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PHYSICOCHEMICAL INDICATORS OF DENTAL PATIENT SALIVA WHO HAVE UNDERGONE AN UNCOMPLICATED CORONAVIRUS INFECTION

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Abstract

Today, it has been proven that saliva is the main medium through which the new COVID-19 coronavirus infection spreads. Since the oral cavity is the gateway for the SARS-CoV-2 virus, the degree of change in the physicochemical parameters of the saliva of people who have had coronavirus infection compared to people who have not had COVID-19 is of interest.

This study involved dental patients of the first and second health groups with a history of chronic generalized periodontitis of moderate degree in the stage of remission. We studied physicochemical parameters of saliva such as pH, surface tension and base buffering capacity. The results of this stage of the study showed saliva acidification, that is a decrease in pH in people who had had a new coronavirus infection compared to the indicators of people from the control group. The average values of the surface tension of saliva in patients of the control group are 30% less than in those who have had COVID-19. This indicates that the saliva of people who have not been sick with the new coronavirus contains more surface-active agents (surfactants). Surfactants provide rinsing and disinfecting functions of saliva, therefore, it can be concluded that these functions are less pronounced in patients who have recovered from COVID-19. The base buffering capacity of the saliva of patients who have had COVID-19 is, on average, 35% higher than that of people from the control group. Thus, the pH and the base buffering capacity are in correlation: the lower the pH value, the higher the acidity of the saliva and the higher the base buffering capacity is.

At the second stage of the study, similar physicochemical parameters of patients' saliva were measured after the application of an oral spray containing a synthetic peptide (ZP2) of the active center of granulocyte-macrophage colony-stimulating factor. This spray was used as an antibacterial therapy for the oral cavity after professional hygiene of patients. In 5 minutes after spray irrigation, an increase in saliva pH was observed in all test subjects within the physiological norm. In patients, regardless of their anamnesis, the surface tension of saliva changed in different ways. In a number of people, it increased, which indicates an increase in the concentration of surfactants in saliva, while in others it decreased, which can be explained by the high rate of penetration of surfactants from saliva through the gums into the blood. After the application of the ZP-2 peptide, the base buffering capacity of saliva decreases or remains unchanged. In patients of the control group, the indicators of the base buffering capacity of saliva change less than in patients who have undergone COVID-19.

All the studied physicochemical parameters of saliva in patients who had had uncomplicated COVID-19, three months after receiving two negative results for the SARS-CoV-2 virus, remained within the physiological norm.

Keywords: *saliva, COVID-19, chronic periodontitis, surface tension, surfactants*

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INTRODUCTION

Today, the pathogenesis and clinical manifestations of a new coronavirus infection are of particular interest for both the scientific and medical communities, on a par with the consequences and complications caused by this disease. This is due to the ability of the virus to influence various systems of the body, causing a disturbance of their functional activity up to multiple organs indirectly, through pathological activation of the immune system, not directly [*Huang N et al., 2021*].

The development of modern industry and the latest scientific advances have made it possible in a fairly short time to produce express test systems, the action of which is based on the interaction of saliva with specific reagents [*Czumbel L et al., 2020*]. In this case, the choice is not accidental. Saliva is a biological fluid of the body, which biochemical indicators may indicate the state of the oral cavity and the body as a whole [*Vavilova T et al., 2014*]. In addition, saliva is one of the main routes of transmission of the COVID-19 virus [*Dave P et al., 2020; Silva J et al., 2021*]. It is already known that saliva analysis is as effective as a throat swab. This is due to the fact that a fairly high level of SARS-CoV-2 viral particles is found in saliva. It is still not fully known why high titers of viral particles are found in saliva. However, there are suggestions that this is due to the presence of cell populations in the salivary glands that have angiotensin-converting factor-2 and TMPRSS receptors on their surface. Replication of viral particles in epithelial cells and their subsequent excretion leads to high titers of SARS-CoV-2 in saliva [*Huang N et al., 2021*].

This disease affects all systems of the body to varying degrees [*Ghalechyan T et al., 2021; Sabahgoulian C, Manvelyan H, 2021; Wardhana M et al., 2021*]. The systems for maintaining homeostasis and the immune system, in particular, those working in the oral cavity, deserve special attention. This is due to the fact that the oral cavity is the gateway for this infection [*Starshinova A et al., 2020*]. The virus, penetrating through the mucous membranes, is able to invade cells while integrating a part of its genome into the cell genome, thereby initiating the replication of viral particles [*Makedonova Yu et al., 2021*].

