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# Saliva and its value as a diagnostic material

## Ślina – jej wartość jako materiału diagnostycznego

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Abstract

In recent years, because of huge advances in medicine and technological progress, coupled with the application of increasingly accurate diagnostic tests, the use of saliva for medical purposes has become increasingly important. Saliva is a natural digestive secretion of the major and minor salivary glands that ensures, among other things, the proper functioning of the occlusion system. Other functions include the protection of dental surfaces from various external influences, and involvement in the formation of the food bolus and in the acts of swallowing, digestion, and speech. The composition of saliva is varied. In addition to water, which is found in saliva in far greater quantities than in any other substance, it also contains various substances which are also present in the blood. Their determination in saliva often has a great diagnostic potential in the early detection of both oral and systemic diseases. The diagnosis of selected systemic diseases using saliva is becoming the subject of a growing number of scientific studies. In this paper, the authors have focused on providing the reader with basic information about the physiology of saliva and on presenting the possibilities for its diagnostic application in selected systemic diseases.

**Keywords:** diagnosis, saliva, viral infections

Streszczenie

W ostatnich latach, dzięki ogromnemu rozwojowi medycyny i postępowi technologicznemu, wraz z zastosowaniem coraz dokładniejszych badań diagnostycznych, wykorzystanie śliny w medycynie zyskuje na znaczeniu. Ślina jest naturalną wydzieliną trawienną gruczołów ślinowych większych i mniejszych, gwarantującą m.in. prawidłowe funkcjonowanie aparatu zgryzu. Do innych jej funkcji należą ochrona powierzchni zębowych przed różnego rodzaju czynnikami zewnętrznymi, udział w formowaniu kęsa pokarmowego oraz współudział w aktach połykania, trawienia i mowy. Skład śliny jest zróżnicowany. Oprócz wody, która znajduje się w ślinie w ilości znacznie przewyższającej ilość innych substancji, zawarte są w niej także różnego rodzaju substancje obecne we krwi. Ich oznaczenie w ślinie niejednokrotnie może stanowić duży potencjał diagnostyczny we wczesnym wykrywaniu chorób zarówno jamy ustnej, jak i ogólnoustrojowych. Diagnostyka wybranych chorób ogólnoustrojowych przy wykorzystaniu śliny staje się przedmiotem rosnącej liczby badań naukowych. W niniejszej pracy autorzy skupili się na przybliżeniu czytelnikowi podstawowych informacji na temat fizjologii śliny oraz przedstawieniu możliwości jej zastosowania diagnostycznego w wybranych chorobach ogólnoustrojowych.

