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Salivary biomarkers in early detection of systemic diseases - A comprehensive review

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Abstract

Saliva has become an attractive non-invasive biofluid source for the early diagnosis of systemic diseases. It reflects the physiological and pathological conditions of the body and its composition, rich in proteins, enzymes, antibodies, nucleic acids, and metabolites. The review covers the possibilities of salivary biomarkers in diagnosing and managing diseases like diabetes mellitus, cardiovascular disease, cancers, autoimmune diseases, and infections. Salivary diagnostics has been improved by the development of omics technologies and biosensor platforms, with sensitivity and specificity approaching that of blood-based assays. Systemic dysregulation is associated with high levels of salivary glucose, inflammatory cytokines, and oxidative stress markers in conditions such as diabetes. Equally, cardiovascular biomarkers such as CRP and troponins can be identified in saliva, which allows risk stratification. Salivary mRNAs and miRNAs in oncology are early warning signs of diagnosis, especially in oral, breast, and pancreatic cancers. Pathophysiological conditions, which are autoimmune conditions like Sjögren syndrome and systemic lupus erythematosus, present immunologic features in saliva, and infectious diseases like HIV and SARS-CoV-2 can also be detected reliably through salivary analysis. Despite such issues as the unstable flow rate and circadian effects, new microfluidic technologies and standardized protocols are overcoming these obstacles. The possibilities of salivary diagnostics are enormous and will revolutionize personalized medicine and population screening.

Keywords:
Salivary biomarkers, systemic diseases, non-invasive diagnostics, saliva, personalized medicine, and omics technologies.

1. Introduction

Identifying a dependable and non-invasive diagnosis tool is a priority area when it comes to early diagnosis and surveillance of systemic illness. It is a relatively new entity that shows promise as a replacement for blood-based diagnostics, mainly because the collection method, unlike blood, is easy, cheap, and non-invasive, increasing compliance and making large-scale screening efforts much easier. An abundant bio-mix is found in saliva; enzymes, hormones, antibodies, cytokines, nucleic acids, and metabolites replicate oral and systemic health [1].

Advanced molecular methods, including proteomics, transcriptomics, and metabolomics, have provided exponential growth of salivary diagnostics in the last 20 years and allowed the detection of particular signs of the disease, such as diabetes and cardiovascular diseases, malignancies, and neurodegenerative disorders [2,3]. Notably, the salivary glands are highly vascular, enabling two-way trafficking of biomolecules between blood and saliva. This physiological characteristic allows disease-related biomarkers circulating throughout the body to be brought into the oral cavity. Thus, saliva is described as a window to the body or a mirror of the body [4].

These include multiple systemic diseases where the changes in the composition of the saliva can be experienced early, before the emergence of the clinical symptoms. For example, elevated concentrations of inflammatory cytokines IL-6 and TNF-α in the saliva of patients with type 2 diabetes mellitus and cardiovascular disease emerged with the systemic inflammatory burden [5, 6]. In the same way, oxidative stress and abnormal miRNA expression are discussed within the salivary profile of patients with neurodegenerative diseases like Alzheimer's and Parkinson's disease [7].

Another well-researched application is cancer diagnostics with salivary biomarkers. Proteomic and transcriptomic profiles of the salivary gland are sensitive and specific in detecting head and neck squamous cell carcinoma, pancreatic cancer, and breast cancer [8]. Other technologies, including electric field-induced release and measurement (EFIRM) and lab-on-a-chip microfluidic systems, have also increased salivary diagnostics adoption rate in a clinical environment [9].

Salivary testing has also been used in infectious diseases such as COVID-19. During the COVID-19 pandemic, saliva-based PCR assays gained extensive use, as an alternative to nasopharyngeal swab tests, because of their safety, ease of use, and similar diagnostic specificity [10]. Furthermore, salivary antibody tests have also given us an idea about immune reactions and seroprevalence investigations in epidemiological conditions [11].

Nevertheless, these developments are encouraging. However, at present, issues including salivary flow and composition variability and the effect of oral hygiene, diet, and circadian rhythms hamper translating salivary biomarkers into clinical routine practice. In addition, using standardized procedures on sample collection, processing, and biomarker validation is essential for reproducibility and diagnostic specificity [12].

Still, the possibilities of saliva as a diagnostic biofluid are huge. Introducing salivary diagnostics to personalized medicine and point-of-care testing can transform the detection and monitoring of systemic diseases in developed and resource-limited environments. This review gives an in-depth discussion on salivary biomarkers and their usefulness, clinical significance, and technological progress in the early diagnosis of systemic diseases.

2. Saliva as a Diagnostic Fluid

The complex and conveniently available biological fluid, saliva, has been identified as a potential substitute for blood in diagnosing and monitoring diseases. It consists of water (about 99 percent), electrolytes, proteins, enzymes, antimicrobial components, hormones, antibodies, and some genomic and proteomic biomarkers, which mirror the physiological condition of the organism. Saliva is a good choice for routine diagnostics and large-scale epidemiological studies because the collection process is non-invasive, the risk of cross-infection is minimal, and the cost of collecting it is low [13].

