Salivary Biomarkers in Prosthodontics: A Comprehensive Literature Review

Abstract

Saliva, often termed the "mirror of the body," is increasingly recognized for its diagnostic potential in oral and systemic diseases. With advancements in proteomics, genomics, and metabolomics, salivary biomarkers offer a non-invasive, cost-effective, and patient-friendly means to support diagnosis, prognosis, and monitoring across many dental disciplines. Prosthodontics particularly benefits from this because prosthetic rehabilitation impacts—and is impacted by—systemic health, mucosal status, and oral microenvironment. This review examines the biochemical basis of salivary diagnostics, categories of relevant biomarkers, and their specific applications in prosthodontic care—covering edentulism, ridge resorption, implant health, xerostomia, oral cancer surveillance, and prosthesis-related complications. Technological advances, limitations, and future directions for integrating chairside salivary diagnostics into personalized prosthodontics are also discussed. The evidence underscores salivary biomarkers' promise in enhancing patient-centered outcomes and shaping the future of biomarker-guided prosthetic therapy.

Keywords: Saliva, Biomarkers, Prosthodontics, Diagnostics, Implantology, Xerostomia, Oral Cancer

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Introduction

Prosthodontics, as a specialized discipline within dentistry, primarily aims to restore oral function, esthetics, and comfort through prosthetic appliances such as complete dentures, removable partial dentures, fixed partial dentures, crowns, and implants. Traditionally, the focus of prosthodontics has revolved around mechanical retention, stability, occlusal harmony, and biomaterial properties. However, with advances in biological sciences and molecular diagnostics, it has become increasingly evident that the long-term success of prosthetic rehabilitation depends not only on mechanical precision but also on the biological environment in which these restorations function. Among the biological determinants, saliva has emerged as a unique and accessible diagnostic fluid that mirrors both local oral and systemic health conditions.

Saliva is a complex body fluid secreted mainly by the parotid, submandibular, sublingual, and numerous minor salivary glands. Its composition is highly dynamic, reflecting physiological, pathological, and environmental changes. It contains a broad range of biomolecules, including electrolytes, enzymes, immunoglobulins, proteins, nucleic acids, metabolites, and microbial signatures, which together provide valuable insights into health and disease[1]. Unlike blood, which requires invasive venipuncture, saliva can be collected easily, painlessly, and repeatedly, without specialized personnel. This makes it highly suitable for chairside testing and longitudinal monitoring of patients[2,3].

Recent developments in **salivaomics**—an umbrella term encompassing salivary genomics, transcriptomics, proteomics, metabolomics, and microbiomics—have significantly broadened the clinical potential of saliva as a diagnostic tool. These approaches have revealed specific salivary biomarkers associated with a wide array of oral diseases, including oral squamous cell carcinoma, peri-implant mucositis, peri-implantitis, denture-related stomatitis, residual ridge resorption, and xerostomia[4]. For prosthodontics, where the interface between prosthetic devices and biological tissues determines patient outcomes, salivary biomarkers offer a non-invasive method to evaluate tissue response, predict complications, and tailor rehabilitation strategies.

Furthermore, the integration of biomarker data into prosthodontic practice promises to advance the field toward **personalized prosthodontics**. Predictive models based on salivary biomarker profiles could allow clinicians to stratify patients by risk, anticipate prosthetic complications, and optimize material and design choices accordingly. This evolution aligns with broader trends in precision medicine, where diagnostics guide individualized treatment planning rather than applying a uniform approach to all patients.

Therefore, this review sets out to explore the current state and future prospects of salivary biomarkers in prosthodontics. The objectives are to:

1. Outline the mechanisms and categories of salivary biomarkers.
2. Summarize their current and potential applications in prosthodontics.
3. Highlight technological innovations facilitating their clinical use.
4. Discuss limitations and challenges to implementation.
5. Propose a future direction for biomarker-based, personalized prosthodontic care.

By synthesizing evidence from 2015–2025, this review underscores the transition of prosthodontics from a primarily mechanical discipline to one deeply informed by biological and molecular diagnostics.