**Słowa kluczowe:** diagnostyka, ślina, infekcje wirusowe

## SALIVA PHYSIOLOGY

Saliva is the secretion of the major salivary glands (parotid, submandibular and sublingual glands) and the minor salivary glands (labial and buccal glands). Its volume and composition depend on age and sex. Salivary secretion in newborns is low and increases with age, reaching a peak at around 10 years of age, while after 30 years of age there is a clear downward trend. Under physiological conditions, an adult produces about 500–600 mL of saliva per day, of which almost half is produced via resting secretion and the other half is secreted in response to various stimuli. Men secrete larger volumes of saliva than women, and it is characterised by a higher mineral content. At night, the parotid glands are completely shut down and the other major glands only produce about 10 mL of saliva during sleep[1]. Physically, saliva is a hypotonic liquid, clear or slightly cloudy, with a density between 1.002 and 1.012 g/mL. Its pH depends on the rate of production and ranges from 6.2 (at night) to 8.0 (when there are many bicarbonate ions in saliva). Basic information on the physiology and function of saliva is shown in Fig. 1[2]. The main component of saliva is water, accounting for about 94–99% of its content. The remainder is made up of organic and inorganic components, the concentrations of which depend on a number of external and internal factors. The main organic components of saliva are proteins, the most important of which are glycoproteins (mucins). These make up about one third of all salivary proteins and are responsible for the physical properties of saliva, such as density and viscosity, as well as being involved in the formation of the food bolus and the act of swallowing. Other proteins found in saliva are albumin, lactoferrin, immunoglobulins, and enzymes. Organic constituents in saliva include non-protein nitrogenous substances and non-nitrogenous organic substances. The inorganic constituents are present in saliva in ionic form ($Na^+$ and $K^+$) and are mainly derived from blood, hence their concentration in saliva is unstable (Tab. 1). Physical exercise causes a significant increase in the concentration of inorganic constituents, mainly sodium ions, in saliva[1]. Other cellular and extracellular elements are also present in the secretions of the salivary glands. Saliva is the natural digestive secretion of the oral cavity due to the carbohydrate-digesting enzyme α-amylase (so-called salivary amylase, formerly known as ptialin). The enzyme breaks down starch hydrolytically into maltose and dextrins. Saliva determines the proper functioning of the occlusion system and protects the tooth surface and the surrounding mucous membranes against mechanical, biological, and chemical agents. It is involved in the perception of taste, temperature, and touch. The correct rate of saliva secretion facilitates speech as well as the processes of digestion and swallowing. Since saliva is in constant contact with the external environment, it contains substances involved in non-specific immune responses (lysozyme, lactoferrin, peroxidase) and specific immune responses (IgA and IgM immunoglobulins). The regulation of salivary secretion depends on the autonomic system. This process is conditioned by the presence of both external (gustatory, olfactory, mechanical, thermal, visual or mental stimuli) and internal (endocrine system, nervous system, oral diseases, systemic diseases) stimuli. The afferent pathway consists of sensory fibres from the lingual nerve which travel to the medulla oblongata, where the relevant reflex centre is located. From there, the efferent pathway, i.e. the secretory fibres of the glossopharyngeal or facial nerve, terminate at the surface of the salivary secretory cells. The rate of the salivary secretion process can vary individually. Basic salivary secretion is thought to average

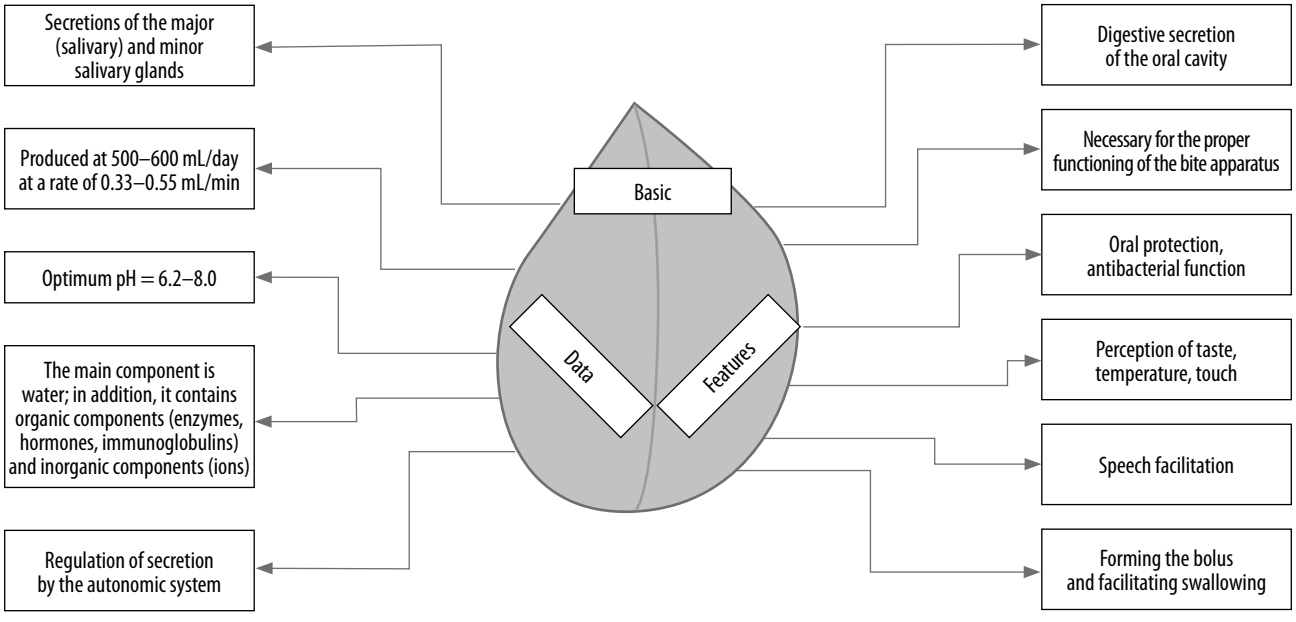


*Fig. 1. Basic information about the physiology of saliva and its functions in the oral cavity (own elaboration)*



