BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 5

DOI: 10.58240/1829006X-2025.21.5-369

ORIGINAL RESEARCH

STUDY OF THE ORAL CAVITY AND DETERMINATION OF THE LEVEL OF PRO-INFLAMMATORY IL-2 AND ɤ-INF IN ORAL FLUID OF PATIENTS WITH VIRAL HEPATITIS C BEFORE AND AFTER COMPLEX TREATMENT

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Received: May 14 , 2025 ***Accepted***: Jun 27, 2025 ***Published***: Jun 30,2025

ABSTRACT

Background: Interest in the study of combined pathology in recent times is explained by the accumulation of new facts, the emergence of new information on interorgan, intertissue and intercellular levels of interaction in the system of the whole organism. In this regard, the issue of the relationship between diseases of internal organs and organs of the oral cavity is relevant

The **aim** of the study was to examine the condition of the oral cavity and the level of proinflammatory IL-2 and ɤ-INF in the oral fluid of patients with viral hepatitis C before and after complex treatment.

Material and methods: The study involved 96 patients with HCV with lesions of the oral mucosa and periodontium, as well as 100 patients of the control group without HCV. All patients had their dental status and index assessment of the periodontal tissue condition studied. Cytokines IL-2, ɤ-INF were determined in the oral fluid. All indicators were studied before and after complex treatment and compared with each other.

Results: Objective examination of the oral cavity of patients with HCV revealed the presence of a generalized inflammatory process in the alveolar part of the gums, as well as damage to the OM ($p<0.001$). In HCV, pro-inflammatory IL-2 significantly increases, and ɤ-INF increases, but not statistically significantly ($p>0.113$). After complex treatment, statistically significant improvements are observed in the OM and alveolar part of the gum ($p<0.001$). Pro-inflammatory IL-2 decreased ($p<0.001$), and ɤ-INF decreased, but statistical significance is not observed ($p>0.121$).

Conclusion: Thus, a comparative study of lesions of the OM and alveolar part of the gingiva before and after the complex treatment for HCV revealed that the main pathognomonic symptoms reliably undergo dynamics towards improvement and are detected with a lower frequency. When comparing the results of interleukin levels in the OF before and after HCV treatment, a decrease in the level of proinflammatory IL-2 is noted, the level of ɤ-INF also decreases (but the difference in the data is insignificant). Further studies are needed to better understand the level of IL-c in patients with HCV and its relationship with damage to the oral mucosa and periodontium.

Key Words: Periodontal tissues, oral mucosa, index PI and SBI, cytokines, HCV.

INTRODUCTION

Interest in the study of combined pathology in recent times is explained by the accumulation of new facts, the emergence of new information on interorgan, intertissue and intercellular levels of interaction in the system of the whole organism. In this regard, the issue of the relationship between diseases of internal organs and organs of the oral cavity is relevant [1-3].

The study of combined lesions of the skin, internal organs, oral mucosa, their connection with general pathology is necessary for the doctor to make a correct diagnosis. There is a relationship between most pathological processes occurring between the oral mucosa, the red border of the lips and various organs and systems of the body, therefore, it is the lesions of the oral mucosa that are often the first signs of metabolic disorders, as well as various general somatic diseases [4].

According to modern concepts, the development and progression of inflammatory periodontal diseases are considered not only as a local inflammation of the periodontal tissues caused by the microflora of the "dental plaque", but also as a reaction of the body to a bacterial infection. Almost all researchers recognize that the imbalance between bacterial invasion and local resistance of the oral cavity is the main factor determining the development and course of periodontal lesions [5-7].

Many authors point to the high frequency and diverse clinical picture of oral lesions in diseases of the gastrointestinal tract, particularly viral liver diseases [8-11]. As a result of diseases of the digestive organs, the functional activity of the salivary glands, the composition and properties of saliva change, which leads to a violation of the dynamic balance of de- and remineralization processes, the development and active course of the carious process. An increase in the content of mucin, C-reactive protein, a decrease in the activity of lysozyme in oral fluid have been established, which indicates a violation of the non-specific resistance of the immune system in diseases of the digestive organs [12, 13].

