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# REVIEW

## FACTORS OF VARIABILITY IN THE COMPOSITION OF MIXED SALIVA (A REVIEW)

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The study of saliva composition attracts much attention and the number of publications in this area is constantly growing. However, the impact individual factors on saliva composition still needs better understanding. The limited use of saliva as a biological fluid for clinical laboratory diagnostics is determined by the lack of standardized preanalytical methods and the absence of reference values for biochemical parameters that take into account a number of factors affecting saliva composition and properties. In this review we have analyzed some factors influencing saliva composition. The impact of these factors on saliva composition is associated with dysfunction of the salivary glands, changes in the salivation rate, salivary viscosity, dry mouth, pH balance, and electrolyte composition, leading to impaired homeostasis of the oral cavity.

**Keywords:** saliva; composition; biochemistry; factors; variability

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## INTRODUCTION

Oral cavity homeostasis depends not only on tissue function, anatomical structures, and blood composition, but also on the composition and properties of mixed saliva. Saliva, the most important biological fluid in the oral cavity, is characterized by multiple functions. It has high potential for diagnosing and monitoring systemic diseases and the results obtained are increasingly used in other areas of healthcare [1, 2]. The analysis of saliva for many clinical and biochemical parameters offers advantages over routine laboratory blood diagnostics. This biomaterial can be widely used in hygiene, toxicology, and immunology studies, as well as for studying the pharmacodynamics of drugs and for specialized scientific purposes. The analysis of mixed saliva for relevant biomarkers of a number of diseases and pathologies can open new prospects for its use [3–5].

The limited use of saliva as a biological fluid for clinical laboratory diagnostics may be due to the fact that there are no standardized methods for the preanalytical stage as well as no reference values for biochemical parameters that would take into consideration a number of factors affecting the composition and properties of saliva. Standardization of protocols for sample collection, processing, and analysis is crucially important for reproducibility and comparability of data obtained in different studies [6]. The composition of saliva can be influenced by various factors, including the circadian rhythm, which determines the volume of saliva and its quantitative and qualitative composition, age, gender, diet, oral hygiene, hormonal changes, and many others [7–9]. Since the composition of saliva is subjected to both quantitative and qualitative changes, which cause a fundamental difference from blood plasma, it is necessary to take into account the impact of certain factors on the composition of saliva for an accurate interpretation of the results obtained. It has been convincingly demonstrated that certain systemic diseases, medications, and psychotropic substances affecting the central and peripheral nervous systems, as well as an unfavorable environment, can have a significant impact on the composition of saliva [10, 11]. Thus, saliva has diagnostic potential, prognostic value, and significance for treatment monitoring, as well as the possibility of integrating certain salivary indicators to improve patient care and develop personalized medicine approaches [12–15].

The aim of this work was to evaluate changes in the quantitative and qualitative characteristics of saliva under the influence of various factors and to determine the relationship between the composition of saliva and physiological and pathological processes in the body.

## 1. AGE AND GENDER CHARACTERISTICS OF SALIVA COMPOSITION

### *1.1. The Effect of Gender*

Using mixed saliva in studies, it is necessary to consider possible differences in saliva composition depending on the patient's gender to be confident in accurate and reliable interpretation of diagnostic results. Certain differences in saliva composition may be associated with the rate of salivation. For example, Inoue et al. has demonstrated that

