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Review Article

Saliva as a Diagnostic Biopsy Fluid: A Review

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Abstract

Saliva is a biofluid secreted mainly by the major and minor salivary glands, which contains a wide variety of biomolecules with diagnostic value. Its molecular abundance, noninvasive collection, molecular richness, and link to systemic conditions have established it as an attractive tool compared with blood or tissue biopsies. The present narrative review aims to integrate up-to-date knowledge about the biology of the salivary glands, the mechanisms of secretion, and the molecular constitution of this biofluid; at the same time, it analyzes its role in oral and systemic health. It highlights advances in salivaomics and its diagnostic role in oral, systemic, metabolic, oncological, autoimmune, and neurodegenerative pathologies. Additionally, it analyzes the impact of prosthetic biomaterials on both salivary composition and the expression of inflammatory markers. Finally, it recognizes the challenges related to biological variability, the need for standardization and validation of biomarkers, highlighting the potential of integrating multi-omic platforms and artificial intelligence to promote a promising path for diagnostic precision in dentistry and medicine.

Keywords
- saliva biomarkers
- salivary diagnostics
- prosthetic biomaterials
- oral disease
- salivaomics

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Introduction

Saliva is a complex biological fluid secreted primarily by the major salivary glands (parotid, submandibular, and sublingual) and minor salivary glands.[1,2] Major and minor glands, under coordinated parasympathetic and sympathetic control, secrete a fluid composed of approximately 98% water, but densely loaded with ions (pH buffers), glycoproteins (acquired film), antimicrobial peptides, hormones, antioxidants, lipids, nucleic acids (DNA; coding and non-coding RNA), enzymes, immunoglobulins, extracellular vesicles, metabolites, desquamated host cells, and a diverse microbiota.[3–5] Adults typically produce between 1,000 and 1,500 mL of saliva per day, although this rate varies according to individual and circadian factors.[5]

Saliva plays an important role in lubricating, moistening, and protecting the oral mucosa and teeth, has antimicrobial activity, and also participates in the healing process.[2–4] The salivary glands are responsible for its secretion and, due to their close anatomical connection to the tissues that make up the stomatognathic, digestive, and endocrine systems, the clinical use of stimulated and unstimulated saliva tests in the search for biomarkers for the diagnosis of diseases affecting these systems is promising.[2,3]

Within this same framework, salivary biomarkers can act as reporters of the physiological and pathophysiological condition of both the general oral environment and the local periodontal environment, as well as systemic[5]; this is because disease states can induce changes in the biochemical composition of saliva. In fact, researchers in the field believe that saliva also provides valuable information, even in diseases that are not directly related. This is particularly beneficial for patients who need to undergo the same test several times and for whom it is difficult to obtain samples of blood or other bodily fluids.[6] Consequently, saliva-based diagnostics have proven useful in detecting a wide range of oral and systemic diseases, including periodontitis, periimplantitis, dental caries, oral lichen planus, head and neck cancer, cardiovascular and renal conditions, diabetes, Down syndrome, and Sjögren's syndrome. These advances in the study of markers are based on an excellent correlation of proteins between saliva and other fluids such as blood serum.[7–9]

Thus, saliva is becoming increasingly important in the study of diseases. Thanks to technological advances, especially in the area of molecular biology and high-throughput sequencing technologies, it has been possible to study different biomarkers in saliva. With regard to various genetic markers, salivary DNA analysis has enabled the recognition of mutations, epigenetic modifications, and microbial profiles associated with certain diseases. At the same time, RNA biomarkers have gained relevance. Along with messenger RNA, various types of non-coding RNA have been described, including lncRNA, miRNA, and circRNA, each of which plays a key role in controlling gene expression and the development of pathological processes.[10]

This narrative review aims to compile current knowledge on the biology of salivary glands, including their structure and function, the mechanism of salivary secretion, the molecular composition and functions of saliva, and methods of collection and preservation. Additionally, it provides a novel and updated perspective that incorporates advances in the impact of prosthetic biomaterials on salivary composition, the latest progress in salivaomics (genomics, transcriptomics, proteomics, metabolomics, and microbiome) and its application in the diagnosis of oral and systemic pathologies, supported by recent literature.