The last decades of the 20th century and the beginning of the 21st century were marked by a sharp increase in the number of viral liver diseases, especially parenteral viral hepatitis, characterized by a high chronicity of the course, the development of multiple complications and mortality, which determined the medical and social importance of the problem of viral hepatitis [14,15]. The 63rd World Health Assembly (2010) recognized viral hepatitis B and C (HBV and HCV) as one of the leading health problems in the world [16, 17]. Chronic HCV affects 71 million people worldwide. It is most common in the WHO Eastern Mediterranean Region and the WHO European Region, where the prevalence of hepatitis C virus infection was estimated at 2.3% and 1.5%, respectively, in 2015. In other WHO regions, HCV prevalence rates range from 0.5% to 1%. In some countries, high rates of HCV may be found in specific population groups. For example, 23% of new HCV infections and 33% of HCV-related deaths are associated with injecting drug use. However, national HCV programmes do not always cover injecting drug users and prisoners [17].

The pathogenetic commonality of many general somatic processes and inflammatory diseases of the oral cavity is due to the development of mechanisms of cellular damage and modification of tissue structures with the acquisition of autoantigenic properties by them, which are common to the entire organism. The leading role in the occurrence of these changes is played by failures and dysfunctions of the cytokine regulation of immunobiological processes. The basis for the chronicity of any inflammatory process is the relationship between the periodontal conditions with proinflammatory properties and anti-inflammatory activity. In this regard, an in-depth study of non-specific detoxifying systems of the oral cavity in patients with various somatic diseases is of undoubted interest to dentists in order to clarify the genesis of damage to inflammatory diseases of the oral cavity and the general pathogenetic mechanism as a whole [18].

As is known, saliva or SS (unstimulated mixed saliva) is of great importance in ensuring mucosal immunity of the oral cavity; it contains a large number of substances with antimicrobial action: lysozyme, lactoferrin, immunoglobulins, antimicrobial peptides and other active substances [19]. The immunoglobulins contained in saliva, especially sIgA, prevent the adhesion of microorganisms, lysozyme destroys the bacterial walls, and lactoferrin deprives bacteria of iron [20]. In addition, saliva contains complement components and cytokines. Saliva testing is a valuable noninvasive method for assessing the general condition of the body and, in particular, the oral cavity. Saliva collection is convenient and simple, it is painless, the risk of infection of medical personnel is significantly lower than when working with blood, and the content of some substances in saliva (e.g. hormones, antibodies, drugs, etc.) reflects their concentration in the blood [21]. Modern technologies for studying proteins in biological environments make it possible to determine the levels of various immune indicators and their biological activity in saliva and other secretions containing the proteins being studied in minimal concentrations [22].

It is known from literary sources that, depending on the severity and duration of the process, the quantitative indicators of all subsystems of local immunity change. But the data on immune reactivity are varied and contradictory, most likely, this is due to different methods and techniques for assessing immune reactivity, the presence of systemic pathology, and the type of reactions [23]. As noted above, the development of inflammatory diseases is determined by the state of cytokine regulation. Most of both pro- and anti-inflammatory cytokines (such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, TNF-α, ɤ-IFN) are present not only in the peripheral blood, but also in saliva [24]. The sources of their production are both lymphocytes and macrophages embedded in the epithelium of the mucous membranes, and epithelial cells of the mucous membranes and the salivary glands themselves. Another source of cytokines in saliva may be their transudation from the blood serum. However, many researchers have noted that the content of cytokines in saliva does not correlate with their level in the blood, which indirectly indicates their local synthesis [25, 26].

Thus, the data from the study will help to develop tactics for conducting preventive methods of diagnostics and prevention of periodontal lesions, which is the basis for drawing up an individual treatment plan and determining the sequence of treatment and preventive measures, saving significant material costs on the part of patients and time costs on the part of specialists.

The **aim** of the study was to examine the condition of the oral cavity and the level of proinflammatory IL-2 and ɤ-INF in the oral fluid of patients with viral hepatitis C before and after complex treatment.

2.MATERILAS AND METHODS

The study included 196 patients before complex treatment, who were divided into 2 groups: Group I patients of the main group with HCV n= 96, Group II persons of the control group n=100. In addition to the main disease, patients with HCV had oral cavity lesions. The age of patients ranged from 37 to 63 years, hospitalized in the infectious diseases clinic of the Mikaelyan Institute of Surgery, Yerevan State Medical University (Yerevan, Armenia) during the period 2023-2025. The control group included 100 individuals without HCV with periodontal tissue and oral mucosa lesions who applied to the Stomatology Scientific and Educational Clinical Center No.1 of Yerevan State Medical University during the same period. Their age ranged from 21 to 57 years. The final diagnosis of HCV was established based on the detection of hepatitis C virus RNA in the blood using the PCR method.The patients underwent traditional clinical and laboratory examination methods, including general blood and urine tests, biochemical blood tests: determination of total bilirubin and fractions, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), ɤ-glutamyl transferase (GGT), total protein and fractions, coagulogram.