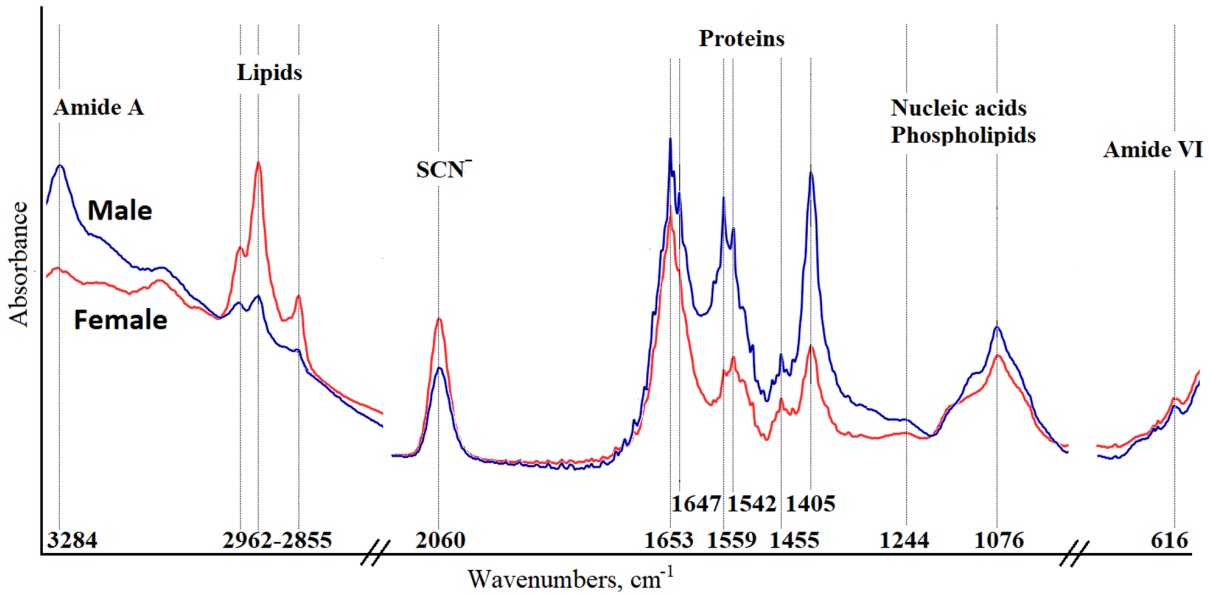


**Figure 1.** An example of IR spectra of human male and female saliva samples [18].

the salivary flow rate in women is significantly lower than in men, as their submandibular glands, which primarily produce unstimulated saliva, are much smaller than in men [16]. Buchan et al. found spectral differences in saliva in men and women [17]. It was shown that Raman spectra of males differed from female ones by an increase in the intensity of the absorption bands at 630 $cm^{-1}$, 760 $cm^{-1}$, and 1003 $cm^{-1}$, with female spectra demonstrating an enhanced response in the bands at 855 $cm^{-1}$, 1300 $cm^{-1}$, and 1400 $cm^{-1}$. The intensity of the absorption band at 630 $cm^{-1}$, attributed to phenylalanine, decreases in female spectra, where salivary metabolites such as taurine and lactate are usually identified. The absorption band at 1340 $cm^{-1}$, associated with collagen, has a higher intensity in women than in men; this is associated with differences in hormonal status. A slight shift in the amide III region (1205–1300 $cm^{-1}$) was also shown, thus indicating gender differences in that the composition of saliva in males and females. Bel'skaya et al. compared the infrared (IR) spectral characteristics of saliva from healthy volunteers in terms of gender and age [18]. Statistically significant gender differences were observed for protein and lipid absorption bands. The intensity of protein and nucleic acid absorption bands was higher for men, while the intensity of lipid absorption bands was higher in the female group (Fig. 1). It was found that the correlation between spectral characteristics and age was weak. Therefore, during selection of criteria for normal and pathologically altered saliva, it is necessary to consider the gender of the subjects, while strict requirements for age classification are not imposed.

Studying gender differences in the composition of saliva, Minty et al. found higher levels of cholesterol (0.71±0.26 mmol/l and 0.40±0.27 mmol/l, $p = 0.0329$),

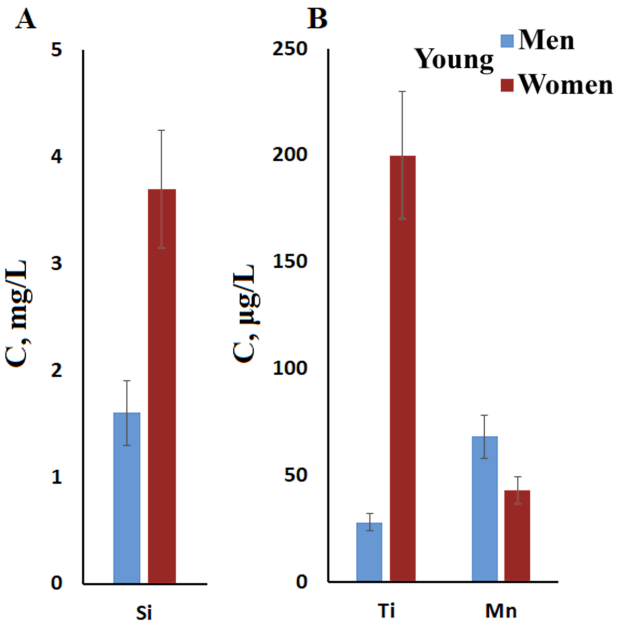


**Figure 2.** Concentrations of Si, Ti, and Mn in the saliva of young men and women. C – microelement concentrations. The figure was prepared using data from [20].

free fatty acids (0.25±0.18 mmol/l and 0.08±0.06 mmol/l, $p = 0.0049$) and triglycerides (0.24±0.15 mmol/l and 0.09±0.04 mmol/l, $p = 0.0060$) in men than in women [19]. Other authors have shown a statistically significant difference in the concentration of macro- and microelements (Si, Ti, and Mn) in the saliva of young men and women. This difference has been demonstrated using the example of the experimental distribution of the logarithm of the Si content in saliva for a subgroup of young men and women. A similar difference was observed for the Ti concentration, while the average Mn content was lower in the saliva of young women than in young men (Fig. 2) [20].

Mineral composition of saliva also depends on gender. Statistically significant differences were found between men and women for pH, inorganic phosphorus concentration, and the Ca/P ratio. The circadian dynamics of salivary pH and the Ca/P ratio showed peaks at 9 a.m. and 3–6 p.m. In general, the pH value of women's saliva is higher throughout the day than that of men; however, in both cases, the obtained values are within the normal range [21]. Consequently, the mineralizing properties of saliva are higher in the female group. Gender differences in the diversity of salivary microbiota may be caused by the endocrine system; these changes can be particularly observed during puberty [22, 23].