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| Water | Organic ingredients | Inorganic constituents |
|---|---|---|
| 94–99% | **Proteins:**<br>• glycoproteins (mucins)<br>• immunoglobulins<br>• enzymes<br>• blood group substances<br>• kallikrein<br>• lactoferrin<br>• epidermal growth factor (EGF)<br>• histatin<br>• cystatin<br>• staterin<br>• sialin<br>• hormones and vitamins A, B, C and K<br>**Non-protein nitrogenous substances:**<br>• urea<br>• uric acid<br>• amino acids<br>• creatinine<br>**Non-nitrogenous organic substances:**<br>• carbohydrates<br>• lipids<br>• hormones | **Cations:**<br>• sodium<br>• potassium<br>• calcium<br>• magnesium<br>**Anions:**<br>• chloride<br>• fluoride<br>• iodine<br>• bicarbonate<br>• hydrogen and dihydrogen phosphate (V) |

*Tab. 1. Composition of saliva (own elaboration)*

0.33–0.55 mL/min, but in response to strong stimulation of the salivary glands, saliva production may increase to 1.5–2.3 mL/min[1]. The transport of substances found in saliva and produced outside the salivary glands occurs from the plasma by passive diffusion, active transport (intracellular pathway) or ultrafiltration (extracellular pathway)[3,4].

## SALIVA AS A DIAGNOSTIC MATERIAL

Saliva is a very valuable biological material that provides information about the health and homeostasis of the entire body. Intensive research into the diagnostic potential of saliva began in the early 1960s, when scientists showed that salivary calcium, sodium and phosphate concentrations were elevated in cystic fibrosis patients. Since then, with increasingly rapid advances in technology and thus diagnostic techniques, research into the diagnostic properties of saliva in systemic diseases has begun to develop rapidly[5–7]. Until now, a major obstacle to the use of saliva for diagnostic purposes was the insufficient sensitivity of available diagnostic methods. Nowadays, following the advent of the era of nanotechnology and omic research, it is possible to analyse substances that are present in saliva in very low concentrations compared to their concentration in blood. It is now possible to determine the presence and/or concentration in saliva of genetic material (DNA, RNA), proteins, drugs and their metabolites, hormones, antibodies, alcohol, selected enzymes, electrolytes and morphotic elements. Bacteriological and virological diagnostics is also available[8]. The advantages of saliva testing include high availability, and ease and non-invasiveness of collecting biological material, also in children, as well as cost efficiency. On the other hand, there are some limitations associated with saliva-based diagnostics, which relate primarily to the correct clinical interpretation of the result obtained. This factor often significantly reduces the practical application of saliva-based diagnostics. The lack of accepted laboratory standards for the determination of selected substances in saliva, as well as the absence of correlation between saliva and blood concentrations of a given substance, also restrict the diagnostic use of saliva. Furthermore, coexisting oral diseases or the presence of proteolytic enzymes in