All patients underwent an assessment of their dental status according to previously developed criteria, which included an assessment of the condition of the marginal and alveolar parts of the gum, as well as various parts of the OM before and after complex treatment. An index assessment of the condition of the periodontal tissues was also performed according to the periodontal index (PI) according to Russell [27], and the gingival sulcus bleeding index (SBI) according to Miihlemann and Son was determined [28] before and after complex treatment. In accordance with the purpose of our work, all the above-mentioned examination methods, including determination of the level of cytokines in the gastrointestinal tract, were carried out in 50 patients of the main group after complex treatment. All patients with HCV received etiotropic treatment with antiviral drugs [17]. In addition to etiotropic treatment, patients in the main and control groups (n=50, respectively) received dental treatment (oral cavity sanitation) and a probiotic. The introduction of probiotics into clinical practice is one of the breakthroughs in medicine in the fight against infection. All patients received “Brefovil” sachets (manufacturer Sacura Italy, S.R.L.; active ingredients: Saccharomyces boulardi 8 mld UFC and zinc 10 mg). The drug was used locally in the form of rinses, 2 sachets for 10 days.

Study of cytokines in oral fluid (OF): Cytokines of the OF were tested among 45 patients with HCV and 30 patients without HCV, who agreed to pass this test. The test material was unstimulated mixed saliva – OF, obtained without stimulation and collected with a sterile syringe into sterile Eppendorf tubes. Samples were frozen and stored at –20 °C. The samples after were thawed at room temperature, centrifuged at 5000 rpm in the cold. Mucin was precipitated using 6 units of Lydase per 1.0 ml of OF by our patented method (Patent RA No. 3295 A dated at May 16, 2019) [30]. The concentrations of cytokines IL-2 and γ-INF was determined by the method of solid-phase enzyme-linked immunosorbent assay (ELISA) using the Vector-Best test systems (Vector-Best JSC, Novosibirsk, Russia) and was registrated on a Statfax 303 Plus photometer (Awareness Technology, Inc. Palm City, FL 34990, USA)

Statistical analysis: Descriptive analysis (Mean ± SD for continuous and frequencies/proportion for categorical variables) were calculated for all variables of interest. Differences between two groups were evaluated using “chi-square” or “Fisher’s exact” tests for categorical variables and “Wilcoxon signed rank test” for continuous variables. Spearmen correlation was performed for

determination of relationships between continuous variables. P-value was considered significant at <0.05 and <0.001 for highly significant results. Analyses were conducted using Excel 2013 and R software software and program Vassar Stats to calculate Odds Ratio (OR) and 95% Confidence Intervals (CI).

RESULTS

The study included 96 patients with HCV, 61 men (63.5%) and 35 women (36.5%). The control group involved 100 subjects without HCV with lesions of OM and periodontium: 62 men (62.0%) and 38 women (38.0%). The average age in HCV patients group was 50,05 ± 13,29, and in the control group 37.99 ± 16.66.

Patient complaints and data from the clinical examination of the oral cavity were taken into account when examining the dental status, including: external examination of the lips and corners of the mouth, assessment of the state of various parts of the oral mucous and periodontium before complex treatment (Table 1). These results indicate that the **monolithic crowns** provide superior fracture strength performance compared to **bilayered crowns**, and the choice between **resin cement and glass ionomer cement** had no significant influence on the outcomes within each crown type (Table 5).

Table 1. Data from clinical examination of the oral mucosa and alveolar parts of the gums in patients with HCV and in control groups before complex treatment

Sign		Control group n=100		HCV n=96		p-value*
		absolute number	%	absolute number	%	
Disorders in the mucous membrane relief						
	Absent	97	97	10	10.4	
	Present	3	3	86	89.6	**<0.001**
Hemorrhages on the buccal mucosa and the hard palate		100	100	21	21.9	
	Absent	0	0	75	78.1	**<0.001**
	Present					
Telangiectasia on the buccal mucosa						
	Absent	100	100	31	32.3	
	Present	0	0	65	67.7	**<0.001**
Coated tongue	Absent	100	100	6	6.2	
	Present	0	0	90	93.8	**<0.001**
Hyperemia	Absent	99	99	77	80.2	
	Present	1	1	19	19.8	**<0.001**
Cyanosis	Absent	75	75	30	31.2	
	Present	25	25	66	68.8	**<0.001**
Bleeding	Absent	89	89	49	51	
	Present	11	11	47	49	**<0.001**