### *1.2. The Effect of Age*

Age-related changes have been observed in the flow rate, volume, and human saliva composition [24]. Histomorphometric studies of healthy salivary gland tissue have revealed an age-related decrease in acinar cell numbers. It has been shown that despite the loss of acinar cells, there is a secretory reserve to maintain salivary gland function, potentially explaining the age-related changes in saliva [25, 26]. Raman spectroscopy has shown that both lysine (1003 $cm^{-1}$) and glycine (1327 $cm^{-1}$) are the most abundant amino acids in saliva, and their concentrations demonstrate the age-related increase in both men and women [17]. Nagler et al. discuss differences in the salivary gland size and its impact on salivary components during the aging process in both men and women [27]. Older patients tend to have frequent xerostomia (also known as dry mouth), saliva production impairments and speech problems, causing oral infections and dental caries. There are changes in intensity observed at the 630 $cm^{-1}$ and 1003 $cm^{-1}$ peaks between younger (the 20–30 years old) and older (56+ years) people, indicating that the concentration of bound amino acids demonstrates the age-related decrease [27]. This is attributed to the age-related decrease in the salivary flow rate accompanied by the resulting decrease in the amino acid concentration [17]. In addition, there is a strong change in the intensity of the lipid peak between age groups with a higher response in the 56+ group at 1076 $cm^{-1}$, which is associated with salivary gland hypofunction in the elderly with loss of acinar cells and an increase in adipose and fibromuscular tissue in both the parotid and submandibular glands [25, 28]. Histopathological samples of salivary glands from young adults show a smoother and more compact lobar structure with a homogeneous pattern of the parenchymatous elements compared to those of the elderly [29]. Furthermore, the amount of salivary glycoproteins increases with age. Sun et al. have found that N-glycoproteins are associated with innate immunity, which humans develop throughout life against microorganisms to protect the oral cavity [30].

In women, the salivary flow rate demonstrates the postmenopausal decrease induced by the effect estrogen on the salivary metabolome [28]. The authors noted that salivary pH values in postmenopausal women were significantly lower. Normal salivary pH is about 6–7, but it can vary from 5.3 to 7.8 [31]. Changes in salivary pH and the salivation rate lead to disruption of the buffering system. It should be noted that at certain periods of life, some changes in saliva composition occur gradually, while others occur rapidly (e.g., during the neonatal period, puberty, and menopause). Furthermore, levels of sex hormones such as dehydroepiandrosterone (DHEA), testosterone, and progesterone change during adrenarche and puberty [32].

A healthy person has 250–300 resident microbiome strains in saliva, which contains over 700 bacterial species. Important bacterial groups found in saliva include *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Fusobacterium*, *Actinobacteria*, and others [33]. *Lactobacilli* strains are the main group of salivary microorganisms. Differences in the salivary microbiome have been observed in older adults [32, 33]. The elderly group is characterized by a relative increase in *Porphyromonas endodontalis* and *Alloprevotella tannerae*, *Filifactors alocis*, *Treponema sp.*, *Lautropia mirabilis*, and *Pseudopropionibacterium sp._HMT_194* [34]. In the oral cavity of people over 65, changes in the mucosa, immune function and salivation associated with endogenous factors were noted [34]. Another possible reason for age-related differences in saliva composition is polypharmacy or high level of drug consumption [35]. The bacterial composition in the saliva microbiome of young people was found to be more diverse compared to that of adults [36]. The saliva microbiome of adults was mainly responsible for the effect on oral health, while in young people it was responsible for body weight [32].

Age-related changes in salivary cytokine concentrations have been demonstrated: the concentration of most salivary cytokines correlated positively with age and the presence of oral pathologies (gingivitis and caries), and negatively with salivary flow [37]. The saliva albumin and iron content increased in older patients with a simultaneous decrease in pH. A correlation between calcium and magnesium content is characteristic of women, while in men, calcium content correlates with inorganic phosphorus; this can be explained by gender-specific metabolic processes in the human body [21]. Thus, different reference ranges for salivary biochemical parameter concentrations should be used for different age groups.

### *1.3. Hormonal Status*

Endocrine changes in humans affect electrolyte composition, pH, and salivary flow rate. For example, it has been noted that estrogen levels influence salivary

secretion [38]. Detection of estrogen receptors β (ER β) in acinar and ductal cells of the salivary glands confirms that estrogens regulate physiology of these tissues, influencing the secretion and composition of saliva, including the bacterial content [39, 40]. Studies have shown that the protective effect of estradiol depends on the estrogen receptor subtype, suggesting that tissue-specific expression of certain sex steroid receptors contributes to susceptibility to bacterial infections [41].

During menopause women are most susceptible to the influence of hormonal changes on the salivary composition: a change in salivary pH is observed due to decreased estrogen levels, which can lead to dry mouth, inflammation, and an increased risk of infection [42].