Function and Structure of the Salivary Glands

Salivary glands (SGs) are essential anatomical structures in the oral cavity. In humans, SGs develop from an epithelial placode, which grows and invaginates into the underlying mesenchyme between the 4th and 12th weeks of embryonic life.[11,12] SGs are composed of a parenchyma consisting of serous and/or mucous acini that secrete fluid and proteins, ductal cells that modify the composition of saliva and transport it to its final destination, myoepithelial cells that participate in the contraction of the acini for the release of the contents of their granules, and a connective tissue stroma that provides support to the gland. Other cell types such as fibroblasts, pericytes, endothelial cells, immune cells, and neuroendocrine cells contribute to nutrient exchange, immune defense, and glandular homeostasis.[13,14]

There are three major SGs: The parotid gland (PG), which is the largest SG in humans, weighs 25 to 30 g and is located immediately in front of the ear. Its excretory duct corresponds to Stensen's duct, which empties into the buccal mucosa near the maxillary second molar. It produces serous saliva, rich in α-amylase. The submandibular gland (SMG) represents the second largest SG in humans, whereas, in mice it is the largest SG. It weighs 7 to 15 g and is located in the submandibular fossa, medial to the mandibular body, inferior to the mylohyoid line of the mandible, and superior to the hyoid bone; its excretory duct is Wharton's duct that empties below the tongue into the sublingual caruncle. It secretes a viscous saliva rich in mucin. The sublingual gland is the smallest of the major SGs, weighing 2 to 4 g with a dimension of approximately 4 to 6 cm in length anteroposteriorly and 2 to 4 cm in width. It is located inferior to the mucous membrane, in the anterior part of the floor of the mouth and immediately superior to the mylohyoid muscle. It has 8 to 10 small ducts, the ducts of Rivinus and a main duct, the Bartholin's duct, which connects to the most anterior end of Wharton's duct and also empties into the sublingual caruncle. Like the SMG, its secretion type is viscous rich in mucin. Together, the three pairs of major SGs account for approximately 90% of saliva production.[15–17]

In contrast, there are approximately 600 to 1,000 minor SGs distributed throughout the aerodigestive tract (present in the submucosa of the sinonasal cavity, pharynx, larynx, trachea, lungs, middle ear, and oral cavity). Particularly minor SGs are concentrated in the buccal mucosa, lingual, labial, palatal, and retromolar region with the exception of

the gums and hard palate. Minor SGs account for the remaining 10% of saliva production. Saliva from minor glands plays a key role in preventing oral dryness by forming a thin lubricating film and contributing high levels of immunoglobulin A. These glands are also primarily responsible for saliva production during sleep. ►**Table 1** summarizes the main characteristics of major and minor SGs.[18,19]

Mechanisms of Salivary Secretion

A healthy adult produces between 0.5 and 1.5 L of saliva daily, with an average flow rate of 0.3 to 0.5 mL per minute, but in various oral and systemic diseases, there may be a negative impact on the salivary flow rate. Salivary secretion provides the oral cavity with fluid and protein. Salivation plays a key role in maintaining oral hydration and lubrication, initiating carbohydrate digestion, and facilitating food transport through the digestive tract.[20] In addition, this process facilitates the transport of food through the digestive tract (oropharynx–esophagus–stomach pathway) which favors subsequent digestion in the following segments. Salivary secretion can be affected by factors such as exercise, drug intake, oral hygiene, mental state, age, taste, and odor.[21,22]

Stimulation of the autonomic nervous system (ANS) regulates salivary secretion. Parasympathetic nerves release acetylcholine, which activates muscarinic receptors stimulating fluid secretion. Sympathetic nerves, on the other hand, control salivation through the release of noradrenaline and activation of α- and β-adrenergic receptors, stimulating first fluid-rich secretion and second protein-rich secretion.[23,24]

Salivary secretion occurs in two stages: first, the acinar cells produce an isotonic primary saliva; second, the fluid is modified by ductal cells to become hypotonic before reaching the oral cavity.[25]

The epithelial cells of the glandular acini arranged like clusters of grapes or blackberries are polarized. They have a basal and apical domain. The basal surface is directed toward the interstitium, while the apical surface faces the lumen of the acini. The preservation of their polarity is determined by cell–cell interactions called tight junctions that tightly seal the glandular epithelial cells and regulate the transport of material (electrolytes) through the paracellular pathway that acts as a selective barrier. Thus, electrolytes cannot pass freely between cells, which is why they require specialized transport systems such as coils and ion channels that regulate the internal and external concentration of each electrolyte.[26,27] A clear example is the Na/K ATPase pump that pumps Na^+ to the outside of the cell, accumulating in the paracellular space that will subsequently diffuse to the acinar lumen. Ca^{2+} is also released from the endoplasmic reticulum and mitochondria by cholinergic stimulation and its concentration increases in the cytoplasm. This leads to the opening of Cl-channels, allowing chloride ions to diffuse into the acinar lumen driven by their concentration gradient. By osmosis, water from the small capillaries will pass into the lumen via parabasal and basal–apical flow through specialized channels, aquaporins (AQP), mainly AQP5.[28] Thus, primary saliva is rich in electrolytes that attract water into the acinar lumen. Subsequently, electrolytes are reabsorbed through the cells of the ductal system to reduce their concentration in the secondary saliva before their release into the oral cavity. In this case, ductal epithelial cells use their Na/K ATPase and HCO_3^- pumps to extract NaCl from the saliva previously formed by the acini which significantly reduces the salt concentration in the fluid. In addition, their multiple tight junctions prevent water loss, resulting in aqueous hypotonic fluid. Simultaneously, sympathetic and parasympathetic nervous stimuli act on the myoepithelial cells for the contraction of the acini, which contributes to the secretion of their granules and the subsequent movement of saliva through the ductal system.[29,30]