Saliva: Composition & Collection

Saliva is a hypotonic biological fluid that plays a central role in maintaining oral homeostasis. Although it is composed of nearly 99% water, the remaining 1% contains an array of electrolytes, proteins, enzymes, antimicrobial peptides, hormones, nucleic acids, metabolites, and microbial components that make it an exceptionally rich diagnostic medium[5,6]. Its secretion arises from the coordinated function of the major salivary glands—parotid, submandibular, and sublingual—as well as hundreds of minor salivary glands scattered throughout the oral mucosa.

The specific contribution of each gland depends on the rate of stimulation, the circadian rhythm, and the physiological state of the individual.

1. Composition of Saliva

- **Electrolytes:** Sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), chloride (Cl^-), bicarbonate (HCO_3^-), and phosphate (PO_4^{3-}) are present in varying concentrations. They regulate pH balance, buffering capacity, and remineralization of enamel[5].
- **Enzymes:** α-amylase and lipase are the most abundant digestive enzymes, initiating carbohydrate and lipid digestion. Salivary peroxidase and carbonic anhydrase contribute to antimicrobial defense and buffering[5,6].
- **Proteins and Mucins:** Glycoproteins such as mucins (MUC5B, MUC7) ensure lubrication, pellicle formation, and microbial aggregation. Statherin and proline-rich proteins stabilize calcium and phosphate, supporting mineral homeostasis[6].
- **Antimicrobial Peptides:** Lysozyme, lactoferrin, histatins, defensins, and cathelicidins protect against bacterial, fungal, and viral pathogens[5].
- **Immunoglobulins:** Secretory IgA predominates, forming the first line of adaptive immune defense. IgG and IgM may also be detected, particularly in inflammatory conditions[6].
- **Nucleic Acids:** Saliva contains extracellular DNA, messenger RNA (mRNA), microRNAs (miRNAs), and exosomal cargo, which can mirror systemic and oral disease states[5].
- **Metabolites:** Urea, glucose, lactate, amino acids, and volatile organic compounds (VOCs) are measurable and vary with systemic conditions such as diabetes or renal disease[5].
- **Microbial Components:** Saliva harbors bacterial, fungal, and viral DNA/RNA fragments. These microbial signatures reflect oral microbiome composition, which changes significantly in peri-implantitis, denture stomatitis, and oral cancer[6,7].

2. Methods of Saliva Collection

The reliability of salivary biomarker detection depends heavily on collection protocols, as factors such as circadian rhythm, hydration status, diet, and stress significantly alter composition[7].

- **Unstimulated Whole Saliva (UWS):** Collected by passive drooling into a sterile container. It reflects baseline salivary composition, making it the gold standard for many diagnostic assays. However, flow rate is low, and volume may be insufficient in patients with xerostomia.
- **Stimulated Whole Saliva (SWS):** Induced by mastication (chewing paraffin or gum) or gustatory stimulation (citric acid, lemon drops). This method increases flow rate and volume, but dilution may reduce biomarker concentration[5].
- **Gland-Specific Collection:** Involves cannulation of individual ducts (e.g., parotid via Stensen's duct, submandibular via Wharton's duct). While highly accurate for assessing gland-specific pathology, it is technically demanding and less feasible for routine use[6].

3. Standardization and Storage

For meaningful diagnostic outcomes, saliva collection must be standardized:

- Patients should avoid eating, drinking, or performing oral hygiene for at least 60 minutes before collection.
- Morning samples are preferred due to diurnal variation.
- Samples should be immediately cooled on ice and centrifuged to remove debris.
- For molecular analysis, rapid storage at –80°C prevents degradation of nucleic acids and proteins[7].

These measures reduce pre-analytical variability and ensure reproducibility. Emerging technologies such as saliva collection kits with stabilizing buffers aim to simplify this process for both clinical and research purposes.