## 2. CIRCADIAN RHYTHMS

Time and biological rhythms influence the concentrations of certain analytes in many biological body fluids. Therefore, the time of collection of biological material must be regulated so that researchers can correctly interpret the obtained test results. Various biological systems follow and change in accordance with well-known diurnal, circadian, infradian and ultradian rhythms [43, 44]. Melatonin and cortisol are examples of hormones that follow diurnal or circadian rhythms with a periodicity of approximately 24 h. An example of a common infradian rhythm that affects fluctuations in progesterone and estradiol levels in women is the menstrual cycle with a periodicity of approximately 28 days. The most studied hormone subjected to these changes is cortisol; in addition, DHEA and testosterone may also be sensitive [44]. In a study by Shang et al., circadian changes in ghrelin (orexigenic hormone) levels in the saliva of healthy men and women were detected for the first time under conditions of food intake for 24 h. The peak values were found at 03:00, then they decreased by 06:00 [45]. Lozano et al. did not find significant circadian variations in the levels of calcium, phosphate, hydrogen peroxide, and total protein [46]. However, lactate, nitrate, nitrite, ammonium, and glucose demonstrated significant circadian variations with pronounced peaks at certain periods of time. Although the circadian rhythm had a limited effect on the overall biochemical profile of saliva, certain analytes demonstrated significant variations [46]. During saliva analysis in pediatric patients, it is important to take into account that acrophases of sodium ion excretion are registered at night. The concentration of potassium ions, on the contrary, reaches a maximum during the daytime in children aged 4 years and 5 years and in the morning hours in children aged 6 years and 7 years [47]. Experiments on adult volunteers have shown that during the daytime the value of the Na/K ratio does not exceed the average value. The observed Na/K dynamics are due to a decrease in sodium levels and an increase in potassium concentration, which may be the result of a significant load on the sympathoadrenal system. A decrease in sodium excretion with saliva in the morning may indicate a transition from passive to active functioning, characterized by increased metabolic processes, increased hormonal activity, and increased sympathetic tone [21]. Therefore, during analysis of saliva, it is crucial to understand its possible changes throughout the day and to carefully plan sample collection times to obtain accurate conclusions about the nature of the biomarker of interest and ensure effective measurements.

## 3. PHYSICAL EXERCISES

The type and frequency of training, physical condition, and overall health of athletes can influence the levels of hormones, immunoglobulins, and salivary enzymes [48]. During sample collection for analysis, it is advisable to document intense physical activity the day before testing or, if possible, to refrain from it, since physical activity can stimulate the production and secretion of hormones such as cortisol and testosterone [49]. A person's level of physical fitness and the amount of exercise performed can determine the degree of increase in the levels of these hormones. A number of authors found that physical exercise significantly increased the concentration of total protein in saliva (before exercise 0.83±0.27 mg/ml, after exercise 1.10±0.58 mg/ml) and the pH value of athletes' saliva (before exercise 7.53±0.33, after exercise 7.89±0.26) [48–50]. Salivary catalase activity significantly increased only after aerobic exercise, as opposed to anaerobic exercise. Salivary bioluminescence increased in athletes engaged in aerobic exercise compared to anaerobic exercise [49]. Physical exercise is a powerful stimulus for the secretion of oxytocin and cortisol in both saliva and urine [52]. The duration and, likely, intensity of exercise influence the adrenal cortisol secretory response, which is reflected in its content in saliva.

Lactate is an important energy source for skeletal muscle metabolism. Measuring blood lactate concentrations provides information on changes in glycolysis and anaerobic performance [53]. Lactate in saliva is probably appeared due to passive diffusion from the salivary glands and blood [54]. It has been suggested that salivary lactate increases due to elevated blood lactate concentrations, leading to increased blood-saliva barrier permeability during exercise. These data can be used to assess the potential for overtraining [55]. Different responses to chronic physical activity have been noted in men and women [56]. A tendency toward increased secretory immunoglobulin A (sIgA) and α-amylase concentrations in saliva during exercise has been observed in women [57].

## 4. THE IMPACT OF SMOKING

Cigarette smoke contains a large number of hazardous chemicals (radicals, aldehydes, isoprene, nitrobenzene, acetone, isoprenoids, pyrene, benzopyrene, naphthols, naphthalenes, etc.); many of them are carcinogenic. Convincing evidence exists, that tobacco smoking in young people impairs salivary function, creating conditions for the emergence and development of various pathological processes in the oral cavity [58–60]. Thiocyanates (SCN, thiocyanates) enter saliva from serum and are formed from hydrocyanic acid with the participation of rhodanese. In saliva, they are oxidized to hypothiocyanates and other derivatives, which participate, together with lactoperoxidase, in salivary protective reactions. The saliva of smokers has a higher level of thiocyanates, and since they are formed from hydrocyanic acid, which is present in large quantities in tobacco smoke, this leads to increased formation of thiocyanates [61]. Normally, thiocyanate oxidation participates in salivary protective reactions, but their elevated levels contribute to a shift in pH, acidifying saliva. The concentration of sphingolipids and ceramides in the saliva of smokers was significantly lower than that of nonsmokers. Moreover, smokers of traditional cigarettes had higher levels of 4-hydroxynonenal and malondialdehyde in both stimulated and unstimulated saliva compared to nonsmokers, while salivary lipid concentrations were decreased [62, 63]. Smoking affects the fatty acid composition of total salivary glycerophospholipids and the main classes of phospholipids (phosphatidylcholine and phosphatidylethanolamine) (Table 1) [62].

Usually, a significant decrease in the content of unsaturated fatty acids in the phospholipids of smokers is observed: radicals contained in cigarette smoke reduce the content of polyunsaturated fatty acids in cell membranes and can affect the physicochemical properties of saliva [64]. The composition of the salivary microbiome is also subjected to changes, leading to higher consumption of tyrosine and tryptophan, while the content of these amino acids decreases [65]. Impairment of saliva properties during smoking often leads to oral diseases (e.g., periodontitis), which contribute to the creation of an oral environment in which gram-positive facultative anaerobes and amino acid-degrading bacteria, such as *Prevotella*, proliferate [61, 66].