Structure and Composition of Saliva: Biomolecules, Cells, and Microorganisms

Structurally, saliva is a clear, foamy, milky solution. The composition of saliva reflects a variety of dynamic changes in the organism making it an excellent tool for the determination of clinically valuable biomarkers in various oral and systemic diseases.[31–33]

Saliva is composed of approximately 94 to 99% water, with 1 to 6% consisting of organic and inorganic components.

- Inorganic matter: It is composed of a variety of electrolytes including sodium, potassium, calcium, magnesium, bicarbonate, and phosphate ions. These act in modulating the pH and buffering capacity of saliva.
- Organic matter: It is composed of a variety of macromolecules such as:
  1. Glycoproteins, which play an important role in the formation of the acquired salivary film, a structure that provides primary colonizing bacteria with a series of receptors that facilitate their binding to the tooth surface and provides one of the first lines of defense in oral cavity.
  2. Antimicrobial peptides, which contribute to host defense against pathogens, as they exhibit antimicrobial activity against Gram-positive and Gram-negative bacteria, viruses, and fungi.
  3. Salivary metabolic hormones, which are associated with the modulation of taste perception.
  4. Salivary antioxidants, which protect against oxidative stress.
  5. Lipids.
  6. Nucleic acids (DNA and RNA).
  7. Exfoliated cells such as oral keratinocytes and neutrophils.
  8. Microorganisms: Bacteria (108–109/mL), viruses, fungi, protozoa. In relation to bacteria, *Streptococcus*, *Neisseria*, *Rothia*, *Prevotella*, *Actinomyces*, *Granulicatella*, *Porphyromonas*, and *Haemophilus* species are recognized.
  9. Water.
- The normal pH of saliva ranges from 6.6 to 7.1, making it slightly acidic.
- Its specific gravity ranges between 1.002 and 1.008 (►**Fig. 1**).

Table 1 Main characteristics of the salivary glands

Salivary glands	Type of acini	Type of secretion	Anatomical location	Irrigation and venous drainage	Innervation	Duct leading to oral cavity	Volume of saliva
Major SGs							
Parotid gland	Serous	Aqueous, rich in α-amylase	Preauricular region	ECA: Superficial temporal artery, and maxillary Retromandibular vein	Glossopharyngeal nerve	Stensen's duct	Non-stimulated saliva: 25% Stimulated saliva: 50%
Submandibular gland	Mixed, predominantly serous	Viscous, mucin-rich	Submandibular fossa	ECA: Facial artery, submental, sublingual arteries Facial, submental, and sublingual veins	Facial nerve	Wharton's duct	Unstimulated saliva:60% Stimulated saliva: 35%
Sublingual gland	Mixed, predominantly mucous	Viscous, mucin-rich	Submucosal plane in the anterior part of the floor of the mouth	ECA: Facial artery, sublingual arteries	Facial nerve	Rivinus ducts Bartholin's duct	Unstimulated saliva: 7–8% Stimulated saliva: 7–8%
Minor SGs							
Buccal glands	Mixed, predominantly mucous	Mucin-rich	Submucous, surrounded by connective tissue or embedded between muscle fibers In the corresponding mucosa	Arteriolar and venular system coming from the terminal branches of the ECA and external jugular vein	Facial nerve	Presence of individual small ducts	Unstimulated saliva: 8% Stimulated saliva: 8%
Lingual glands	Serous	Aqueous, rich in lipase			Glossopharyngeal nerve		
Labial glands	Mixed, predominantly mucous	Mucin-rich			Facial nerve		
Palatine glands	Mucous	Mucin-rich			Facial nerve		
Retromolar glands	Mucous	Viscous, mucin-rich			Facial and glossopharyngeal nerve		

Abbreviations: ECA, external carotid artery; SGs, salivary glands.