The recent progress in molecular diagnostics and biosensing technologies has allowed the detection of many disease biomarkers in saliva. DNA, RNA, proteins, metabolites, and microbiota could be analyzed to identify oral and systemic diseases. Salivary diagnostics has been effectively used in infectious diseases, autoimmune diseases, hormonal imbalances, and cancer. For example, interleukin-8 (IL-8) and IL-1 beta in salivary RNA biomarkers have been promising biomarkers in detecting oral squamous cell carcinoma [14]. Similarly, the elevation of cortisol and chromogranin A in the saliva is linked to psychological stress and can be used to monitor stress-related disorders [15].

Saliva is critical in the detection of infectious diseases. The COVID-19 pandemic also highlighted saliva-based testing, as it is non-invasive and easy to sample on your own. It was established that SARS-CoV-2 RNA can be successfully detected in the saliva, and the sensitivity of this method was similar to nasopharyngeal swabs [16]. Besides, viral infections like HIV, hepatitis A, B, and C, and Epstein-Barr virus (EBV) are also detected using salivary-based diagnostics, which makes salivary-based diagnostics a valuable tool in the surveillance of infectious diseases [17].

Salivary glucose in systemic diseases like diabetes mellitus relates well with blood glucose. This opens the door for inventing non-invasive point-of-care devices to measure glucose [18]. Salivary biomarkers such as C-reactive protein (CRP), myoglobin, and troponins have been promising in early detection and risk assessment in cardiovascular diseases [19].

Saliva can also be used in neurology. The salivary levels of tau protein and amyloid-beta peptides were studied as potential neurodegenerative disease-related biomarkers, including

Alzheimer's disease [20]. In autoimmune diseases like Sjögren syndrome, changes in salivary composition, e.g., reduced flow and elevated immunoglobulin levels, can be clinically useful [21].

Although saliva has excellent potential, some challenges restrict its routine clinical application. These are the variability in the flow rates of saliva, the effect of circadian patterns, diet, and the possibility of contamination. However, these challenges are gradually being addressed by technological progress in microfluidics, biosensor incorporation, and lab-on-a-chip technologies, and salivary diagnostics are becoming more and more reliable and accessible [22].

Finally, saliva is an essential diagnostic fluid for many illnesses. As analytical technologies constantly improve, their implementation in everyday clinical work appears to be on the horizon, transforming how early diseases are detected and monitored, and personalized medicine.

3. Salivary Biomarkers in Specific Systemic Diseases

3.1. Diabetes Mellitus

Serum glucose has been positively correlated with salivary glucose, particularly in uncontrolled diabetic patients. On top of this, there is increased salivary amylase, insulin, and oxidative stress indicators like malondialdehyde (MDA) [23]. There is also increased inflammatory cytokines such as TNF-alpha, IL-6, and CRP in the saliva of diabetic patients [24].

3.2. Cardiovascular Diseases (CVD)

Saliva has been found to contain C-reactive protein (CRP), myoglobin, and troponin I, and these are correlated with myocardial infarction [25]. MMP-8 and MMP-9 are salivary matrix metalloproteinases that are noted to be high in patients with atherosclerosis and coronary artery disease [26].

3.3. Cancers

Cancer Salivary diagnostics is promising, especially with oral squamous cell carcinoma (OSCC), breast cancer, and pancreatic cancer. IL-8, IL-1beta, CD44, and MMPs are the biomarkers that are highly upregulated in OSCC [27]. The miRNAs (e.g., miR-125a, miR-31) have become sensitive early biomarkers of malignancies [28].

3.4. Autoimmune Diseases

In Sjögren syndrome, the concentration of beta-2 microglobulin, lactoferrin, and cytokines (e.g., IL-1, IL-6) becomes prominent [29]. The salivary concentration of anti-dsDNA and ANA autoantibodies was shown to reflect the same in the serum of systemic lupus erythematosus (SLE) [30].

3.5. Infectious Diseases

Salivary diagnostics have been used to detect HIV, hepatitis C, and SARS-CoV-2 early. For example, ELISA can be used to detect HIV-specific antibodies in saliva, a non-invasive, reliable screening technique [31]. Salivary PCR has become a standard diagnostic method in most settings during COVID-19 [32].

Conclusion

Saliva has proved to be an adequate, non-invasive diagnostic fluid with massive potential in detecting and monitoring different systemic diseases early. The abundance of biomarkers in it (proteins, nucleic acids, hormones, and metabolites) provides information about diabetes, cardiovascular disease, cancer, autoimmune disorders, and infections. Biosensors, microfluidics, and molecular tests are technological advances that further improve the precision and reliability of salivary diagnostics. Although some of these constraints are still present (e.g., flow variation and the impact of external factors), they are being surmounted quickly due to standardized protocols and innovative tools. Saliva-based diagnostics will revolutionize the current screening, disease surveillance, and personalized medicine, especially in resource-constrained environments, with additional clinical validation and integration with healthcare systems.

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