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Salivary biomarkers in stomatology, an adjunct for the detection of other diseases: A literature review

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Abstract
Introduction: Salivary biomarkers allow for the identification, monitoring, and prediction of altered molecules in certain diseases. Saliva contains more than 2000 quantifiable proteins; therefore, it is an excellent source of non-invasive information collection for the identification, treatment and monitoring of oral diseases and possible detection of systemic diseases.
Objective: To analyze the literature on salivary biomarkers commonly used in the diagnosis and monitoring of some oral and systemic diseases.
Methodology: An electronic search was conducted in PubMed, Scopus, and Google Scholar databases. The keywords "biomarkers", "oral diseases", "systemic diseases", "saliva", and "diagnosis" were used with the aim of finding in the scientific literature the classification and uses of salivary biomarkers in both the medical and stomatology fields.
Results: There is a wide variety of biomarkers used in the medical field. Salivary biomarkers are a group of markers that, according to the consulted literature, have high potential in the diagnosis of both systemic and oral diseases.
Conclusion: Salivary biomarkers could be used as a non-invasive test for the early detection of an existing systemic disease in the dental office. This initial approach could facilitate timely medical attention and help establish a relationship between oral health and systemic health.

Keywords: Biomarkers, oral diseases, systemic diseases, saliva, diagnosis

1. Introduction

Biomarkers are defined as "cellular, biochemical or molecular alterations that can be quantified in human tissues, cells or fluids" [1-3]. Biomarkers can be analyzed by various laboratory studies such as automated immunoassays (e.g. enzyme-linked immunosorbent assay or ELISA, radioimmunoassay or RIA and chemiluminescence or CLIA), Western Blotting, immunofluorescence, Flow Cytometric Assay, among others [4]. Saliva is a mucous exocrine secretion with a normal pH between 6.8 and 7.2. 99% of saliva is water and 1% is composed of organic and inorganic molecules. Its organic components include proteins, vitamins, lipids, glucose, enzymes, plasma proteins, amylase, fibronectin, mucins, among others. Inorganic components include ammonia, bicarbonate, calcium, chloride, fluoride, iodine, magnesium, phosphates, potassium, sodium, sulfates and nitrogenous products [5]. More than 2,000 proteins have been identified in the salivary proteome as potential physiological or pathological biomarkers that can be identified and quantified [6]. Salivary biomarkers represent a reliable non-invasive source of information because systemic molecules enter saliva from blood serum by passing through capillary barriers, interstitial spaces, acinar and ductal cell membranes until they reach the salivary excretory tubules; therefore saliva can reflect physiological status, emotional state, hormonal variations, immunological variations including neurological effects and metabolic variations as well as detection of synthetic substances such as drugs [4,7].
According to the World Health Organization (WHO), oral health is an indicator of overall health, well-being, and quality of life [8].

In 2019, the WHO estimated an increase in global life expectancy to an average of 73 years, and the aging population has led to a greater number of people with multiple comorbid diseases [9, 10]. Cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases have been the most common in recent decades [9].

On the other hand, oral diseases affect almost 3.5 billion adults and older people [11]. This population not only suffers from oral diseases, but also comorbidities that affect their quality of life. Salivary biomarkers are a valuable and attractive tool in the prevention, detection, diagnosis, prognosis, monitoring, risk assessment, and treatment [3,4] not only of oral diseases but also of systemic conditions.

2. Materials and Methods

A review of original articles published on salivary biomarkers was conducted using the databases PubMed, Scopus, and Google Scholar. The emphasis was placed on the last 5 years. The quality of the articles was evaluated by identifying, reviewing, choosing, and including full-text articles with abstracts reporting on salivary biomarkers in dentistry and systemic diseases written in English. The search was conducted using the Boolean logical operators AND, OR, and NOT, with the keywords "biomarkers," "salivary biomarkers," "diseases," "comorbidities," and "oral diseases." The keywords were used individually, as well as in combination with each other.