## 5. NUTRITION

Saliva has a significant impact on the colonization and clearance of microorganisms; it plays an important role in the physical, chemical, and immunological protection of the oral cavity. In this regard, it is considered as a reservoir for the oral microbiota [67, 68]. It can be assumed that since the oral cavity is the entry point for food, a person's diet should affect the composition of the oral microbiome. At the same time, saliva is a buffer system, involved in pH maintaining within the neutral values. This provides a stable environment for oral bacteria in the absence of disturbing external factors. Eating is accompanied by chewing and stimulation of salivation; food is actually in the mouth only for a limited time during the day [69]. However, consumption of foods high in sugar provides a favorable environment for bacteria, and this leads to an imbalance in the oral cavity microbiome [70]. The degree of mineralization of drinking water also influences the buffering capacity of saliva, since minerals, especially phosphates and carbonates contained in water, are part of the main buffer systems of oral fluid [71]. Simple carbohydrates obtained from food are the main substrate for oral bacteria, especially for *Streptococci* and *Lactobacilli*, thus leading to an imbalance in the oral microbiome [72]. Bacterial glycolysis results in the formation of a large number of organic acids (lactic, butyric, propionic, acetic, etc.), which are surfactants and reduce the surface tension of oral fluid [73, 74]. Frequent snacking leads to a short-term increase in the salivation rate [75]. Thus, a diet high in sugar can, through the glycolytic pathway and the production of acids, lead to a change in the pH of saliva. Moreover, the pH of saliva changes during the day: in the morning, pH values are lower (6.74±0.19) than in the middle of the day (6.89±0.14),

*Table 1*. Fatty acid composition (percent of total fatty acid content) of phosphatidylcholine, phosphatidylethanolamine, and total lipid phosphorus) in smokers and nonsmokers

| **Fatty acids** | **Phosphatidylcholine** | | **Phosphatidylethanolamine** | | **Total lipid phosphorus** | |
|---|---|---|---|---|---|---|
| | Nonsmokers | Smokers | Nonsmokers | Smokers | Nonsmokers | Smokers |
| 14:00 | 6.7±0.9 | 8.0±0.9 | 12.5±0.6 | 5.0±0.9 | 4.8±0.6 | 5.2±1.0 |
| 16:00 | 31.5±2.5 | 25.2±2.8 | 30.7±1.9 | 13.5±0.6 | 27.1±1.2 | 19.5±1.0 |
| 16:1, n-7 | 11.1±0.8 | 11.0±0.9 | 12.0±0.8 | 11.1±0.8 | 11.1±0.8 | 14.7±0.8 |
| 18:00 | 15.2±1.1 | 23.0±1.8 | 18.0±3.6 | 25.3±2.6 | 17.1±1.6 | 24.3±1.5 |
| 18:1, n-9 | 9.1±0.8 | 15.2±1.1 | 12.1±0.9 | 11.1±0.8 | 12.4±0.9 | 15.2±1.1 |
| 18:3, n-3 | 25.0±1.3 | 9.1±0.8 | 19.5±1.0 | 29.1±1.3 | 16.8±1.5 | 17.2±1.6 |
| 20:00 | 4.7±0.8 | 6.7±0.8 | 3.3±0.5 | 3.6±0.3 | 4.6±0.5 | 4.3±0.5 |

Adapted from [62].

in the evening it increases (7.05±0.13), then decreases again during sleep (6.66±0.20) [76, 77]. This indicator also changes in response to food intake: pH increases during meals due to increased salivary flow and decreases after meals. The average pH value is restored within 1–2 h.

Therefore, studying the microbiome and salivary biochemical parameters, it is important to monitor sample collection times based on food intake when.

## 6. CHANGES IN SALIVA COMPOSITION IN VARIOUS DISEASES AND MEDICATIONS

The presence of concomitant pathologies in the body can lead to changes in the composition and properties of saliva, thus causing a decrease in the cleansing ability of saliva, deterioration of its antimicrobial, buffering, and remineralizing functions [78]. There is evidence that adverse hormonal, microvascular, and neuronal changes in poorly controlled diabetes can contribute to salivary gland hypofunction [79]. Organic damage to the salivary glands caused by medications or disease, as well as disruption of neural pathways, can lead to dry mouth. For example, some anticholinergic drugs (antihistamines, antispasmodics, antidepressants) can block the acetylcholine binding to muscarinic receptors in the salivary glands [80]. In some diseases, such as Sjogren's syndrome, ductal and acinar cells of the salivary glands may be damaged, thus affecting saliva secretion [81, 82].

### *6.1. Oral Diseases*

The diagnostic and prognostic potential of saliva diagnostics is actively studied in relation to inflammatory and neoplastic diseases of caries, periodontitis, and the oral mucosa, as well as many systemic diseases of various origins [83].

**6.1.1. Caries.** Caries is the most common oral disease, which is primarily caused by an imbalance in the microbiome [84]. In a low pH environment, the number of acidogenic and acidophilic bacteria increases, and these mixed communities can cause caries by producing acids, forming a strong biofilm, and tooth enamel demineralization. It has been shown that the oral microbiome of children with caries differs from the microbiome of healthy children [85, 86]. Caries is not caused by an isolated organism, such as *Streptococcus mutans*, but is more polymicrobial in nature. A potential factor in the development of caries is an increase in the number of bacteria such as *Bifidobacterium*, *Veillonella*, *Granulicatetta*, *Scardovia*, *Fusobacterium*, *Prevotella*, and *Actinomyces* [85, 86]. Caries is characterized by a significant decrease in the amount of all electrolytes: hydrogen ions, calcium, phosphate ions. Their negative dynamics corresponds to an increase in the degree of caries and an increase in the number of extracted teeth. A decrease in pH and these electrolytes by more than 2 times disrupts the mineralizing potential of saliva and converts it to the demineralizing one [87]. Proteomic profiling of saliva samples revealed an increase of concentration of specific salivary proteins, such as keratin 3 and mucin 21 in caries [88, 89].