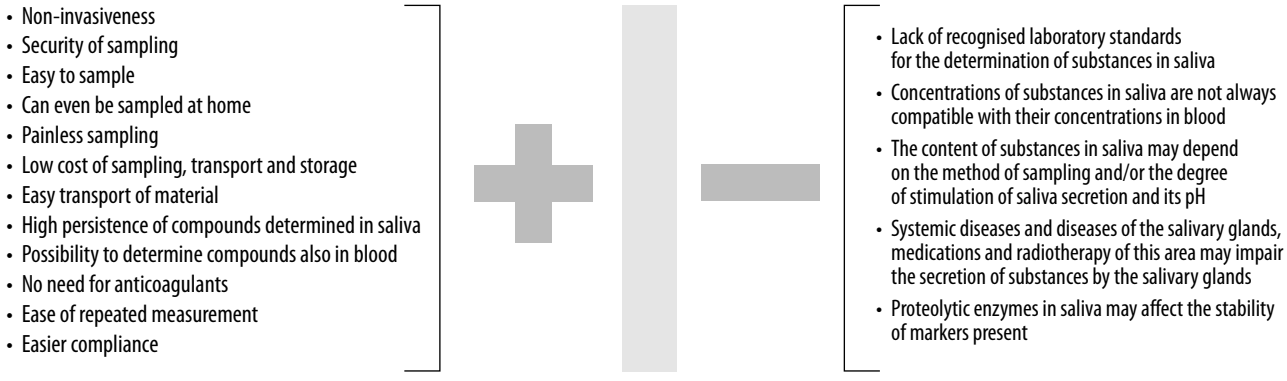


*Fig. 2. Advantages and disadvantages of saliva as a diagnostic material (own elaboration)*



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| **Criterion/group name** | ERA | CRA | Control group |
|---|---|---|---|
| Gender | Women – 85% | Women – 82% | Women – 88% |
| Age | 51 ± 15 years | 52 ± 11 years | 56 ± 13 years |
| Duration of RA | 10.4 ± 17.1 months | 14.5 ± 9.7 years | Healthy persons |
| **ERA** – early rheumatoid arthritis; **CRA** – chronic rheumatoid arthritis; **RA** – rheumatoid arthritis. | | | |

*Tab. 2. Characteristics of the study and control groups participating in the study[24] (own elaboration)*

saliva can significantly impede the assay itself (e.g. by altering the pH of saliva). All the advantages and disadvantages of saliva as a biological material are summarised in Fig. 2[8–11].

## SYSTEMIC DISEASES

In the saliva of cystic fibrosis (CF) patients, the concentrations of chloride, sodium and potassium ions are higher than in healthy individuals. In addition, a study among children with CF showed a positive correlation between chloride and sodium ion concentrations in saliva and sweat[12]. The concentration of the proteolytic enzyme cathepsin D in saliva was also found to be higher in CF patients. This may indirectly indicate an ongoing inflammatory process and cell breakdown[13]. The aim of a study conducted in 2020 was to analyse cytokines found in saliva in CF patients with selected respiratory conditions (diseases of the paranasal sinuses, inferior turbinate hypertrophy, nasal polyps, and lung diseases at various stages). Salivary concentrations of interleukin 6 (IL-6), interleukin 8 (IL-8) and tumour necrosis factor alpha (TNF-α) were measured in healthy subjects and CF patients. The results showed statistically significantly higher concentrations of the analysed cytokines in CF patients. Additionally, CF patients with inferior nasal turbinate hypertrophy showed higher concentrations of IL-6 and IL-8 compared to CF patients without this condition. In contrast, TNF-α levels were lower in CF patients with nasal polyps as well as in end-stage lung disease[14].

Assessment of salivary 17-hydroxyprogesterone (17-OHP) concentrations may be helpful in diagnosing the non-classical form of congenital adrenal hyperplasia without salt-wasting. Morning salivary 17-OHP concentrations (measured by enzyme-linked immunosorbent assay, ELISA) have been shown to correlate well with blood concentrations of this compound, and the use of this measurement in screening for non-classical forms of congenital adrenal hyperplasia may be considered[15,16].