3. Results and Discussion

Types of biomarkers

The Food and Drugs Administration (FDA) and the National Institute of Health (NIH) have defined a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions" [1]. Biomarkers can be molecular, histological, radiographic, or physiological characteristics that provide relevant information for evaluating laboratory technique results [1].

There are different types of biomarkers, depending on the specific function assigned to them, which are summarized in a classification in the following table (Table 1).

Table 1: Classification of Biomarker Types

Type	Characteristics	Applications
Diagnosis	Confirms the presence of a disease or a subtype of this condition through protein detection or quantification [1, 12].	In the field of neuropathology, it has been used to redefine classifications of brain tumors based on more precise molecular imaging rather than organ-based classifications [2, 3].
Follow-up or monitoring	Serial measurements are used during the evaluation of a disease (exposure to a medical product or environmental agent) and in pharmacodynamics [1].	Monitoring the concentration of tobacco-specific nitrosamines as a biomarker allows for tracking and assessing direct or indirect exposure to tobacco smoke [13].
Pharmacodynamic response	Indicates the biological activity of a medical product without drawing conclusions about its outcome. This biomarker is used in dose selection, measuring response, or potential harm assessment [1].	High-sensitivity C-reactive protein, interleukin-6, and fibrinogen have been evaluated as biomarkers to assess the inflammatory response associated with the use of electronic nicotine delivery systems [14].
Surrogate endpoint response	Assesses the clinical benefit or harm based on epidemiological, therapeutic, physiopathological, or other scientific evidence [1].	An example is the outcome after 6 months of tuberculosis treatment, where the sputum culture status is considered a probable alternative endpoint criterion to predict the resolution of pulmonary tuberculosis [15].
Prediction	Predicts whether an individual is more likely to experience a favorable or unfavorable effect due to exposure to a medical product or environmental agent [1].	The absolute eosinophil count (AEC), C-reactive protein, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antigen, among others, have been used as predictive biomarkers in cancer patients [16].
Prognosis	Identifies the probability of a clinical event, recurrence, or progression of the disease [1].	The levels of interleukin-6, lactate dehydrogenase, and ferritin have been used as prognostic biomarkers in patients with COVID-19 pneumonia after treatment with tocilizumab [17].
Safety	The biomarker is measured before and after exposure to a medical intervention or environmental agent to indicate toxicity as an adverse event [1].	A safety biomarker would indicate the development of toxicity before clinical signs and before any irreversible damage occurs in a specific organ as a result of the treatment [1].
Risk or susceptibility	Indicate the potential to develop a disease or medical condition in an individual who currently does not have a clinically apparent illness [1].	High-sensitivity C-reactive protein levels, leptin, IL-6, and intercellular adhesion molecule are examples of risk biomarkers in patients with type 2 diabetes who have a higher susceptibility to develop cardiovascular disease [18].
Digital	These biomarkers allow for continuous and rapid acquisition of complex measurements such as exercise level, cognitive abilities, vital signs, through personal electronic devices [2].	In the field of neurology, there has been a focus on developing digital biomarkers on mobile devices that allow for the measurement of neurodegenerative cognitive decline in diseases such as Alzheimer's or Parkinson's disease [19].

FDA-NIH Biomarker Working Group [Actualization 2021 Nov 29], Zehnder M 2021, Califf 2018, Cagney 2018, Schick SF 2017, Christensen CH 2021, Meyvisch P 2018, Les I 2023, Tom J 2022, Wilson JM 2022, Kourtis L.C 2019

Biomarkers are more precise diagnostic tools, and technological advancements have allowed the development of various types of them. Although there is little experience in the use of digital biomarkers in real clinical practice, it is expected that the detection of not only vital signs but also biomarkers of certain diseases through portable electronic devices will become possible [20].

Use of salivary biomarkers in systemic diseases

Since many pathologies can be associated with biomarkers detected in different bodily fluids, salivary biomarkers have gained popularity as a non-invasive and reproducible data collection technique [4]. The perfection in the collection and processing techniques of salivary samples can reinforce the relationship between oral health and overall health.

