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Morphological Changes in the Oral Mucous Membrane in Patients with COVID-19

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Abstract The objects of the study were 105 patients with Covid-19 disease. The aim of the study is to examine morphological changes in the oral mucosa and taste sensitivity in patients with COVID-19 with varying degrees of severity. COVID-19 is predisposing factors for oral lesion formation. Stress-induced oral ulcers may increase among patients due to pandemic-associated fear. The study determined morphological and taste changes in the oral cavity. Conclusions: lesions of the oral mucosa (oral manifestation) indicate the highest expression of ACE-2 receptors in the oral cavity, which requires special attention to the organization of therapeutic and preventive consultations by dentists for patients in order to actively treat diseases of the oral cavity and prevent oral-vascular diseases. pulmonary route of development of the COVID-19 virus.

Keywords COVID-19, Oral mucous membrane, Osseointegration, Microcirculation, Vacuum therapy

1. Relevance of the Problem

Today, COVID-19 is a very common disease worldwide. Coronavirus disease 2019 (COVID-19), caused by RNA coronavirus 2 severe acute respiratory syndrome (SARS-CoV-2), belonging to the beta-corona virus subfamily, is the most urgent, socio-economic public health problem that has acquired pandemic proportions. Up to date, a new strain of COVID-19 has been identified. Given the ongoing trend of strain modification, COVID-19 is an unprecedented, serious medical and social problem of all mankind, far from being solved. [2,3].

Today, it has been established that age over 65 years, male gender [4], cardiovascular disease [5], diabetes mellitus [6], obesity [7], chronic obstructive pulmonary bronchitis [8], smoking, lack of oral hygiene [9], neoplastic disease, liver disease, opportunistic infections, stress, immunosuppression, vasculitis, and COVID-19-induced hyperinflammatory response are predisposing factors for oral lesions in this category of patients. Stress-induced oral ulcers may increase among patients due to pandemic-associated fear. Also, older age and higher severity of COVID-19 disease is associated with severe oral disease [10-12].

At present, in the world practice, the most relevant questions remain regarding the complex diagnosis of clinical forms and courses of this disease based on determining the initial state of the oral mucosa in combination with the study of markers of the body's immune and inflammatory responses. Numerous scientific studies are ongoing to investigate the direct/indirectly proportional effect of baseline oral mucosal health on clinical disease, clinical outcome, and convalescence in SARS-CoV-2, as well as the association of baseline relative abundance of oral bacterial species with pro-inflammatory cytokine response and associations local immune response with the clinical course of the disease.

The mucosal immune system is the largest component of the entire immune system, which has evolved to provide protection at the main sites of infection: in the mucosa. Since COVID-19 primarily affects the upper respiratory tract, its first interactions with the immune system should occur predominantly on the mucosal surfaces of the respiratory tract during both the induction and effector phases of the response. However, almost all research on the immune response in COVID-19 has focused exclusively on serum antibodies and systemic cell-mediated immunity, including innate responses [2,5].

At the present stage of domestic healthcare development, large-scale work continues on social protection of the population and healthcare system reform. In the field of virology, in particular, in improving the timely diagnosis and detection of high-risk SARS-CoV-2 patients, and in the rehabilitation of patients after this virus transfer, positive results have been achieved. At the same time, in order to improve an immediate and long-term treatment results, as well as to prevent severe complications after the passing active phase of the disease, these patients require evidence-based studies to assess the comprehensive oral mucosa assessment state within the study of morphological changes in the oral cavity.

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PURPOSE OF THE WORK study of morphological changes in the oral mucosa and taste sensitivity in patients with COVID-19 with varying degrees of severity.

2. Materials and Research Methods

The study included 105 patients (total number of patients 254 patients) (62 men and 43 women) aged 18 to 55 years (mean age 41.6 ± 4.7 years), who were included in the study, since 149 patients were excluded by exclusion criteria - 3 patients were under 18 years of age, 7 patients were over 55 years, 15 patients were smokers, 30 were severely obese, 1 patient was pregnant, 87 patients had comorbidities, and 6 patients refused to provide consent to complete the questionnaire. All patients were positive in the polymerase chain reaction test for COVID-19.