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

Pathological processes occurring directly in the oral cavity, such as periodontitis, significantly reduce local immune reactivity, thereby facilitating the penetration of viral particles. The ability of the COVID-19 virus to penetrate is due to the action of angiotensin-converting factor-2, which is a kind of transporter for the virus into the host cell [*Shatunova P et al., 2020; Baghizadeh F, 2020; Brandini D et al., 2021*]. At the same time, the penetration of SARS-CoV-2 due to angiotensin-converting factor-2 leads to a decrease in inhibition of the metabolic pathway of angiotensin. This change can significantly affect the normal functioning of tissues. Changes in the normal tissue structure, as well as cell death due to their depletion, trigger immune mechanisms that contribute to the elimination of damaged and dead structures, as well as recognized foreign agents [*Mustafin R, 2020*]. Thus, the SARS-CoV-2 virus can suppress the production of type 1 interferon in the host body, thereby inhibiting the ability of the immune system to respond. These features lead to a pronounced lymphocytic reaction, the production of cytokines and chemokines, such as tumor necrosis factor, interleukin 6, 12 and some others. Along with the ineffectiveness of the immune response, this causes depletion of the immune system, massive death of lymphocytes and macrophages. Also, the COVID-19 virus can affect blood counts. The development of disseminated intravascular coagulation was noted in people who have undergone coronavirus infection. This is due to an increase in the level of active thromboplastin against the background of cytokine expression, activation of thrombin formation, and further development of hypercoagulability. The result of these changes is intravascular coagulation and multiple microthrombosis [*Preobrazhenskaya I, 2020*]. At the same time, the activity of various buffer and protective systems of saliva decreases. Changing the action of these systems leads to an increase in the risk of developing various dental diseases since opportunistic pathogens are activated and pathogenic microorganisms join [*La Rosa G et al., 2021*].

Currently, dental products containing synthetic peptides have become widespread [*Sarkisyan N et al., 2019a*]. The main feature of these drugs is that

the mechanism of action of the peptides is aimed at destroying the normal structure of the bacterial cell, that is, its lysis, which eliminates the risk of developing resistance in bacteria, in contrast to the usual antibiotics [*Ana Maria Carmona-Ribeiro, Letícia Dias de Melo Carrasco, 2014*]. This action is due to the ability of peptides to interact with cells due to electrostatic effects, as well as to integrate into the cell wall and form pores of various shapes. At the same time, synthetic peptides have almost no effect on the cells of the body, which minimizes their negative impact. Preparations based on synthetic peptides are used not only in the treatment of dental diseases of bacterial genesis but also in preventive measures since they can have a positive effect on tissue regeneration and are also capable of being active against viral particles and fungi [*Sarkisyan N et al., 2019b*]. Synthetic peptides also have significant effects on the immune system. Some peptides are attractants for cells of the immune system, thereby stimulating the production of cytokines, and also indirectly affect the migration of monocytes, T-cells and immature dendritic cells.

When the oral fluid interacts with various peptide-containing preparations, its physicochemical properties change, which, in turn, affects the well-being of the dentoalveolar system. We should pay particular attention to the effect on the pH values and buffering systems of saliva. Replication of viral particles by the salivary glands leads to the development of a local immune response, a decrease in the production of A and M immunoglobulins.

The study aimed to identify the degree of change in the physicochemical parameters of the saliva of people who have had a coronavirus infection, compared to people who did not have COVID-19. To assess the level of influence of the synthetic peptide ZP2 on the studied parameters of saliva.

Material and methods

The study involved the participation of 20 volunteers aged 20 to 40, who are dental patients of one of the private clinics in Yekaterinburg. All study participants underwent laboratory tests for COVID-19. Out of 20, 10 patients have had uncomplicated COVID-19 and were examined 3 months (± 2 weeks) after receiving two negative results for the SARS-CoV-2 virus. In the remaining 10 people, the control group, the disease was not laboratory confirmed. All study participants have a history of moderate chronic generalized periodontitis in remission and belong to 1-2 health groups. These patients underwent professional oral hygiene at the dental clinic with the following treatment of the oral cavity with a synthetic peptide of the active center of granulocyte macrophage colony-stimulating factor ZP2. This peptide has a broad effect both on the immune system and on the bacterial and viral flora [*Zurochka A et al., 2010*]. The GM-CSF ZP2 peptide has a stimulating effect on the activity of immunocompetent cells, including lymphocytes, stem cells, etc., and also blocks the growth and colonization of microflora; it has a significant effect on the activation of reparative processes in damaged tissues [*Gritsenko V et al., 2012; Dobrynina M et al., 2015*].