* p-value test result from the comparison between HCV and control group

According to the results of the examination of patients with HCV, disorders in the mucous membrane relief were detected in 89.6%, hemorrhages on the mucous membrane of the cheeks and hard palate were observed in 78.1%, telangiectasia was detected in 67.7% of patients, the presence of plaque on the surface of the tongue was detected in 93.8% of those examined with HCV (p<0.001). Hyperemia was observed in 19.8%, cyanosis - in 68.8%, bleeding gums were detected in 49% of those examined, which is statistically significant (p<0.001) compared to the control group. To assess the degree of periodontal damage in patients with HCV, the periodontal index (PI) according to Russel and the gingival sulcus bleeding index (SBI) according to Mühlemann and Son were determined before complex treatment (Table 2).

Table 2. Index assessment of the periodontal tissue condition in patients with HCV before complex treatment (mean± SD)

Sign	Control group	HCV	p-value*
PI, points	0.95±0.48*	4.51±0.64*	**<0.001**
SBI, points	1.68±1.66*	3.02±0.1*	**<0.001**

* p-value test result from the comparison between HCV and control group

The content of proinflammatory cytokines - IL2, ɤ-INF and anti-inflammatory cytokines - IL4 and IL10 in the oral fluid of patients with HCV before complex treatment was studied (Table 3).

Table 3. Oral fluid cytokines levels in the control group and in patients with HCV before complex treatment (mean ± SD)

Cytokines	Control group (n=30)	HCV (n=45)	Odds Ratio	95% CI	p value*
IL2	2.83±5.67	25.99±17.86	-23.17±2.86	[-28.89; -17.44]	**<0.001**
ɤ-INF	0.72±3.04	2.46 ±6.52	-1.74±1.12	[-3.98; 0.49]	>0.113

* p-value test result from the comparison between control and HCV groups

A comparative analysis of OF cytokine indices in HCV and in the control group revealed that the amount of pro-inflammatory IL-2 in HCV increases by 9.2 times ($p<0.001$), and the increase in ɤ-INF is statistically insignificant ($p>0.113$).Local treatment of the oral cavity was carried out against the background of etiotropic (antiviral) treatment of HCV according to the accepted protocol. In order to correct the disturbances of the microbiocenosis in the oral cavity, the probiotic "Brefovil" was used - 2 sachets per day for 10 days. Then an examination of the oral cavity was carried out, as well as determination of the final indicators of periodontal indices. The same level of IL in the OF was determined.The examination data of the OM and alveolar part of the gum after complex treatment in patients with HCV are presented in Table 4.

Table 4. Data from clinical examination of the oral mucosa and alveolar parts of the gums in patients with HCV before and after complex treatment

Sign		Before n=50		After n=50		p-value*
		absolute number	%	absolute number	%	
Disorders in the mucous membrane relief						
	Absent	8	16	27	54	
	Present	42	84	23	56	**<0.001**
Hemorrhages on the buccal mucosa and the hard palate						
	Absent					
	Present	10	20	28	56	
		40	80	22	44	**<0.001**
Telangiectasia on the buccal mucosa						
	Absent	16	32	32	64	
	Present	34	68	18	36	**<0.001**
Coated tongue	Absent	3	6	26	52	
	Present	47	94	24	48	**<0.001**
Hyperemia	Absent	40	80	44	88	
	Present	10	20	6	12	>0.18
Cyanosis	Absent	11	22	29	58	
	Present	39	78	21	42	**<0.001**
Bleeding	Absent	27	54	38	76	
	Present	23	46	12	24	**<0.001**

* p-value test result from the comparison between before and after complex treatment

In an objective study of the OM and periodontium in HCV, positive changes after complex treatment are obvious. Thus, after treatment, disorders in the mucous membrane relief - 1.5 times, hemorrhages on the mucous membrane of the cheeks and hard palate - 1.8 times and telangiectasia - 1.9 times less often than before treatment.