The study design was a cross-sectional survey based on a questionnaire. This survey contains the following demographic data: gender, age, weight, height, educational level, and overall health. The questionnaire was divided into two parts:

1) The first part includes the oral hygiene assessment state results obtained by a group of dentists.
2) The second part contains data on the COVID-19 severity, which was obtained through a phone call.

All patients underwent a daily visual examination of the oral cavity, registration and clinical course assessment, temperature severity, symptoms of intoxication.

3. Study Results

On examination, changes were found in the oral mucosa in 91 patients (86.6%) (Table 1).

It should be noted that 13 (12.4%) patients had hemorrhagic manifestations on the buccal mucosa, while the anamnesis of this disease was not aggravated. In addition, there were petechial hemorrhages on the the lips and cheeks mucous membrane. Moreover, lips cyanosis was established in these patients. Color of the oral mucosa varied from the usual pale pink to cyanotic due to the appearance on the lips mucous membrane inner surface of different levels according to the vascular pattern severity.

Pigmentation in the gums attachment area to the upper and lower jaws occurred in 45 (42.8%) patients, while in 5 (4.7%) pigmentation was observed in the hard palate area. Also, lentigo - a brown spot caused by the accumulation of melanin, rising above the surface of the upper and lower lips mucous membrane, was detected in 13 (12.3%) patients.

Mycological culture analysis was performed in all cases and was positive in 6.6% of patients (n = 7). Other mucosal manifestations were aphthous stomatitis in 10.5% of patients (n = 11) and mucositis in 5.7% (n = 6). 8.5% of the patient (n = 7) complained of glossalgia, which is the appearance of tongue or the entire oral mucosa burning sensation.

In addition, the most common manifestation of a change in the tongue mucous membrane was pronounced angular cheilitis, consisting mouth corner inflammation, characterized by the formation of cracks, crusts and redness in the area of mouth mucous membrane in 26 (24.7%) patients.

Particular attention was paid to transient U-shaped papillitis detected in 15 patients (14.3%), while tongue edema was detected in 8 patients (7.6%). Tongue inflammatory disease, characterized by glossitis with focal depapilation, which was observed in 5 patients (4.7%).

Plaque on the tongue mucous membrane was detected in 90 patients (85.7%), the color of which varied from white to light cinnamon and brown. At the same time, the plaque was easily removed by scraping, papillae, uniform in severity, were also noted over the entire surface of the tongue.

Table 1. Oral mucosal changes in hospitalized COVID-19 patients (n=105)

Types of change	n (%)
Changes in the oral mucosa	91 (86,6)
Plaque of the tongue mucous membrane	90 (85,7)
Parageusia	64 (60,9)
Pigmentation in the gums attachment area to the upper and lower jaw	45 (42,8)
Angular cheilitis	26 (24,7)
U-shaped papillitis	15 (14,3)
Hemorrhagic manifestations on the buccal mucosa	13 (12,4)
Lentigo	13 (12,4)
Aphthous stomatitis	11 (10,5)
Glossalgia	7 (8,5)
Tongue swelling	8 (7,6)
Oral candidiasis	7 (6,6)
Mucositis	6 (5,7)
Hard palate pigmentation	5 (4,7)
Glossitis with focal depapilation	5 (4,7)
Dysfunction of the olfactory organ	
Parosmia	85 (81)
Anosmia	11 (10,5)

A perversion of taste sensitivity, the appearance of taste sensations in the absence of an appropriate stimulus - parageusia was determined in 60.9% of patients (n = 64), which is often accompanied by complaints of distorted perception of smells - parosmia in 81% of patients (n = 85) after 5 days of observation. In addition, 10.5% (n = 11) of patients had a lack of odor perception - anosmia.

According to the results of the questionnaire data on the initial state of the oral cavity, 84 (80%) patients had a severe severity of COVID-19, while a mild degree was found in 21 patients (20%) (Table 2).