4. Clinical Relevance

The non-invasive nature of saliva collection is especially advantageous in prosthodontics, where many patients are elderly, medically compromised, or have reduced tolerance for invasive procedures. Moreover, longitudinal monitoring—such as assessing peri-implant inflammation or evaluating bone turnover markers in residual ridge resorption—is feasible due to the repeatable and painless collection process. Saliva thus serves as both a diagnostic and a monitoring tool, bridging the gap between laboratory science and chairside prosthodontic care[5–7].

Categories of Salivary Biomarkers

Salivary biomarkers can be broadly classified based on their molecular nature and functional significance[5–8]:

1. **Proteomic Biomarkers**
    - Include cytokines such as IL-1β, IL-6, and TNF-α, and matrix metalloproteinases (MMP-8, MMP-9).
    - Reflect inflammation, tissue remodeling, and stress responses in the oral cavity.
2. **Immunological Markers**
    - Secretory IgA, lactoferrin, and antimicrobial peptides (e.g., histatins) provide insight into host defense and mucosal immunity.
3. **Oxidative Stress Indicators**
    - Molecules like malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG) indicate reactive oxygen species activity and tissue damage.
4. **Genomic and Transcriptomic Markers**
    - mRNA transcripts (e.g., SAT1, DUSP1) and microRNAs (miR-125a, miR-21) can signal cellular changes, malignant transformation, or early disease.
5. **Metabolites**
    - Small molecules including glucose, lactate, urea, amino acids, and volatile organic compounds reflect systemic metabolism and oral microbial activity.
6. **Microbiome Signatures**

- DNA from Candida albicans, Porphyromonas gingivalis, and Treponema denticola provides information on infection, dysbiosis, and prosthetic-related complications.

Each biomarker category offers complementary information: while cytokines and enzymes indicate inflammation, transcriptomics and miRNAs may detect early neoplastic changes, and metabolites or microbial profiles provide insight into the oral microenvironment[7,8].

Applications in Prosthodontics

Salivary biomarkers have emerged as valuable tools in prosthodontics, providing insights into the biological environment surrounding prosthetic devices, predicting potential complications, and guiding personalized rehabilitation strategies[9–14]. By reflecting both local oral conditions and systemic health, these biomarkers complement conventional clinical assessments, imaging, and mechanical evaluations, enabling more precise and proactive patient care.

1. Edentulism and Residual Ridge Resorption

Residual ridge resorption (RRR) is a common consequence of tooth loss, characterized by progressive alveolar bone loss that affects denture stability, retention, and function. The rate and pattern of RRR are influenced by multiple factors including mechanical stress, hormonal status, bone metabolism, and inflammatory processes. Salivary biomarkers such as **osteocalcin**, **alkaline phosphatase (ALP)**, and the **RANKL/OPG ratio** have been shown to correlate with osteoblastic and osteoclastic activity, reflecting bone remodeling dynamics[9]. Inflammatory cytokines such as IL-1β and TNF-α may indicate ongoing alveolar inflammation, which can accelerate resorption. Monitoring these markers over time allows clinicians to anticipate changes in the residual ridge, plan denture relining or adjustments, and optimize the timing of implant placement. Furthermore, these biomarkers may help identify patients at higher risk for rapid RRR, facilitating preventive interventions and personalized prosthetic design[9].

2. Implant Health and Peri-Implant Disease

Successful implant prosthodontics relies on stable osseointegration and maintenance of peri-implant tissue health. Peri-implant diseases, including mucositis and peri-implantitis, are inflammatory conditions that can compromise implant longevity. Saliva analysis has demonstrated that **elevated levels of IL-1β, IL-6, TNF-α, prostaglandin E_2, and MMP-8** correlate with peri-implant inflammation and early bone loss[10]. Additionally, the **OPG/RANKL ratio** in saliva reflects osteoclastic activity and provides predictive information about ongoing bone resorption. Regular monitoring of these biomarkers enables early detection of peri-implant pathology, allowing timely nonsurgical interventions such as improved oral hygiene, antimicrobial therapy, or prosthetic adjustments. Integrating salivary biomarker profiles into routine implant maintenance protocols may improve patient outcomes by preventing progression to severe peri-implantitis, which often necessitates surgical intervention[10].