Diabetes

Unstimulated saliva has been used as a diagnostic biomarker for detecting diabetes mellitus. A study in 2021 demonstrated that levels of salivary alpha-amylase increase significantly in diabetic individuals compared to controlled patients and healthy individuals. Salivary samples from 80 participants were analyzed by kinetic enzyme assay [21]. Another study in 2020 detected diabetes mellitus by applying salivary 1, 5-anhydroglucitol as a diagnostic biomarker (an indicator for evaluating short-term glycemic control) through liquid chromatography-mass spectrometry, compared to fasting plasma glucose. The levels of 1, 5-anhydroglucitol in saliva of subjects with diabetes mellitus were lower than in healthy subjects [22]. Saliva contains similar elements to blood, and a study conducted in 2018 aimed to determine if salivary glucose could be reliable in detecting, diagnosing, and monitoring type 2 diabetes mellitus. The study included 75 patients divided into three groups: Normal fasting glucose, impaired fasting glucose, and provisional diabetes mellitus (based on their fasting blood glucose level). Unstimulated saliva samples were collected and analyzed by spectrophotometer. The results showed that salivary glucose has a sensitivity of 88.5% and a specificity of 61.5%, with a positive predictive value of 45.8% and a negative predictive value of 97.1%. Therefore, the authors concluded that it is a convenient and non-invasive tool for detecting diabetes mellitus [23].

Hypertension

In 2020, a study was conducted in a pediatric population of 53 children with hypertension, in which nitrosative stress biomarkers (peroxynitrite and nitrotyrosine) and uric acid levels were measured in whole saliva samples, using spectrometry techniques. The results showed that children with hypertension had higher concentrations of the markers compared to children without hypertension, and the authors concluded that nitrosative stress salivary biomarkers and uric acid levels could be potential biomarkers of hypertension in children [24]. At the other end of the life spectrum, a study was conducted in a Japanese adult and elderly population, where free insulin-like growth factor (flGF-1) and salivary growth hormone (GH) were evaluated in saliva samples. The sample consisted of 80 patients over 60 years of age who had not only hypertension but also diabetes mellitus. The samples were obtained from unstimulated saliva and processed for evaluation using the ELISA kit fIGF-1/IGF-1 for humans. The results showed higher levels of salivary fIGF-1 in women compared to men with hypertension and diabetes mellitus [25].

COVID-19

Currently, COVID-19 represents a public health emergency, according to the latest official data from the World Health Organization, there have been 761,071,826 confirmed cases of COVID-19, including 6,879,677 deaths worldwide [26]. The exact mechanism of COVID-19 infection is not fully understood, studies have shown that microRNAs play an important role in host cell infection caused by some types of SARS-COV [27]. In 2020, a study was conducted in Brazil to determine the utility of miR-200c-3p expression (a microRNA that is part of a family of small RNAs) as a diagnostic and prognostic biomarker for COVID. The studied groups were: Group I (39 healthy patients), group II (37 symptomatic patients without hospitalization), group III (21 symptomatic patients with hospitalization), and group IV (14 patients with severe conditions requiring oxygen therapy admitted to the Intensive Care Unit). MicroRNA extraction from total saliva samples was performed using the Easy Extract DNA-RNA kit (Interprise®), and the expression levels of hsa-miR-200c-3p (478351_mir) were analyzed by real-time PCR (Applied Biosystems). The results showed that miR-200c-3p expression increased according to the severity of the patients, age, and groups where there were more complications associated with comorbidities [28]. Due to the increase in COVID cases in 2022, a group of researchers proposed the use of IL-17 quantification in saliva as a biomarker to identify patients at risk of developing severe COVID-19. Salivary samples were evaluated using ELISA, showing that the level of salivary IL-17 was associated with disease severity [29]. The same group of researchers also evaluated the expression of IL-19 in COVID-19, finding that asymptomatic patients had higher levels of IL-19 than healthy control patients. The authors also observed that patients treated with beta interferon during hospitalization had lower plasma concentrations of IL-19 than those who received corticosteroids [30].