**6.1.2. Periodontal diseases.** Periodontal diseases (periodontitis, periodontosis) are one of the leading causes of irreversible tooth loss, especially in the elderly and senile population [90–92]. A number of cytokines and growth factors are involved in stimulating the regeneration of connective tissue and the oral mucosa. For example, almost 40 cytokines including interleukins, neurotrophic factors, and various growth factors (VEGF (vascular endothelial growth factor), platelet-derived growth factor, placental growth factor, insulin-like growth factor, epidermal growth factor, fibroblast growth factor, etc.) have been found in periodontal tissues [93]. Moreover, the content of most cytokines significantly increases in the saliva samples of patients with periodontitis compared to healthy controls. Periodontitis is accompanied by an increased level of proinflammatory cytokines; this shifts the balance between pro- and anti-inflammatory cytokines towards local inflammation [94]. VEGF is one of the most potent growth factors, regulating endothelial cell proliferation and participating in the formation of the vascular network: inflammatory periodontal diseases are accompanied by a decrease in VEGF levels in saliva [95].

### *6.2. Systemic Diseases*

**6.2.1. Neurodegenerative diseases.** The microelement composition of saliva has been analyzed in elderly patients with neurodegenerative diseases, particularly, with Parkinson's disease. An increase in the content of aluminum, cadmium, lead, barium, nickel, arsenic, and zinc, as well as a decrease in the content of iron, chromium, and selenium were found in the group of patients with Parkinson's disease (Fig. 3) [96].

A study of the saliva composition in men with schizophrenia revealed a significant increase in the concentration of aluminum, iron, lithium, magnesium, sodium, and vanadium compared to the control group. The study has shown that it is also necessary to take into account the elemental composition of drugs used to treat schizophrenic patients (Fig. 4) [97].

**6.2.2. Cardiovascular diseases (CVD).** In CVD, the concentration of sirtuins in saliva is altered. Sirtuins (Sirt) are highly conserved histone deacetylases that play an important role in maintaining homeostasis of cardiovascular cells [98, 99]. They are involved in heterochromatin formation, transcriptional silencing, ion channel regulation, and modulation of redox processes [100]. In middle-aged and elderly patients with coronary heart disease (CHD), the concentration of Sirt1, Sirt3, Sirt6, and Sirt7 in saliva decreases

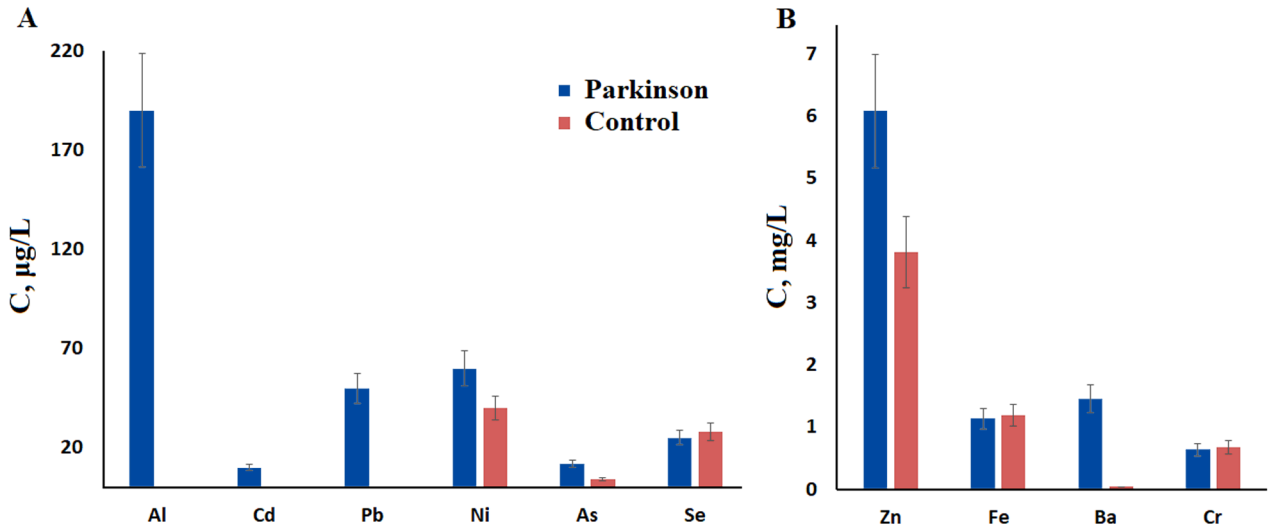


**Figure 3.** Trace element composition of saliva from patients with Parkinson's disease compared to the control group. **A**: Al, Cd, Pb, Ni, As, and Se; **B**: Zn, Fe, Ba, and Cr. C: – microelement concentrations. The figure was prepared using data from [96].