## AUTOIMMUNE DISEASES

A classic example of the use of saliva in the diagnosis of autoimmune diseases is Sjögren's syndrome (SS), a condition characterised by a decrease in the volume and daily secretion of saliva and tears. The current diagnostic standard is the serological determination of antibodies specific for this syndrome, i.e. anti-Ro/SSA and anti-La/SSB, routinely detected in serum but also detectable in saliva[17]. Hu et al. showed that saliva was a reservoir of different types of autoantibodies. Some of these form a set of biomarkers that can distinguish SS patients from systemic lupus erythematosus patients and from healthy individuals[18]. A group of 34 patients with SS and 34 with systemic lupus erythematosus were compared in terms of salivary levels of selected protein biomarkers and mRNA biomarkers. ELISA method was used to detect proteins, while the polymerase chain reaction (PCR) method was used to identify mRNA biomarkers. The results showed that the levels of these biomarkers were significantly increased only in patients with SS. Their detection in saliva may therefore be useful in the diagnosis of this disease in early, sparse symptomatic stages[19]. There are also many other proteins present in saliva, the levels of which differ in SS patients compared to healthy individuals. These include α-amylase precursor, carbonic anhydrase VI, β-2-microglobulin, cathepsin D, α-enolase, cystatins, defensins, and immunoglobulin light chains[20]. A different salivary cytokine profile has also been shown in these patients, which may indirectly indicate the level of disease activity[21].

The qualitative composition and quantity of saliva secretion is greatly affected by rheumatoid arthritis (RA). The total volume of secretion is reduced. Majid et al. in their 2016 study assessed the presence of total protein and iron in saliva in RA patients. The results obtained were analysed in relation to the severity of the disease according to the Disease Activity Score 28 (DAS28), but revealed no statistically significant differences in salivary iron levels in healthy volunteers and RA patients. However, there was a significant reduction in saliva volume and total protein concentration in the study group (RA patients) compared with the control group (healthy volunteers). The severity of the disease did not significantly affect the changes in salivary concentrations of the assessed parameters[22]. A study by Kaczyński et al. in RA patients with coexisting periodontitis showed that salivary concentrations of IL-6, IL-8, IL-17A and TNF-α were higher in RA patients than in healthy subjects. Disease-modifying drugs used in RA patients appear to reduce oral inflammation[23]. Another study published in 2018[24] analysed blood and saliva concentrations of selected substances: metalloproteinase 8 (MMP-8), tissue inhibitor of metalloproteinases-1 (TIMP-1), and IL-6 together with an assessment of oral status in RA patients. The study group was divided into two subgroups: the first group included previously untreated patients with early rheumatoid arthritis (ERA), while the second group comprised patients with chronic rheumatoid arthritis (CRA)



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who had a poor therapeutic outcome after taking disease-modifying drugs. The full characteristics of the studied groups are shown in Tab. 2. The severity of periodontitis was assessed using PD (pocket depth) and BOP (bleeding on probing) indices. In the RA group, substance concentration analysis and oral assessment took place twice. The first examination was performed before the initiation of pharmacological treatment in the ERA group (first-line disease-modifying drugs in monotherapy or various combinations) and before the application of the next line of pharmacological treatment in the CRA group (biological drugs in combination with methotrexate or used alone). Patients were re-examined after a follow-up period [approximately 1.5 years (15.9 ± 6.1 months) after treatment initiation]. During the first measurement, salivary MMP-8 levels were statistically significantly higher in the ERA group than in the CRA group and in the control group (ERA vs. CRA $p = 0.016$; ERA vs. control group; $p = 0.008$), while during the second measurement no such relationship was demonstrated. Similar results were obtained during the determination of IL-6 in saliva. The TIMP-1 concentrations obtained during the first and second measurements did not differ in a statistically significant manner. However, salivary MMP-8 levels were found to correlate positively with the degree of periodontitis in all studied groups[24].