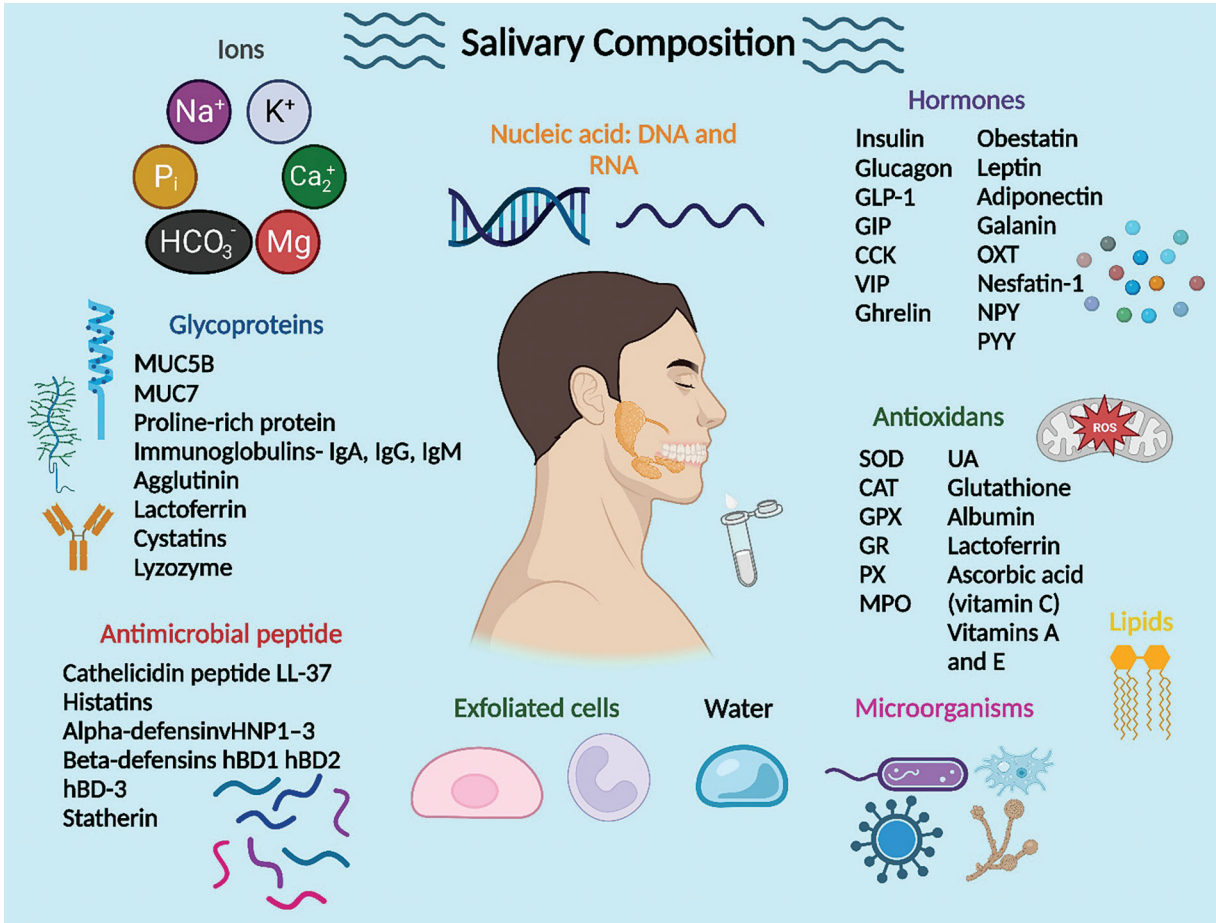

Fig. 1 Salivary composition. (Created in BioRender. Sánchez, M. [2025] https://BioRender.com/nehydwp).

Influence of Different Prosthetic Biomaterials on Oral Fluid Composition: Saliva and Gingival Crevicular Fluid