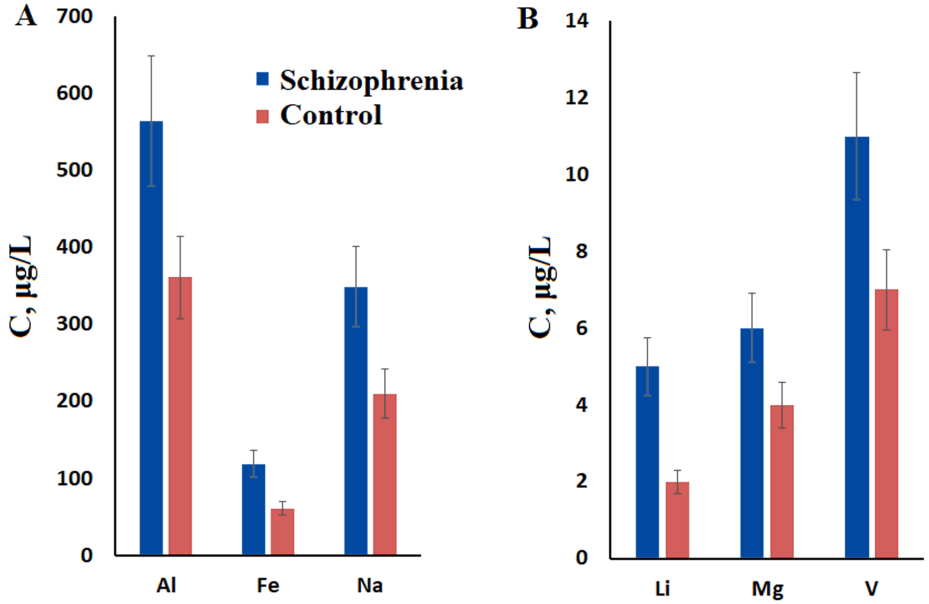


**Figure 4.** Trace element composition of saliva from patients with schizophrenia compared to the control group. **A**: Al, Fe, and Ni; **B**: Li, Mg, and V. C – microelement concentrations. The figure was prepared using data from [97].

by 1.4–4.2 times compared to the control group. In addition, elderly CHD patients showed a significantly more pronounced decrease in the concentration of sirtuins in saliva compared to middle-aged individuals [101]. The presence of arterial hypertension (AH) can decrease the pH and increase the viscosity of saliva in patients, and this subsequently leads to changes in the quality and quantity of secreted saliva and affects oral health and the patient's quality of life [102]. Some authors demonstrated changes in the oral microbiota in CVD patients. The oral microbiota is closely associated with AH, probably through the transfer of microorganisms from the oral cavity to the intestine. Ectopic colonization of the intestine by *Veillonella* isolated from saliva can aggravate AH [103].

**6.2.3. Diabetes mellitus (DM).** DM is a non-infectious chronic metabolic disease characterized by impaired insulin action, its secretion, or both. Insulin deficiency leads to impaired carbohydrate, protein, and lipid metabolism. Genetic and environmental factors play a role in the DM development [104]. Decreased insulin secretion, decreased glucose utilization, or increased gluconeogenesis ultimately lead to hyperglycemia and pathological changes in various organs, including the oral cavity [105, 106]. Complications, arising in the oral cavity due to DM, result from poor neutrophil function, microangiopathy, neuropathy, decreased collagen synthesis, and decreased collagenase activity [107]. In diabetic patients, concentrations of glucose (11.00±2.00 mg/dl, versus 3.00±0.03 mg/dl in healthy controls),

urea (27.0±1.0 mg/dl, versus 17.0±1.0 mg/dl in controls), and IgA (238 μg/ml, versus 103 μg/ml in controls) were significantly higher, while the total protein level was significantly lower (0.30±0.03 mg/dl, versus 2.00±0.10 mg/dl in controls) in saliva [108]. These results are likely related to the elevated levels of *S. mutans*-specific antibodies and anti-insulin antibodies, which were also observed in these patients [109]. Also, a number of studies of the microelement composition of saliva in diabetic patients have shown changes in the calcium and phosphorus content; this causes impairments of certain functions (e.g. cleansing, mineralizing, protective), and can lead to a predominance of demineralization processes over remineralization [110].

**6.2.4. Oncological diseases.** Systemic diseases, including oncological ones, affect the entire human body [111–113]. First of all, changes in the composition of saliva in cancer of the oral cavity and salivary glands have been studied [114], and an increase in tumor markers and cytokines was noted in saliva [115]. The composition of saliva in breast cancer has also been studied, and a significant increase in the level of CYFRA 21-1 in saliva was shown in luminal A (11.60 [4.47; 18.51] ng/ml) and luminal B HER2-negative (7.16 [4.74; 37.72] ng/ml) breast cancer compared to the control (3.38 [0.39; 8.47] ng/ml) [116]. During tumorigenesis and metastasis, the tumor microenvironment alters glycosylation of salivary glycoproteins, such as mucin-5B, mucin-7, salivary agglutinin, β-2-microglobulin, and proline-rich glycoprotein [117]. There are indications on association between altered salivary microbiome and lung cancer [117, 118].

### *6.3. Medication Intake*

Various medications (e.g., diuretics, antihypertensives, antihistamines, barbiturates, etc.) reduce salivary flow and can cause changes in salivary pH and viscosity. A single drug can potentially affect salivary analytes through multiple pathways or mechanisms; concomitant administration of multiple drugs may exacerbate this phenomenon [119]. Therefore, collecting saliva samples, it is necessary to consider medication history, timing, and dosage.