## DIAGNOSIS OF INFECTIOUS DISEASES

The use of saliva for the diagnosis of infections is mainly based on the identification of viral genetic material (DNA, RNA), specific antigens and/or antibodies present in saliva. Untreated or late diagnosis of human immunodeficiency virus (HIV) infection leads to opportunistic infections and malignant tumours which are the result of a steadily progressing dysfunction of the immune system (continuous decrease of CD4 T-lymphocytes). Saliva is not a source of HIV infection. The presence in saliva of many anti-infective substances (defensins, mucins, lysozyme, lactoferrin) inhibits HIV infectivity; moreover, the hypotonicity of saliva, by causing leukocyte lysis, inhibits by about 10,000-fold viral multiplication. However, saliva plays a major role in the diagnosis of HIV infection. Its use as a biological material is mainly related to the serological diagnosis of infection. In order to screen for specific antibodies to HIV-1 and HIV-2, the so-called plate tests are used. The determination of the result is quite simple – it consists in a qualitative visual assessment of the presence of a test band on the plate. However, the diagnosis is possible only after the period of virus seroconversion (at least 4 weeks after a potential infection). A positive screening test result must be confirmed by a Western Blot or PCR verification test. In practice, these tests are usually performed using venous blood, but the Western Blot test also allows the use of saliva as the test biological material. Despite the availability on the medical market of many tests for detecting the presence of HIV in saliva, only one of them, i.e. OraQuick ADVANCE Rapid HIV-1/2 Antibody Test (company OraSure Technologies), was approved in 2004 by the U.S. Food and Drug Administration (FDA). According to the manufacturer, in addition to determining the presence of antibodies in saliva, the test can be used to analyse capillary blood, venous blood, and serum. Analysis of the result on the plate should take place within 20–40 minutes from the delivery of the biological material to the plate[25]. This test is characterised by a high ability to detect IgG class antibodies against HIV-1 and 2 antigens[26]. A 2018 study shows that it can also be used to detect IgM class antibodies, which appear as early as approximately 20–25 days after the potential infection, during acute retroviral illness[27]. Due to the negligible amount of HIV genetic material in saliva, the detection of HIV RNA in saliva is currently out of the main line of research, but studies are ongoing to improve these methods.

The diagnosis of hepatitis C caused by hepatitis C virus (HCV) using saliva is based on the similar principles as the diagnosis of HIV infection. It relies on the detection of specific anti-HCV antibodies in saliva using a plate test. Researchers in Italy have used the new OraQuick HCV Rapid Antibody Test (from the same company that produced the HIV rapid test) for the early detection of anti-HCV antibodies in saliva. The sensitivity and specificity of this method are 97.8% and 100%, respectively[28]. To date, this test has not been approved by the FDA for application in saliva analysis. Furthermore, Drobnik et al. compared the results obtained with the above-mentioned test (using saliva as diagnostic material) with the results of the Abbott HCV EIA 2.0 test using the ELISA method (from capillary blood), which is commercially available and FDA-approved. Positive results were confirmed by Western Blot test. There was almost 98% agreement between the results obtained using the OraQuick HCV Rapid Antibody test and the enzyme assay[29].

Non-invasive methods can also be used to diagnose infectious diseases caused by the dengue virus. Viral RNA and NS1 (non-structural protein 1) antigen can be determined in saliva with a sensitivity of 60% and 56%, respectively. The analysis of the presence of viral RNA genetic material in saliva was performed 7–13 days after the onset of symptoms and had a higher sensitivity than the analysis of viral genetic material in blood (50% vs. 31%)[30].

## CONCLUSIONS

Over the last two decades, research into the diagnostic potential of saliva has advanced considerably. Saliva is a valuable biological material that contains a vast array of different substances, and their possible changes in concentration occur faster in saliva than in blood. This gives hope that the often time-consuming diagnostic process of chronic diseases will be possible at an early stage, reducing the time to diagnosis. The attention of researchers is also focused on the diagnostic importance of saliva in the early detection of



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cancer, which is not described in this paper due to its limited scope[31].

The limitations associated with the use of saliva in the diagnostic process are also significant. The lack of accepted standards for the determined substances is still a barrier to their quantitative determination. Therefore, at present it is possible to make a preliminary diagnosis of certain conditions based on saliva testing, but still the main part of the diagnosis is based on blood analysis, where the reference values for the substances tested are known. In addition, a number of salivary assays are strongly dependent on the health of the oral cavity itself, which makes the diagnosis of systemic diseases such as RA difficult. However, in an era of emerging new and more accurate diagnostic methods, tests using saliva as a diagnostic material are needed, primarily as an auxiliary tool to the main diagnostic process, and as early, rapid and non-invasive tests that can determine the correct diagnostic pathway.

### Conflict of interest

*The authors declare no financial or personal relationships with other persons or organisations that could adversely affect the content of the publication and claim rights to this publication.*

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