Patients with tooth loss or oral infections such as caries and periodontal disease often require prosthetic rehabilitation to restore function and esthetics. The biomaterials used must be biocompatible with oral tissues to avoid adverse biological response. Fillings and/or dental prostheses are considered foreign body materials with different chemical, mechanical, and biological properties.[34] Ideally, they should provide longevity, esthetics, and safe patient use; however, some materials may contribute to tissue deterioration. Commonly used prosthetic biomaterials for patient rehabilitation are Ni-Cr, Co-Cr, or Ti base metal dental alloys that are used for the fabrication of fixed and removable dental prostheses.[35] In fixed prosthesis, porcelain-fused-to-metal (PFM) restorations have the characteristic of being more economical and withstand the forces of mastication; however, in addition to presenting a poor marginal and internal fit when manufactured by conventional methods, they have a high tendency to corrosion, which facilitates the accumulation of dentobacterial plaque causing damage to the supporting tissues of the teeth.[36] PFM prostheses have been associated with increased bacterial colonization, including species such as *Campylobacter rectus*, *Eubacterium saphenum*, *Mogibacterium timidum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Alloprevotella tannerae*, and *Tannerella forsythia*, when compared with natural teeth (without prosthesis).[37,38] These prostheses also elevate levels of proinflammatory cytokines (e.g., interleukin-1 α [IL-1α], interleukin-1 β [IL-1β], interleukin-6 [IL-6], interleukin-8 [IL-8], tumor necrosis factor α [TNF-α], interleukin-1 receptor antagonist [IL-1ra], C-reactive protein [CRP], prostaglandin E2 [PGE_2], macrophage inflammatory protein-1 [MIP-1], fractalkine [CX3CL1], and immunoglobulin G [IgG]) and enzymes (e.g., resistin, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and matrix metalloproteinases [MMPs], mainly MMP-2, MMP-8, MMP-9, and active MMP-8 [aMMP-8]) in gingival crevicular fluid (GCF), contributing to periodontal inflammation.[8,9] These findings suggest that, in prostheses with some types of dental alloy, corrosion resistance decreases, creating rough and irregular surfaces that favor a greater accumulation of bacteria that come into contact with keratinocytes and gingival fibroblasts that are responsible for producing proinflammatory cytokines, perpetuating the inflammatory state and causing greater damage to the periodontium.[39,40]

Grinding debris from dental prostheses has been shown to have cytotoxic effects, likely due to its cellular internalization and induction of lipid peroxidation, oxidative stress, and lactate dehydrogenase release.[41] On the other hand, metallic

dental restorations increase the concentration of 8-iso prostaglandin F2 α in unstimulated saliva. The presence of this product results from the interaction of free radicals with cell membrane lipids.[42] Particularly, Co-Cr alloys can exert cytotoxic and inflammatory effects through activation of Nrf2 signaling in gingival fibroblasts and osteoblasts.[43] In fact, these alloys may increase ROS levels in oral fluids, promoting the risk of developing oxidative stress in oral cavity.[44,45]

The introduction of new metal-free prosthetic biomaterials and the use of CAD/CAM technology has increased in recent years. On the one hand, although metal-free ceramic prostheses such as monolithic zirconia, lithium disilicate, and feldspathic porcelain have the advantage of being more esthetic, with better mechanical properties (high flexural and fracture strength) and are more biocompatible, they are more expensive than metal-ceramic prostheses.[8] On the other hand, CAD/CAM systems have the advantage of reducing prosthesis fabrication time and improving marginal and internal fit.[46] The combination of CAD/CAM systems with the choice of dental alloy-free biomaterials has been surprisingly successful. It has been shown that the best results in both qualitative and quantitative composition of microflora in the gingival sulcus were achieved in subjects with zirconia prostheses using CAD/CAM technology; therefore, the use of these biomaterials favors a faster recovery of periodontal tissues.[47] Similarly, the levels of proinflammatory cytokines and enzymes that cause destruction are lower compared with the use of prostheses with some type of dental alloy.[9] A recent study evaluated nanoceramic resin, glass-ceramic, and composite resin fabricated via CAD/CAM under acidic conditions (similar to saliva) with the aim of investigating biocompatibility and sustainability in human fibroblasts and keratinocytes. The authors observed no oxidative stress in both cell types treated with the CAD/CAM materials and found that fibroblasts adhere on all three prosthetic biomaterials. These findings suggest that the tested CAD/CAM restorative materials are biocompatible and form a support for cell attachment and spreading.[48]

Functions and Properties of Saliva

The functions of saliva are directly related to its biochemical composition and can be classified into four main types[49]:

1. Oral health maintenance functions: Lubrication and protection of the different surfaces of the oral cavity, cleansing, buffering capacity, formation of the acquired salivary film, mineralization of teeth, and antimicrobial effects.
2. Role in tissue repair.
3. Digestive functions: Involved in taste, chewing and initial digestion, bolus formation and swallowing.
4. Function in speech articulation.

Methods of Saliva Collection and Preservation

Whole saliva can be collected in two forms: stimulated saliva, typically induced by chewing and taste stimulation, and unstimulated saliva, which is secreted under basal regulation of ANS.[50] Stimulated saliva is commonly collected using agents such as chewing gum, citric acid, and powdered beverage crystals.[51] Unstimulated saliva is typically collected using the spitting method (simply instructing the patient to spit into a sterile container) or the passive drooling method, in which saliva naturally drains into a collection without stimulation.[52] These standardized devices allow safe, simple, and convenient collection of patient samples, which facilitates the study of biomarkers.[53–55] The recently patented saliva collection kit (US11805995B1) offers an innovative approach to obtaining high-quality saliva samples for diagnostic purposes. This system integrates a gum-like hydrogel that is chewed to absorb saliva, which is subsequently compressed within a syringe-like housing using a plunger. The compressed hydrogel releases purified saliva that passes through a cotton filter, reducing mucins, food particles, and potential contaminants. This design minimizes manual handling of specimens and ensures consistent, cleaner sample for downstream microbiological, immunological, or genetic testing. Such a user-friendly, contamination-resistant device holds promise for rapid point-of-care applications and research requiring noninvasive biofluid collection.[56]