The difference between all these indicators before and after treatment was highly statistically significant ($p<0.001$). After treatment, the same patterns were observed in the study of the tongue. Thus, plaque on the surface of the tongue was detected almost 2 times less often ($p<0.001$). Of the symptoms indicating the presence of a generalized inflammatory process in the alveolar part of the gum, the following significantly changed after treatment: cyanosis ($p<0.001$) and bleeding ($p<0.02$). The detection of both symptoms decreased almost 2 times. The difference in the detection of hyperemia was statistically insignificant ($p>0.18$).

In patients with HCV, the periodontal index values differed statistically significantly before and after the complex treatment (Table 5).

Table 5. Index assessment of the periodontal tissue condition in patients with HCV before and after complex treatment (mean± SD)

Sign	Before treatment	After Treatment	p-value*
PI, points	4.25±0.78*	2.54±0.49*	**<0.001**
SBI, points	2.82±0.09*	1.74±0.31*	**<0.001**

* p-value test result from the comparison between before and after complex treatment

The PI and SBI index values decreased by more than 1.5 times with a high degree of reliability (p<0.001).

Studies of OF cytokines after the complex treatment for HCV showed that the content of pro-inflammatory IL-2 decreased almost 5 times (p<0.001), and the level of ɤ-INF decreased, however, the difference in data before and after treatment is statistically insignificant (p>0.121) (Table 6).

Table 6. Oral fluid cytokine levels in patients with HCV patients before and after complex treatment (mean ± SD)

Cytokines	Before treatment (n=45)	After treatment (n=45)	Odds Ratio	95% CI	p value*
IL2	25.99±17.86	4.98±11.76	21.01±3.19	[14.66; 27.36]	**<0.001**
ɤ-INF	2.46±6.52	1.58 ±6.89	0.89±1.41	[-1.93; 3.7]	>0.121

* p-value test result from the comparison between control and HCV groups

DISCUSSION

There is practically no pathology that would not affect the condition of the oral mucosa (OM). At the same time, the similarity of clinical manifestations in the oral cavity of diseases of different etiology and pathogenesis contributes to difficulties in making a final diagnosis [4, 31]. Most researchers consider the periodontium as an integral part of the whole organism and recognize the close pathogenetic connection between periodontal diseases and somatic pathology. Patients with periodontitis who have concomitant and background diseases require special attention, both in the diagnosis of combined pathology and in treatment and prevention [32]. Lesions of the OM and periodontium aggravate the course of the disease and serve as an important addition to the characteristics of the general clinical picture of HCV [33-35]. Viral liver lesions occupy an important place in the assessment of the state of dental health of patients [36]. At the same time, dentists and doctors of other specialties do not pay due attention to the state of the oral cavity in liver diseases [37]. The experience of a dentist working in infectious disease departments has shown that the effectiveness of diagnosis and treatment of OM lesions depends on the earliest possible examination of the admitted patient [38].

In a comparative study of the criteria we selected that characterize the state of various OM sections in HCV with the data of the control group, it was established that in the latter (except for isolated cases) OM lesions are practically not encountered. According to the results of our studies, pathognomonic symptoms of OM and periodontal lesions in HCV were reliably established [39,40].

Analyzing the frequency of occurrence of symptoms of lesions of the OM, it was found that in HVC, the leading positions with a high degree of reliability are occupied by two leading pathognomonic symptoms (disorders in the mucous membrane relief, the presence of plaque on the surface of the tongue) with fluctuations from 75.6% to 100% of cases. As for hemorrhages on the mucous membrane of the cheeks and hard palate, they are characteristic only of HCV. Foci of epithelial desquamation on the surface of the tongue and, especially, telangiectasia on the mucous membrane of the cheeks are more often detected in HCV [41].

The data on the condition of the marginal and alveolar parts of the gum in patients with HCV are of interest. As noted, only cyanosis is reliably more often established with HCV. It is appropriate to note that according to Fedeli U. et al. (2017), who studied the features of damage to the OM and periodontium in patients with chronic liver diseases of viral etiology, with chronic hepatitis and cirrhosis of the liver caused by the hepatitis B virus, more severe dystrophic and inflammatory changes are observed in the OM and periodontal tissues compared to those caused by the HCV [42]. Our data indicate that it is probably difficult to make a definitive conclusion regarding the

comparison of the severity of OM and periodontal damage in HCV, since some symptoms were detected significantly more often, while others had an insignificant statistical difference.