3. Xerostomia and Prosthesis Comfort

Xerostomia, or dry mouth, significantly impacts denture retention, mucosal lubrication, and overall patient comfort. Salivary biomarkers provide objective measures to assess both the quantity and quality of saliva. **Flow rate, pH, buffering capacity, mucin concentration, and amylase activity** are essential parameters for evaluating glandular function and guiding interventions[11]. Additionally, markers such as **histatins** and **lactoferrin** can help differentiate true hyposalivation from subjective dry mouth, which may be influenced by medications, systemic conditions, or psychological factors. Understanding these biomarkers allows prosthodontists to recommend appropriate interventions, including saliva substitutes, salivary stimulants, or implant-supported prostheses that reduce reliance on natural salivary lubrication. Moreover, tracking these biomarkers over time can provide feedback on treatment efficacy and patient compliance[11].

4. Denture-Related Stomatitis

Denture stomatitis is a common inflammatory condition, often associated with **Candida albicans** colonization. Salivary analysis reveals elevated levels of **IL-6, TNF-α**, and other pro-inflammatory cytokines, along with reduced levels of **secretory IgA**, reflecting impaired mucosal immunity[12]. By monitoring these biomarkers, clinicians can assess disease severity, optimize antifungal therapy, and guide modifications to denture base materials or design to reduce microbial adherence. Salivary biomarkers also allow longitudinal monitoring of treatment response, helping prevent recurrence and ensuring long-term mucosal health.

5. Oral Cancer and Maxillofacial Rehabilitation

Saliva is increasingly recognized as a medium for **non-invasive detection of oral squamous cell carcinoma (OSCC)** and monitoring post-oncologic rehabilitation. Biomarkers including **p53 antibodies, EGFR, VEGF**, and specific **miRNAs** have shown sensitivity and specificity comparable to biopsy in detecting OSCC recurrence[13]. This has significant implications for prosthodontics, as early detection of recurrence allows timely modification of prosthetic devices and rehabilitation strategies, ensuring both function and esthetics are maintained. Furthermore, salivary biomarker profiles can aid in stratifying patients based on recurrence risk, guiding follow-up intervals and personalized prosthetic care.

6. Digital Prosthodontics and Personalized Care

The integration of salivary biomarkers with digital workflows represents a major advance in personalized prosthodontics. AI-driven **CAD/CAM systems** can utilize biomarker data to inform prosthetic material selection, design contours, and predict tissue responses. For example, patients with elevated inflammatory biomarkers may benefit from materials with reduced microbial adhesion or modified occlusal load distribution[14]. Such an approach facilitates **precision prosthetics**, where prosthesis design is tailored not only to anatomical and functional requirements but also to the patient's biological profile. In the future, chairside biomarker analysis may enable real-time adjustments in prosthetic fabrication, ushering in a new era of proactive, biology-driven prosthodontic care.

Discussion

Salivary biomarkers offer a transformative adjunct to conventional prosthodontic diagnostics, providing insights that go beyond mechanical assessments and imaging. Their non-invasive collection, repeatability, and ability to reflect both local oral and systemic conditions make them particularly appealing for prosthodontic patients, many of whom are elderly, medically compromised, or have difficulty undergoing invasive procedures[15].

Clinical Significance

In prosthodontics, saliva serves as a dynamic window into tissue health, inflammation, and microbial activity. For instance, monitoring inflammatory cytokines such as IL-1β and TNF-α in patients with implants or residual ridges allows clinicians to anticipate complications like peri-implantitis or accelerated residual ridge resorption[9,10]. Similarly, salivary markers such as histatins, lactoferrin, and mucins provide objective measures of xerostomia severity, guiding prosthetic design and the use of salivary substitutes[11]. Denture-related stomatitis can also be effectively monitored through Candida DNA levels and immune biomarkers such as secretory IgA, enabling targeted antifungal therapy and long-term prevention[12].