Table 2. Impact of baseline oral health on COVID-19 severity (n=105)

Oral cavity baseline health		Severity COVID-19		*P*
		Severe degree	Mild degree	
Poor	n	62	1	<0,001
	%	73,8%	4,7%	
Satisfactory	n	17	17	
	%	20,2%	80,9%	
Good	n	5	3	
	%	5,9%	14,2%	
General indicator	n (%)	84 (80%)	21 (20%)	

Based on the primary endpoint analysis, severe COVID-19 showed a statistically significant association with poor oral hygiene (p<0.001). Accordingly, patients with good oral hygiene had a significantly lower incidence of severe COVID-19 disease (p<0.001, r=-0.457) (Table 3).

Table 3. Correlation between baseline oral health and COVID-19 severity (n=105)

Parameter		Severity of COVID-19
Oral health baseline	*r*	-0,457
	P	0,001
	n	105

Subgroup analysis for the COVID-19 severity showed that patients with baseline good, fair, and poor oral hygiene had a mild course in 79.4%, 17.4%, and 3.2% of cases in the first follow-up week, respectively. In patients with initial good, satisfactory, poor oral hygiene, a severe course occurred in 9.1%, 25.7%, 65.2% of cases in the first week observation, respectively (Figure 1).

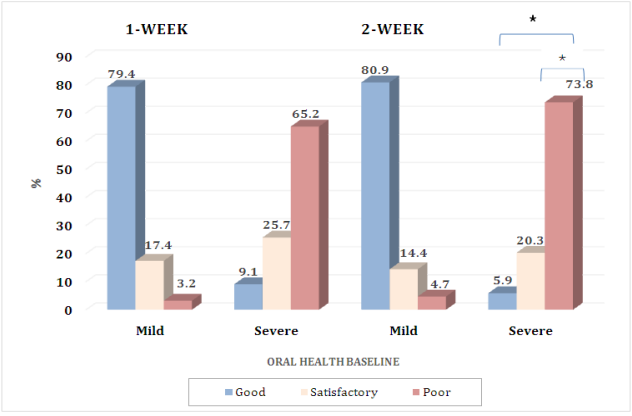

Figure 1. Explore the primary endpoint. Clinical course of the disease relationship with the initial state of oral health in the first and second weeks of observation (n=21 - a group with a mild course (20%); n=84 - a group with a severe course (80%). **p <0.001

In the second week of observation, in the group of patients who had an initial poor state oral hygiene worsened significantly in 73.8% of cases than in patients with a good initial oral hygiene state (5.9%) (p<0.001). Also, patients with an initial satisfactory oral hygiene suffered a worsening of the clinical course in the second week in 20.3% of cases, which is significantly lower than in patients with an initial poor oral hygiene state (p<0.001). Accordingly, in the second week of hospitalization, a mild course of the disease was observed in patients with good, fair and poor oral health in 80.9%, 14.4% and 4.7% of cases (Figure 1).

Clinical recovery at weeks 4 and 6 of clinical follow-up was significantly more frequent in COVID-19 patients with poor oral health at baseline (41.2% and 48.4%, respectively) compared with patients with good oral health at baseline (8.9% and 5.3%, respectively) (p<0.001). A speedy recovery period (at week 2 follow-up) was significantly more common in COVID-19 patients with baseline good oral health (85.8%) compared with baseline poor oral health (10.4%) (p < 0.001) (Figure 2).

Clinical recovery of patients with satisfactory oral health was observed up to two weeks of clinical follow-up in 56.8% of cases compared with four-week (33.4%) and six-week (9.8%) follow-ups of patients in this category (Figure 2).

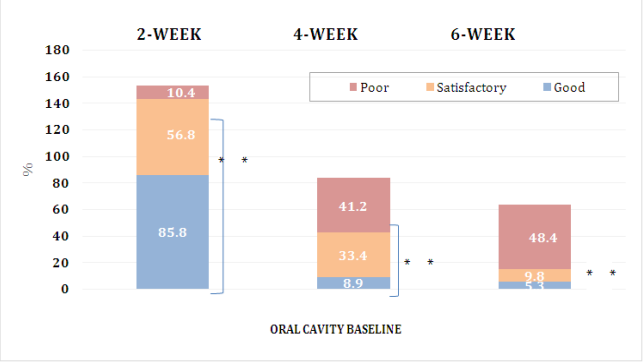

Figure 2. Exploring the secondary endpoint. Initial state of oral health relationship with the period of clinical recovery. ***p* <0,001