There are few works in the available literature that have studied and systematized the symptoms of damage to the OM and periodontium in HCV, especially in the early manifestations of the disease. The reliability of the frequency of occurrence of one or another symptom of the lesion has not been studied either. Some authors even point to the contradictory nature of the data indicating the connection between OM lesions and viral hepatitis [41]. In our opinion, these findings are related to the incorrectness of the research. Thus, Nagao Y. et al. (2014) studied the nature of OM lesions in patients suffering from chronic hepatitis (HBV - 20, HCV - 23 patients) and liver cirrhosis caused by HBV infection (15 patients) and HCV (16 patients). Presenting data on a small number of cases of OM damage using descriptive analysis, the authors came to the conclusion that there is no connection between chronic HBV and HCV, as well as the stage of the disease with the frequency and nature of OM damage [32]. Given the small number of patients and the lack of proper statistical analysis, one has to doubt the reliability of the authors' conclusions.

There are isolated works that describe individual, few signs in a small number of patients. No comparative analysis of data on the above signs in patients with viral hepatitis C has been conducted. In our opinion, this is important, since both patient management protocols and treatment regimens differ. It should be noted that the literature provides reviews on this problem, which describe in detail the epidemiological data and pathophysiological mechanisms of extrahepatic lesions in viral hepatitis [43-45]. However, there are few original studies in this area. We will try to discuss and compare those individual works that were found in the available literature.

Hepatitis C virus is a sialotropic virus. HCV-infected patients may often have features of Sjogren's syndrome such as sialoadenitis with mild or even absent clinical symptoms. The role of HCV in the pathogenesis of Sjogren's syndrome has not been fully studied. However, in 57% of cases of chronic liver diseases associated with HCV, histological changes in the salivary glands characteristic of Sjogren's syndrome were detected [46]. We did not set such a task for ourselves and therefore cannot conduct a comparative analysis of the obtained results.

The basis of the inflammatory process of any etiology is the launch of the cytokine cascade, which includes, on the one hand, proinflammatory cytokines, and on the other, anti-inflammatory mediators. The balance between the two opposing groups largely determines the nature of the course and outcome of the disease [26]. The main problem is the lack of accessible laboratory diagnostic methods that would clearly reflect the shift in the cytokine balance towards inflammatory or anti-inflammatory/immunosuppressive reactions. Given the multiplicity, as well as the synergism and pleiotropy of the cytokines involved in these reactions, it is clear that determining the concentration of any one of them in the blood will not adequately reflect the state of the entire cytokine balance. Perhaps only a one-time assessment of the level of several mediators (at least 2-3 of the opposing subgroups) may be more correct.

In connection with the above, we consider it appropriate to discuss some methodological aspects of our work in studying cytokines. The latter can come from the blood serum as a result of their transudation, but the content of cytokines in saliva does not correlate with their level in the blood, which indirectly indicates the prevalence of their local synthesis [25, 26]. Taking into account the recommendations of the literature, we studied the content of proinflammatory - interleukin 2 (IL-2), ɤ-interferon (ɤ-INF) in the oral fluid (OF), which is more accessible and non-invasive. As for age, it is clear that the average age of patients in the main group significantly differs (with HCV - 50.33 years) from the average age of the control group (26.93 years). This is explained by the fact that it was almost impossible to select patients in the control group in the age category from 40 to 50 years, who would not have any changes in the oral cavity. Patients in the main and control groups are not comparable in age, however, in our opinion, this is acceptable, since according to the literature, the composition of saliva undergoes changes with age only in older people [47,48]. According to WHO data, old age is from 60 to 75 years [49]. It was found that age in the groups we studied does not affect the level of OF cytokines [30,50].

There are a sufficient number of works in the literature devoted to the study of the content and ratio of pro- and anti-inflammatory cytokines in oral fluid in various pathologies [51-53]. However, it should be noted that the available data are very contradictory. This also applies to the data of the control groups, which creates certain difficulties in terms of a clear understanding of the normal cytokine levels in the oral fluid. There are isolated works in the literature devoted to the study of this issue in viral hepatitis C, but there are no works on the one-time study of proinflammatory (IL-2, ɤ-INF) in the same group of patients.

Given the high variability of the normal cytokine levels in the OF, we found it interesting to analyze the available literature data on the cytokines identified in our study. According to various authors, the IL-2 content in the OF in healthy individuals ranges from 0.1 ± 0.02 pg/ml to 10.0 (8.5; 28.5) [54, 55], ɤ-INF from 18.35 ± 0.47 to 23.8 ± 1.5 pg/ml [56]. Our data on IL-2 levels in the control

group coincide with the literature data, but there are discrepancies in ɣ-INF levels, which once again proves the high variability of the normal cytokine levels in the OF.