In addition to saliva collection, another important factor for the successful analysis of its components is its proper storage. It is recommended that, once the sample is collected, it should be kept in a cold network between 2 and 8°C and transported to the laboratory as soon as possible for processing or otherwise stored at −80°C in a deep freezer. Accurate sampling and preservation are essential steps in ensuring the validity of salivary biomarker detection in both research and clinical diagnosis.[54]

Salivary Biomarkers for Oral and Systemic Disease Diagnosis

Salivary diagnostics can contribute to a better understanding of the overall health status, and thus to more effective treatment methods and better prognosis.[57] Saliva contains different biological components such as DNA, RNA, proteins, microorganisms, and metabolites that are potential markers for the diagnosis of different oral and systemic diseases.[58] Biomarkers, defined as molecular indicators of physiological or pathological states, are essential tools in precision medicine.[59] Therefore, a comprehensive analysis and identification of the various components in human saliva will help us in development of biomarkers related to human health and disease status, early identification of diseases, assessment of prognosis and disease risk, and monitoring the effect of treatment (►**Table 2**).[60,61]

The study of salivaomics includes the following fields of research: genomics and epigenomics, which investigate the biochemical characteristics of DNA and epigenetic changes in a cell (activation and/or deactivation of genes); transcriptomics, which investigates the set of RNA molecules in the cell; proteomics, which investigates the protein profile of the cell; metabolomics, which investigates the set of metabolites in the cell; and the microbiome, which investigates the set of

Table 2 Systemic/oral diseases and associated salivary biomarkers

Disease	Salivary biomarkers identified	Clinical relevance/diagnostic utility	Reference
Periodontitis	IL-1β, IL-6, TNF-α, MMP-8, MMP-9, malondialdehyde, 8-hydroxy-2'-deoxyguanosine	Evidence of active periodontal destruction, a potential predictor of progression, and highlights inflammatory status and oxidative stress	[1,3]
Dental caries	Salivary α-amylase, acidic proline-rich protein-1, histatin-5, lactoperoxidase, mucin-1, carbonic anhydrase 6, proteinase-3, and statherin, salivary pH and buffering capacity	Predictors of cariogenic risk and progression, associated with acidic microenvironments and increased risk of dental demineralization	[64]
Cardiovascular disease	IL-6, CRP, myeloperoxidase, MMP-8, MMP-9	Linked to endothelial dysfunction, the risk of atherosclerosis, and an estimated risk of acute myocardial infarction	[65]
Type 2 diabetes mellitus	Glucose, insulin, advanced glycation end products, malondialdehyde, 8-hydroxy-2'-deoxyguanosine	Indicator of glycemic status, oxidative damage, and potential microvascular complications	[66]
Chronic kidney disease	Urea, creatinine, β2-microglobulin	Consistent relationship with serum levels and glomerular filtration rate; a noninvasive alternative for renal function	[67]
Oral squamous cell carcinoma	IL-1α, IL-1β, IL-6, TNF-α, specific proteins (p53)	Early diagnosis, molecular evaluation of the tumor, and recurrence monitoring	[68]
Lung cancer	miR-21, miR-200, exosomes with tumor mRNA	Outstanding sensitivity and specificity in early diagnosis; potential in screening programs	[69]
Sjögren's syndrome	β2-microglobulin, lactoferrin, anti-Ro/La antibodies, alterations in the oral microbiome	Differential evaluation of autoimmune conditions, monitoring of clinical activity	[70]
Systemic lupus erythematosus/ Rheumatoid arthritis	IL-6, TNF-α, specific autoantibodies	Monitoring of systemic inflammation and association with clinical activity	[71]
Alzheimer's disease	t-tau protein, p-tau, α-synuclein	Evidence of axonal damage and neuronal alterations; useful for early diagnosis	[72]
Parkinson's disease	α-synuclein, specific oligomers	Diagnostic differentiation of neurodegenerative conditions and monitoring of progression	[73]

Abbreviations: CRP, C-reactive protein; IL-1α, interleukin 1α; IL-1β, interleukin 1β; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor α; MMPs, matrix metalloproteinases; miRNAs, microRNAs; mRNA, messenger RNA, p-tau, phosphorylated tau; t-tau, total tau protein.

bacteria, viruses, protozoa, and fungi and their relationship with the organism. Together, these fields support the use of saliva as a diagnostic tool and provide information about disease mechanisms, progression, and therapeutic response.[62,63]

