLUSION

This review underscores the pivotal role of PICF biomarkers in the diagnosis, monitoring, and management of peri-implant diseases. Inflammatory markers like IL-1β, IL-6, and TNF-α; MMPs such as MMP-8; and bone metabolism markers like RANKL, OPG, and sclerostin have proven to be reliable indicators of peri-implant health and disease. These biomarkers provide insights into disease pathophysiology and have potential applications in evaluating therapeutic outcomes.

However, challenges such as biomarker variability, methodological discrepancies, and the lack of standardized thresholds limit their clinical implementation. Emerging markers like soluble ST2 and calprotectin, along with multi-biomarker panels, offer promising pathways for improving diagnostic accuracy and therapeutic strategies.

Future studies should focus on validating these biomarkers in diverse populations, exploring their interactions with systemic factors, and developing cost-effective diagnostic tools. Addressing these challenges will facilitate the integration of biomarker-based approaches into clinical practice, enhancing early detection and personalized care for peri-implant diseases, ultimately improving patient outcomes and implant success rates.

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