Table 4. Correlation between the initial state of the oral cavity and the period of clinical recovery (n=105)

Parameter		Clinical recovery period
Oral health baseline	*r*	-0,614
	P	0,001
	n	105

Table 5. Impact of COVID-19 Severity on Clinical Recovery Period (n=105)

The study secondary endpoint			COVID-19 severity		*P*
			Severe	Mild	
Clinical recovery period	6 weeks	n	42	2	<0,001
		%	50,0%	9,5%	
	4 weeks	n	35	4	
		%	41,6%	19,0%	
	2 weeks	n	7	15	
		%	8,3%	71,2%	
General indicator		n (%)	84 (80%)	21 (20%)	

It should be noted that a negative correlation was established between the initial state of oral health and the period of clinical recovery of patients with COVID-19

($p < 0.001$, $r = -0.614$) (Table 4).

Delay frequency in the clinical recovery period at the sixth week of clinical observation was significantly higher in the group of patients with severe COVID-19 (50.0%) compared with the group of patients with mild clinical course (9.5%) ($p<0.001$) (Table 5).

Clinical recovery at the second week of follow-up was 7 times more common in the group of COVID-19 patients with a clinical mild course (71.2%) compared with the group of patients with a severe course (8.3%) ($p<0.001$), when at the fourth week of observation in the group of COVID-19 patients with a clinical mild course, clinical recovery was established in 19.0% of cases, and in the group of patients with a severe course, this figure was 41.6% ($p<0.001$) (Table 5).

4. Conclusions

According to the analysis, a high level of damage to the oral mucosa was determined, which occurred in 91 patients (86.6%). It should be noted that 13 (12.4%) patients had hemorrhagic manifestations on the buccal mucosa, while the anamnesis of this disease was not aggravated. In addition, there were petechial hemorrhages on the lips and cheeks mucous membrane. Also, lips cyanosis was established in these patients. The color of the oral mucosa varied from the usual pale pink to cyanotic due to the lips inner surface mucous membrane appearance of different levels according to the vascular pattern severity. Pigmentation in the area of gums attachment to the upper and lower jaws occurred in 45 (42.8%) patients, while in 5 (4.7%) pigmentation was observed in the hard palate area. Also, lentigo - a brown spot caused by the accumulation of melanin, rising above the surface of the upper and lower lips mucous membrane, was detected in 13 (12.3%) patients. Mycological culture analysis was performed in all cases and was positive in 6.6% of patients (n = 7). Other mucosal manifestations were aphthous stomatitis in 10.5% of patients (n = 11) and mucositis in 5.7% (n = 6). 8.5% of the patient (n = 7) complained of glossalgia, which is the appearance of a burning sensation of the tongue or the entire oral mucosa. In addition, the most common change manifestation in the tongue mucous membrane was pronounced angular cheilitis, consisting in the mouth corners inflammation, characterized by cracks formation, crusts and redness of the mouth mucous membrane in 26 (24.7%) patients. Particular attention was paid to transient U-shaped papillitis detected in 15 patients (14.3%), while tongue edema was detected in 8 patients (7.6%). Inflammatory disease of the tongue, characterized by glossitis with focal depapilation, was observed in 5 patients (4.7%). Plaque of the mucous membrane of the tongue was detected in 90 patients (85.7%), the color of which varied from white to light cinnamon and brown. At the same time, the plaque was easily removed by scraping, papillae, uniform in severity, were also noted over the entire surface of the tongue.

A perversion of taste sensitivity, the appearance of taste sensations in the absence of an appropriate stimulus - parageusia was determined in 60.9% of patients (n = 64), which is often accompanied by complaints of distorted perception of smells - parosmia in 81% of patients (n = 85) after 5 days of observation. In addition, 10.5% (n = 11) of patients had a lack of odor perception - anosmia.

Thus, the above high level of manifestation in the form of oral mucosa lesion (oral manifestation) indicates the highest expression of ACE-2 receptors in the oral cavity, which requires special attention in the organization of treatment and preventive consultations by dentists for patients in order to actively treat oral cavity diseases, and oral-vascular-pulmonary route development prevention in the COVID-19 virus, as well as monitoring compliance with clinical guidelines developed by the European Federation of Periodontology [1].

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