All study participants were sampled with mixed saliva before use of the GM-CSF ZP2 peptide and 5 minutes after use. The physicochemical parameters of saliva were determined: pH and base buffer capacity (B_b, *mmol eq/l*) – by the colorimetric method (color scale step 0.25 units), surface tension (σ, *erg/cm*^{2}) – based on the method of T.L. Redinova.

The research was carried out on the basis of the Department of General Chemistry, USMU, Yekaterinburg. Statistical data processing was carried out using the SPSS SigmaStat 3.0 software.

Results and discussion

The physicochemical parameters of the saliva of the study participants are shown in table 1. The pH of the mixed saliva of all patients ranges from 6.5 to 7.25, which corresponds to the physiological norm. Slight acidification of saliva can be noted in people who have had a new coronavirus infection compared to the indicators of people from the control group. Lowering the pH of saliva is due to the presence of acidic proton-containing substances in the oral fluid. Acids, which are proton donors, can be formed as a result of the vital activity of acid-fast bacteria, for example, staphylococcus and streptococcus.

The index of the surface tension of saliva is less than the surface tension of distilled water that is equal to 72.75 *erg/cm*^{2}, which indicates the presence of surface-active agents (surfactants) in the composition of the oral fluid. Surface-active properties are possessed by molecules of protein, glycosoaminoglycans, glycoproteins (including mucins), which provide wetting, cleansing and anti-

TABLE 1

Physicochemical parameters of SARS-CoV-2-infected (Inf) and non-infected (Non-inf) dental patient saliva

pH		**Surface tension (*erg/cm²*)**		**Base buffering capacity (B_b), *(mmol·eq/l)***	
Inf	Non-inf	Inf.	Non-inf	Inf.	Non-inf
6.75	6.75	57.9	57.2	5	5
7.25	6.5	52.3	52.3	5	5
7.25	7.0	57.1	59.1	5	1.25
6.5	7.25	60.0	57.1	2.5	1.0
6.75	7.0	58.7	52.7	2.5	2.5
6.5	7.0	58.2	56.9	2.5	1.25
6.75	6.75	56.2	55.0	1.7	1.7
6.75	6.75	52.3	53.3	5	1.7
6.5	7.0	56.2	57.1	2.5	2.5
7.0	7.25	54.0	53.2	5	1.7

Note: *Statistically significant differences between indicators ($p<0.05$)*

bacterial functions of mixed saliva. Normally, $\sigma_{of\ saliva}$ = 40-60 *erg/cm²*. As it can be seen from table 1, all indicators of the surface tension of saliva of previously COVID-infected people and those who have not had COVID-19 are within normal limits. The average value $\sigma_{of\ saliva}$ in patients of the control group is 30% less than in those who have had COVID-19, which indicates a higher concentration of surfactants in their saliva.

Buffer systems contained in saliva (protein, phosphate, hydrocarbonate) maintain the pH of the oral fluid in a constant numerical range from 5.8 to 7.6 [*Vavilova T et al., 2014*]. This is an important factor in keeping the teeth and gums healthy. Buffer systems contained in saliva (protein, phosphate, hydrocarbonate) maintain the pH of the oral fluid in a constant numerical range from 5.8 to 7.6 [*Vavilova T et al., 2014*]. This is an important factor in keeping your teeth and gums healthy. The base buffering capacity of saliva allows it to neutralize basic compounds and avoid a shift in pH to an alkaline medium. According to the data presented in table 1, it can be seen that the B_b of the saliva of patients who have had COVID-19 is, on average, 35% higher than that in people of the control group. This may be due to a higher concentration of proton-containing acids in the composition of the oral fluid because it is them that will neutralize the bases and provide the base buffering capacity of saliva.

At the second stage of the study, the physicochemical parameters of the patients' saliva were measured after the application of the GM-CSF ZP2 peptide (Tables 2 and 3). Previously, studies were carried out on the physicochemical parameters of a water solution of the ZP2 peptide in the composition of the spray [*Sarkisyan N et al., 2019c*], in addition, the effectiveness of this spray in the complex treatment of chronic generalized periodontitis was assessed [*Preobrazhenskaya I, 2020*].