Other diseases

Dementia is one of the leading causes of disability worldwide. Alzheimer's disease is the most common form of dementia and may account for 60% to 70% of cases. Dementia-related diseases are a public health problem, as it is estimated that more than 55 million people worldwide suffer from dementia, generating a cost to economies around the world of $1.3 trillion in 2019 [31]. β-amyloid (Aβ42) is a biomarker used in Alzheimer's disease detection [32]. A study in Italy confirmed high levels of salivary Aβ42 using the ultrasensitive ELISA kit for human Aβ42. The results showed a sensitivity of 84% and specificity of 68%. The authors propose increasing studies on salivary samples for the detection of mental illnesses as a non-invasive method [33].

Oxidative stress is a risk factor along with lifestyle for developing diseases. In 2020, levels of 8-hydroxyguanine (8-OHGua) in saliva were evaluated as a new biomarker of oxidative stress in Japan. The relationship between lifestyle and levels of 8-OHGua in salivary samples analyzed by chromatography was analyzed. Salivary levels of 8-OHGua were significantly elevated in older people, as well as those who smoke, have hypertension, or excess visceral fat. On the other hand, statistically significantly lower levels of 8-OHGua were observed in people who engaged in moderate exercise or drank green tea [34].

In 2022, a tsRNA signature was suggested to develop a non-invasive biomarker based on salivary exosomes for human esophageal squamous cell carcinoma (ESCC). Small cancer-enriched RNAs were previously validated through RNA sequencing of salivary exosomes obtained from esophageal cancer patients. In a pilot study, in which the detection of sequences was statistically validated, salivary samples were collected from 159 cancer patients and 74 control patients and analyzed. The results showed that the bio-signature composed of small RNA fragments could discriminate esophageal cancer patients from controls with high sensitivity (90.50%) and specificity (94.20%) [35].

Salivary biomarkers in oral diseases

Caries

Oral diseases affect nearly 3.5 billion people worldwide [11]. Dental caries is a multifactorial disease, with factors including cariogenic microorganisms, hyposalivation, immature immune systems, cariogenic diet, and oral hygiene care in early childhood [36]. In 2021, a case-control cross-sectional study was conducted to determine the role of the diagnostic biomarker Salivary Cystatin in early childhood caries. Statistically, the sensitivity of salivary cystatin levels in diagnosing caries was 95%, with a specificity of 65%. Additionally, the authors found the protective effect of salivary cystatin on the balance of calcium and phosphate in enamel remineralization, as well as its antimicrobial and antiviral effects on oral mucosa [37]. The levels of sCD14, a soluble salivary glycoprotein, is considered an important element in the innate immune response and a biomarker of susceptibility to developing caries. A study in India of 52 children aged 2 to 5 years showed that elevated levels of sCD14 are directly proportional to oral health [38]. Another group of researchers also confirmed the relationship between sCD14 and the presence of dental caries in children and adolescents aged 6 to 17 years [39].

Periodontal disease

According to the World Health Organization, it is estimated that periodontal disease affects about 19% of the world's adult population [40]. Research in the UK identified quantitative mass spectrometry proteomic biomarkers present in saliva. The research found that salivary biomarkers associated with health, gingivitis, and periodontitis are matrix metalloproteinase-9 (MMP9), S100A8, alpha-1-acid glycoprotein (A1AGP), pyruvate kinase, MMP9, pyruvate kinase, among others [41]. A study used liquid-phase C3c protein (a complement system protein) as an inflammation biomarker in patients with periodontitis and as a predictive biomarker after periodontal treatment in salivary samples, quantified by sandwich ELISA technique. Patients with periodontitis had higher salivary levels of C3c compared to healthy patients, and C3c levels decreased after periodontal treatment [42]. Salivary biomarkers have been used in stomatology to evaluate the effectiveness of mouthwashes, with the aim of detecting, predicting, and monitoring the course of treatment for periodontitis and peri-implantitis. PerioSafe and ImplantSafe, and the reader (ORALyser) have been developed by Medix Biochemica Ltd (Espoo, Finland) and dentognostics GmbH (Jena, Germany). The test strips measure levels of matrix metalloproteinases 8 (MMP-8), an enzyme present in periodontitis and peri-implantitis. Commercial companies describe these innovative tests as complementary, reliable, quantitative, non-invasive, and cost-effective tools for the diagnosis, detection, control, and prevention of periodontal and peri-implant diseases for use in the office or at home [43, 44].