In the context of oral health, saliva has established itself as a noninvasive diagnostic biofluid that reliably reflects the local mechanisms associated with periodontitis and dental caries. Regarding periodontitis, various studies have shown that the composition of saliva is altered in the presence of chronic inflammation of the periodontal tissues. Studies have shown increased levels of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, as well as increased concentrations of MMPs, particularly MMP-8 and MMP-9, enzymes directly involved in collagen degradation and periodontal tissue destruction. The clinical parameters of the pathology, which include probing depth, clinical attachment loss, and bleeding on probing, are closely correlated with these biomarkers, supporting their usefulness as diagnostic tools and for monitoring the progression of periodontal disease. Additionally, they have shown an increase in oxidative stress mediators, such as reactive oxygen species and lipid peroxidation products, which promote the persistence of tissue alteration and the distinctive inflammatory profile of

periodontitis.[1,3] In the field of dental caries, saliva has become a preferred fluid for the identification of certain risk factors and early biomarkers of this condition. Changes in salivary pH and buffering capacity have been consistently linked to enamel demineralization and increased susceptibility to carious lesions. In parallel, studies have shown increases in host salivary components including elevated levels of salivary α-amylase, proline-rich acid protein-1, histatin-5, lactoperoxidase, mucin-1, carbonic anhydrase 6, proteinase-3 and statherin, indicating an activation of salivary defense mechanisms against dental biofilm. The combination of microbiological and biochemical indicators makes saliva a highly important diagnostic tool for anticipating the onset and progression of caries, as well as for analyzing the efficiency of preventive and therapeutic measures.[64]

In recent years, saliva has gained attention as a noninvasive way to detect signs of various systemic illnesses. Particularly in cardiovascular disease, elevated levels of IL-6, C-reactive protein, myeloperoxidase, as well as MMP-8 and MMP-9 have been observed. These increases are closely associated with endothelial dysfunction, the development of atherosclerosis, and a heightened risk of acute myocardial infarction.[64]

For metabolic diseases such as type 2 diabetes, saliva tests have found elevated levels of insulin, glucose, and compounds formed by advanced glycation. These markers show a strong connection with glycemic control. Additionally, oxidative stress indicators like malondialdehyde and 8-hydroxy-2'-deoxyguanosine have also been found in greater concentrations, pointing to a systemic oxidative imbalance in individuals with diabetes.[65]

Within the scope of chronic kidney disease and acute kidney damage, saliva has been considered as a very useful noninvasive diagnostic matrix, allowing to indicate some systemic metabolic alterations linked to renal function.[66] Certain studies have identified that salivary values of urea and creatinine are significantly increased in patients with renal dysfunction and exhibit a close correlation with their serum levels and with the estimated glomerular filtration index (eGFR), supporting their implementation as indirect markers of the functional condition of the kidney. Similarly, salivary β2-microglobulin, a low molecular weight protein frequently filtered through the glomerulus and reabsorbed by means of the proximal tubule, has shown increased levels in saliva of patients diagnosed with advanced chronic disease. This increase was directly associated with the decrease of eGFR, strengthening its importance as a salivary biomarker to identify tubular damage and supervise the progression of kidney disease.[66]

Saliva has become a very promising noninvasive diagnostic tool in the field of oncology, allowing to detect systemic molecular alterations linked to the development and progression of different types of cancer; in this same framework, it is considered a very useful strategy for treatment monitoring, and the surveillance of tumor recurrences.[67] In patients with oral squamous cell carcinoma and precancerous oral manifestations, a significant increase in proangiogenic and proinflammatory cytokines has been observed in saliva compared with healthy subjects. Consequently, these biomarkers can be considered as surrogate indicators of carcinogenic transformation, contributing to timely diagnosis and follow-up monitoring of precancerous lesions leading to oral cancer.[68] In particular, lung cancer is one of the most widely studied for associated with salivary biomarkers, with greater emphasis on early detection and molecular characterization of the tumor. Some research has shown that salivary concentration identifies specific molecular signatures derived from the tumor, specifically highlighting microRNAs (miRNAs) such as miR-21 and miR-31, as well as messenger RNA (mRNA) present in salivary extracellular vesicles, such as exosomes. The latter are characterized by a high specificity and diagnostic sensitivity, managing to differentiate with effectiveness and precision in oncological patients.[68]

When it comes to autoimmune and endocrine disorders, saliva has shown real promise as a helpful tool for both research and diagnosis. For example, in Sjögren's syndrome, researchers have found that certain proteins in saliva, like β2-microglobulin, lactoferrin, and anti-Ro/La antibodies, can be useful in detecting the condition and keeping track of how active the disease is over time. Additionally, changes in the oral microbiome and increased levels of proinflammatory molecules in saliva have been observed in conditions such as systemic lupus erythematosus and rheumatoid arthritis, providing further insight into these diseases.[69]