Sobczak-Jaskow et al. examined how saliva composition and properties change in treated individuals with osteoporosis compared to a control group. The study included the following salivary parameters: pH, buffering capacity, calcium ions, phosphate ions, total protein, lactoferrin, lysozyme, sIgA, IgA, cortisol, neopterin, and α-amylase [120]. Statistically significant differences in salivary calcium and phosphorus ion concentrations were observed between patients of the osteoporosis group and the control group [120]. In addition, increased levels of lysozyme, neopterin, and cortisol were observed, while sIgA content decreased compared to the control group (Fig. 5) [119].

Use of combined oral contraceptives (COCs) can alter concentrations of certain analytes in women's saliva. Since exogenous/synthetic hormones in COCs alter the normal balance of the endocrine system, this leads to a decrease in the rate of salivary secretion [119].

Side effects of medications used to treat mental illnesses are most often the cause of salivary secretion disturbances [121, 122].

In recent years, changes in salivary parameters have been noted in somatic pathology patients, who needed regular and long-term take medications. In particular, in CVD patients, changes in the oral cavity are caused by impaired systemic and local blood flow. In AH patients changes in the oral mucosa are characterized primarily by vascular, proliferative, and atrophic deviations [123]. The salivation rate was reduced in patients taking statins. The amount of total protein significantly increased in the group of patients taking angiotensin-converting enzyme inhibitor and statins, and decreased in patients taking β-blockers and calcium channel blockers.

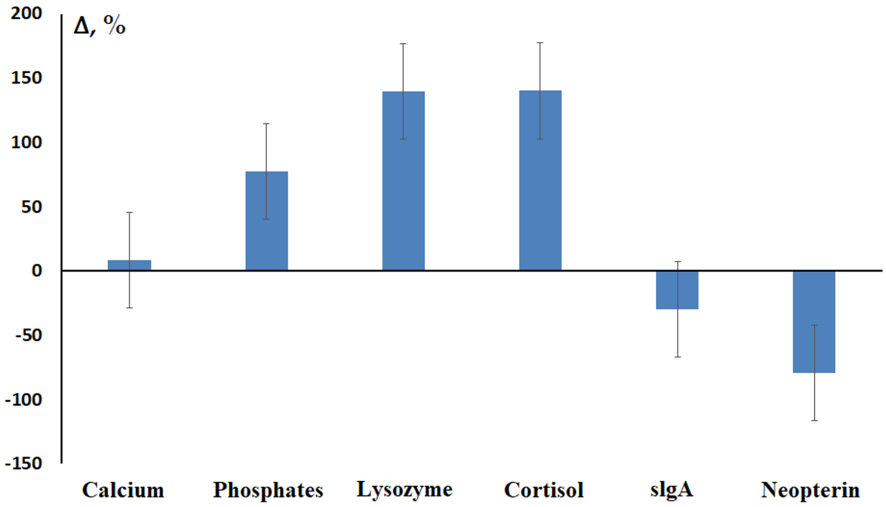


**Figure 5.** Relative content of calcium, phosphates, lysozyme, cortisol, neopterin, and sIgA in saliva in osteoporosis compared to the control group. The figure was prepared using data from [119].

Lactate dehydrogenase activity was the highest in patients taking statins (221.0±40.9 IU/l compared to the control 44.9±25.0 IU/l), thus indicating activation of anaerobic bacteria in the oral cavity. The highest alkaline phosphatase activity was determined in patients taking β-blockers (63.0±27.9 IU/l compared to the control 26.3±15.0 IU/l), the lowest was in patients taking calcium channel blockers (12.10±0.96 IU/l).

## CONCLUSIONS

The study of saliva composition attracts widespread attention from researchers, and the number of studies in this area is growing. However, the influence of individual factors on saliva composition has still been insufficiently studied. Available literature data are fragmentary and often contradictory. All authors agree that the influence of the considered here factors on saliva composition is associated with dysfunction of the salivary glands, changes in salivation rate, saliva viscosity, dry mouth (xerostomia), pH balance, and electrolyte composition, leading to impairments of homeostasis throughout the oral cavity. Furthermore, these factors lead to generalized alterations in the oral microbiome, lipid profile, and amino acid levels in saliva. Systemic and inflammatory diseases increase the levels of cytokines and tumor markers in saliva. Therefore, conducting studies of human saliva and properly analyzing the obtained biochemical data, it is ultimately important to consider all possible factors leading to changes in its composition.

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## COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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# ФАКТОРЫ ВАРИАБЕЛЬНОСТИ СОСТАВА СМЕШАННОЙ СЛЮНЫ (ОБЗОР ЛИТЕРАТУРЫ)

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Изучение состава слюны широко привлекает внимание исследователей, и количество работ в этом направлении растёт. Однако влияние отдельных факторов на состав слюны изучено недостаточно. Ограничение применения слюны как биологической жидкости для клинической лабораторной диагностики может быть связано с тем, что нет стандартизированных методик преаналитического этапа, а также с отсутствием референсных значений биохимических параметров с учётом ряда факторов, оказывающих воздействие на состав и свойства слюны. В настоящем обзоре представлен анализ литературных данных факторов, влияющих на состав слюны. Влияние факторов на состав слюны связывают с нарушением функций слюнных желёз, изменением скорости саливации, вязкости слюны, сухости во рту, баланса pH и электролитного состава, что приводит к нарушению гомеостаза всей полости рта.

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**Ключевые слова:** слюна; состав; биохимия; факторы; вариабельность

**Финансирование.** Работа не имела внешних источников финансирования.

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