Other stomatological diseases

Salivary biomarkers have been employed in the field of stomatology not only for major oral diseases, but also to measure anxiety and pain levels such as in burning mouth syndrome, with quantification of alpha-amylase and immunoglobulin a levels [45]. Salivary biomarkers such as cortisol, C-reactive protein (CRP), interleukin 1β (IL-1β), and interleukin 6 (IL-6), have been evaluated in acute inflammatory processes such as pulpitis and periodontitis [46], as well as in patients with various types of lichen planus, evaluating the salivary expression of lncRNA DQ786243 and IL-17 and their association with chronic inflammation, with potential malignancy of lichen planus [47]. In routine treatments, biomarkers have been used for monitoring, in quantifying salivary alpha-amylase levels in pre and postoperative pain in third molar surgery [48]. In more complex entities such as Behçet's disease (BD), a chronic multisystemic disorder of unknown etiology characterized by recurrent oral and genital mucocutaneous lesions, uveitis, and vasculitis. Salivary biomarkers have been employed, in which the concentrations of 12 cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IFN-γ, TNF-α, TNF-β) have been evaluated for understanding the disease, diagnosis, and seeking treatment alternatives that improve the quality of life of patients who suffer from it [49].

4. Discussion

Recently, the field of stomatology has presented a preventive philosophy, seeking early diagnoses and minimally traumatic treatments for patients [50]. Saliva is a powerful diagnostic tool, its contents are practically the same as blood, with its main advantages being low collection cost, simple acquisition techniques, economical storage, and, mainly, its minimal invasiveness. The usefulness of salivary proteins in the detection of hormones, heavy metal poisoning or organic substances, as well as the detection of cigarette smoking and drug and alcohol abuse have been widely described in the literature [51]. Salivary biomarkers have been used for diagnosis, monitoring, follow-up, and prediction in various oral diseases such as caries, periodontal disease, painful and chronic oral diseases [11, 36-49], as well as in systemic diseases (e.g., cardiovascular disease, diabetes, mental illnesses, certain types of carcinomas, among others) [21-33,35,51].

There are some inconveniences in salivary samples, for example, the collection time, the presence of medications in the circulatory system, hormonal changes with age, as well as the volume of salivary flow, among others. Another inconvenience is the processing of the samples, which is not simple and requires different laboratory techniques for the quantification of specific salivary proteins, such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), chemiluminescence immunoassay (CLIA), high-performance liquid chromatography (HPLC) associated or not with mass spectrometry (LC/MS), among others [21,22,23,25,28]. Refinement and standardization of oral fluid detection and diagnostic tests can help understand the fundamental relationship between oral health and general health. This can play a preventive and diagnostic role in developing community and public health initiatives in clinics and hospitals in the short and long term in a rapid and simple way.

5. Conclusions

Salivary biomarkers have the potential to be used as a non-invasive test for early detection of systemic disease from the dental office, with the aim of timely referral to the specialist physician and receiving appropriate care to improve and prolong the patient's quality of life. The relationship between dentistry and medicine could implement health initiatives and detection and prediction programs through dental visits, with a simple saliva sample. Similarly, perceived oral health could help motivate patients to prevent oral diseases and improve outcomes of associated diseases.

Conflict of Interest

Not available

Financial Support

Not available

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