Application of the synthetic peptide ZP2 after 5 minutes after irrigation led to a slight increase in saliva pH in all test subjects (Tables 2 and 3). Despite the fact that the ZP2 peptide forms acidic solutions with pH=6.56, the pH values of mixed saliva in all patients increased or remained unchanged. This can be explained by a shift in the equilibrium of dissociation of weak protolytic acids of saliva towards the molecular form and a decrease in the content of free hydrogen ions in the oral fluid. The less hydrogen cations in the solution, the higher the pH value. There were no significant differences in the effect of the GM-CSF ZP2 peptide on the saliva pH of patients from different study groups (Tables 2 and 3).

TABLE 2

Physicochemical parameters of saliva in patients who have not had COVID-19, before and after the application of the synthetic peptide GM-CSF ZP2

pH		**Surface tension, (*erg/cm²*)**		**Base buffering capacity, *(mmol·eq/l)***	
before	after	before	after	before	after
6.75	7.0	57.2	55.8	5	2.5
6.5	7.0	52.3	48.8	5	5
7.0	7.25	59.1	55.0	1.25	1.7
7.25	7.25	57.1	54.0	1.0	5
7.0	7.0	52.7	55.2	2.5	1.25
7.0	7.5	56.9	60.0	1.25	1.25
6.75	7.0	55.0	59.2	1.7	1.7
6.75	6.75	53.3	59.3	1.7	1.25
7.0	7.25	57.1	54.0	2.5	1.7
7.25	7.25	53.2	61.4	1.7	1.7

Note: *Statistically significant differences between indicators ($p<0.05$)*

TABLE 3

Physicochemical parameters of saliva in patients who have had COVID-19, before and after the use of the synthetic GM-CSF ZP2 peptide

pH		**Surface tension, (*erg/cm²*)**		**Base buffering capacity, (*mmol·eq/l*)**	
before	after	before	after	before	after
6.75	6.75	57.9	57.1	5	2.5
7.25	7.5	52.3	57.1	5	2.5
7.25	7.5	57.1	55.0	5	2.5
6.5	6.75	60.0	55.8	2.5	1.7
6.75	6.75	58.7	58.8	2.5	2.5
6.5	6.75	58.2	60.9	2.5	2.5
6.75	6.75	56.2	68.9	1.7	1.7
6.75	6.75	52.3	50.1	5	2.5
6.5	6.75	56.2	59.2	2.5	2.5
7.0	7.25	54.0	57.1	5	5

Note: *Statistically significant differences between indicators ($p<0.05$)*

The synthetic peptide in the spray is stabilized by a cationic surfactant and has surface activity ($\sigma_{\text{of spray}}$ = 48.7 *erg/cm²*); therefore, the expected result after mixing the ZP2 peptide with saliva was a decrease in its surface tension. But, in the course of the study, there was not only a decrease but also an increase in the surface tension of saliva in different patients after the application of the spray (Tables 2 and 3), such a trend in the change in the σ value can be traced in patients who have and have not had COVID -19. An increase in surface tension indicates a decrease in the content of surfactants in the oral fluid, which can be explained by the rapid rate of penetration of these substances from saliva through the gums into the blood.

After the application of the ZP-2 peptide, the base buffering capacity of saliva decreases or remains unchanged (Tables 2 and 3). This can be explained by the fact that the peptide of the basic nature neutralizes protolytic acids in the oral fluid, their quantitative content decreases and, as a consequence, the buffering capacity of saliva in relation to the bases decreases. It can be noted that in patients of the control group, who have not had coronavirus infection, the buffering properties of saliva are better pronounced, since, after the application of the synthetic peptide GM-CSF ZP2 peptide, the indicators of the base buffering capacity of saliva change significantly less than in patients who underwent COVID-19.

CONCLUSION

The studied physicochemical parameters of saliva in patients with a confirmed diagnosis (uncomplicated COVID-19), three months after receiving two negative results for the SARS-CoV-2 virus, remained within the physiological norm.

Compared with healthy patients of the control group, people who have had a new coronavirus infection during the study period showed the following differences in the indicators of mixed saliva: a decrease in pH value (that is, saliva acidification), a decrease in the amount of surfactants and a decrease in buffer properties in relation to bases.

The use of the synthetic peptide GM-CSF ZP2 as a prevention of the development of inflammatory periodontal diseases did not have a significant effect on the change in the physicochemical parameters of the mixed saliva of patients who have and have not had COVID-19.

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