Beyond oral disease detection, salivary biomarkers have emerging applications in **oncology-driven prosthodontics**. Non-invasive detection of oral squamous cell carcinoma (OSCC) recurrence using p53 antibodies, EGFR, VEGF, and specific miRNAs offers opportunities for early intervention, which is critical in post-oncologic rehabilitation[13]. Furthermore, integrating these biomarkers into digital workflows allows **personalized prosthodontic planning**, including CAD/CAM-based design modifications that consider predicted tissue responses and inflammation risk[14].

Advantages Over Conventional Diagnostics

Saliva has several advantages compared to traditional diagnostic fluids:

- **Non-invasive and painless** collection encourages patient compliance[2,3].
- **Repeatability** facilitates longitudinal monitoring of prosthetic outcomes and tissue response[6].
- **Multimodal data** enables simultaneous assessment of proteins, metabolites, nucleic acids, and microbial signatures[7].
- **Chairside potential** with lab-on-chip devices and biosensors promises near real-time clinical decision-making[16].

Limitations and Challenges

Despite these advantages, several challenges limit widespread adoption in routine prosthodontic practice. Salivary composition can vary due to circadian rhythms, hydration status, diet, medication use, and systemic disease, introducing intra- and inter-patient variability[7,15]. Many biomarkers exist in low concentrations, requiring highly sensitive detection methods such as ELISA, mass spectrometry, or PCR-based assays. Standardization of collection protocols, storage conditions, and analytical techniques is essential to ensure reliability and reproducibility. Furthermore, while individual biomarkers provide useful information, multi-analyte panels analyzed with machine learning may offer superior predictive accuracy, though these approaches are still largely in the research phase[16].

Future Directions

The future of prosthodontics lies in **precision, preventive, and personalized care** guided by salivary biomarkers. Potential developments include:

- **Multiplex biomarker panels** to simultaneously assess inflammation, bone turnover, microbial load, and tissue remodeling.
- **Integration with AI and CAD/CAM workflows** to customize prosthetic design based on predicted biological responses.
- **Chairside biosensors** for real-time monitoring of peri-implant disease, xerostomia, or residual ridge resorption.
- **Longitudinal patient monitoring** to track treatment efficacy and guide preventive interventions.

Such advancements will allow prosthodontists to move beyond reactive treatment toward proactive, biomarker-informed rehabilitation, optimizing both functional and esthetic outcomes while minimizing complications. Importantly, salivary diagnostics should complement—not replace—clinical judgment, imaging, and conventional mechanical assessments

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Conclusion

Salivary biomarkers represent a paradigm shift in prosthodontics, bridging the gap between traditional mechanical approaches and modern biologically informed care. Their non-invasive nature, ease of collection, and ability to reflect both local and systemic health provide clinicians with powerful tools for diagnosis, prognosis, and longitudinal monitoring of prosthetic outcomes. Applications span a wide range of prosthodontic concerns, including residual ridge resorption, peri-implant disease, xerostomia, denture-related stomatitis, and oral cancer surveillance, as well as integration into digital prosthetic workflows for personalized rehabilitation[9–14].

By enabling early detection of pathological changes, salivary biomarkers facilitate **preventive and proactive interventions**, reducing the risk of complications and improving long-term prosthetic success. Moreover, they support **precision prosthodontics**, where treatment planning is guided not only by anatomical and functional requirements but also by the patient's unique biological profile. This aligns with broader trends in medicine and dentistry toward personalized, data-driven care[2,3,14].

Despite their promise, challenges remain. Variability in saliva composition, low analyte concentrations, and the need for standardized collection and analytical protocols limit routine clinical adoption[15,16]. Advances in sensitive detection technologies, chairside biosensors, multiplex biomarker panels, and AI-driven predictive models are critical for translating research findings into everyday prosthodontic practice.

In conclusion, the integration of salivary biomarkers into prosthodontics heralds a **future where prosthetic care is both mechanically precise and biologically informed**. The development of standardized chairside assays, incorporation into digital workflows, and ongoing research into biomarker validation will enable clinicians to deliver truly personalized, predictive, and preventive prosthodontic care, enhancing patient outcomes and satisfaction. As evidence continues to grow, saliva is poised to become an indispensable diagnostic medium in the prosthodontist's armamentarium.

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