Finally, neurology is considered one of the most promising frontiers to implement saliva as a noninvasive diagnostic instrument; certain studies have explored using saliva concentration to detect central neuropathological processes, placing it as an accessible instrument with regards to early detection and monitoring of neurodegenerative conditions. Specifically, Alzheimer's disease has taken on special relevance in this area. The presence of important biomarkers such as the total tau protein (t-tau) and its phosphorylated form (p-tau) in the salivary flow are linked to axonal damage and dysfunction considered neuronal in Alzheimer's. Pilot research showed significantly modified levels of t-tau and p-tau in participants with Alzheimer's versus healthy patients, with preliminary associations with values observed in brain tissues and cerebrospinal fluid, which indicates a neurological origin of these biomarkers in saliva. Additionally, the salivary α-synuclein biomarker identified in the context of Parkinson's disease has been considered as a differential marker between types of neurodegenerative conditions due to its contribution to the production of Lewy bodies and its participation in pathogenic mechanisms common to Alzheimer's disease.[70]

Limitations and Future Studies

Although salivaomics has emerged as a promising diagnostic approach, several limitations must be addressed before its full integration into clinical practice. First, the high biological variability of saliva, influenced by circadian rhythms, diet, age, sex, oral hygiene, and systemic conditions, complicates the establishment of universal reference values for

biomarkers. Second, the lack of standardized protocols for sample collection, storage, and processing generates heterogeneity in study outcomes, limiting the comparability and reproducibility of findings. Furthermore, most current evidence is derived from cross-sectional or small-scale studies, which reduces the strength of associations between salivary biomarkers and disease states. Analytical challenges, including the low abundance of some molecules and interference from the oral microbiota, further restrict diagnostic accuracy.

Future studies should prioritize the development of standardized, validated protocols for saliva collection and analysis. Large-scale, multi-center cohorts and longitudinal designs are essential to confirm diagnostic and prognostic value. The integration of multi-omics platforms, namely, genomics, transcriptomics, proteomics, metabolomics, and microbiomics, coupled with machine learning algorithms could improve biomarker discovery and predictive modeling. Moreover, evaluating how prosthetic biomaterials, lifestyle factors, and systemic therapies alter salivary profiles will enhance the interpretation of results. Finally, translating these advances into point-of-care devices will facilitate real-time, minimally invasive diagnostics in both dental and medical settings.

Conclusions

Saliva is emerging as a biological fluid with significant diagnostic potential given its accessibility, noninvasive nature, and abundance of biomolecules, allowing it to indicate both oral and systemic health. Recent advances in this biofluid have facilitated the identification of complex molecular profiles with promising prospects for early diagnosis, risk stratification, and disease monitoring.

The incorporation of salivary biomarkers, in combination with multi-omic approaches and metal-free biomaterials, promises new possibilities for optimizing biocompatibility and deciphering local inflammatory mechanisms in detail. At the same time, the integration of salivary analysis with artificial intelligence strengthens clinical predictive capabilities and guides individualized therapies. In this sense, saliva is establishing itself as a fundamental tool for the development of precision medicine and dentistry.

Availability of Data and Materials

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Authors' Contribution

M.A.A.-S., S.M.L.-M., L.S.E.-V., J.S.B.-R., and A.H.: conceptualization; M.A.A.-S., S.M.L.-M., L.S.E.-V., and A.H.: methodology; M.A.A.-S., S.M.L.-M., L.S.E.-V., and A.H.: software; M.A.A.-S., S.M.L.-M., M.A.-M., L.S.E.-V., J.S.B.-R., R.R.-S., Z.K., and A.H.: validation; M.A.A.-S., S.M.L.-M., L.S.E.-V., M.A.-M., J.S.B.-R., Z.K., and A.H.: formal analysis; M.A.A.-S., S.M.L.-M., L.S.E.-V., and A.H.: investigation; M.A.A.-S. and A.H.: resources; M.A.A.-S., S.M.L.-M., M.A.-M., L.S.E.-V., J.S.B.-R., R.R.-S., and A.H.: writing—original draft preparation; M.A.A.-S., S.M.L.-M., M.A.-M., L.S.E.-V., Z.K., and A.H.: writing—review and editing; M.A.A.-S., S.M.L.-M., M.A.-M., L.S.E.-V., R.R.-S., and A.H.: visualization; M.A.A.-S., S.M.L.-M., M.A.-M., L.S.E.-V., J.S.B.-R., R.R.-S., Z.K., and A.H.: supervision; M.A.A.-S. and A.H.: project administration. All the authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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