Polushina L.G. et al. (2017) determined the clinical and pathogenetic significance of some cytokines in periodontitis. According to their data, in patients with periodontitis, the concentration of IL-2 increased by 31.1% ($p<0.05$). In the same patients, a significant increase in the level of IL-4 by 26 times was observed ($p<0.001$). This gives grounds to assume that the cytokine balance in periodontitis is characterized by the predominance of Th2-produced factors, i.e. activation of anti-inflammatory immune-mediated mechanisms. The authors note that the obtained data correspond to the idea that the development of chronic periodontitis is accompanied by a violation of local immune mechanisms. This is manifested by an imbalance in cytokine production, primarily by the activation of IL-4 production. It can be assumed that this cytokine realizes its pathogenetic (immune-mediated tissue destruction) and protective (stimulation of antimicrobial immunity) effects in periodontitis. Their ratio most likely determines the rate of progression and development of complications of the disease [55].

There are a number of works in the literature devoted to the development of periodontitis in viral hepatitis [32, 53, 57-60]. However, there are practically no works on the study of cytokines in the GC in HCV. Therefore, the results of our studies partly coincide, and in some cases diverge from the literature data.

Thus, it has been proven that in patients with chronic hepatitis C, the course of periodontitis is characterized by more frequent and prolonged exacerbations with a shorter period of remission in comparison with the group of patients without background hepatitis. This is due to the development of periodontitis in patients with chronic hepatitis C against the background of endogenous intoxication, activation of lipid peroxidation processes and a decrease in enzymatic and non-enzymatic antioxidant potentials, caused primarily by chronic hepatitis. The author found that an increase in microbial contamination and activation of proinflammatory cytokines in periodontal pockets play a major role in the formation of a local inflammatory reaction in periodontitis against the background of chronic hepatitis C, and the degree of shifts in laboratory parameters significantly correlates with the severity of periodontitis [61,32].

A comparative study of OM lesions before and after treatment clearly shows that symptoms such as cracks in the corners of the mouth, disorders in the mucous membrane relief, and tongue plaque, which are common in viral hepatitis C, undergo almost identical reverse dynamics with a high degree of reliability ($p<0.001$) after complex treatment. Similarly, the indicators for the presence of hemorrhages on the mucous membrane of the cheeks and hard palate improve in viral hepatitis C. Desquamation of the epithelium on the tongue surface, on the contrary, is more often detected in HCV with reliable dynamics towards reverse development after complex treatment. As for telangiectasias, the latter is a pathognomonic symptom of HCV, undergoing reliable reverse dynamics after treatment.

When studying the dynamics of changes in the main criteria for damage to the marginal and alveolar part of the gum before and after treatment, it was found that with viral hepatitis C, only some symptoms with varying degrees of reliability undergo reverse dynamics.

We also studied the content of cytokines in oral fluid after treatment. When comparing the results for viral hepatitis C, the following pattern is observed: a decrease in the level of proinflammatory IL-2. When comparing the results of these indicators before and after treatment, the difference in data is highly reliable. The level of ɣ-INF also decreases, but the difference in data is unreliable.

The problem of liver diseases of viral etiology is still extremely relevant due to their wide distribution. The global coverage of territories and the high epidemic potential of this group of diseases maintain their social and economic significance. Pathologies caused by HCV are most often found in young, working-age individuals, leading to disability and fairly high mortality. Thus, the study of the state of the OM and periodontium in viral hepatitis C, the features of the cytokine profile of the RG and their comparative assessment before and after treatment is very relevant, in connection with which our study was conducted.

4.CONCLUSION

Thus, a comparative study of lesions of the OM and alveolar part of the gingiva before and after the complex treatment for HCV revealed that the main pathognomonic symptoms reliably undergo dynamics towards improvement and are detected with a lower frequency. When comparing the results of interleukin levels in the OF before and after HCV treatment, a decrease in the level of proinflammatory IL-2 is noted, the level of ɣ-INF also decreases (but the difference in the data is insignificant). Further studies are needed to better understand the level of IL-c in patients with HCV and its relationship with damage to the oral mucosa and periodontium.

DECLARATIONS

No funding was received from any financially supporting body, and there was no associated grant number. No funder was involved in manuscript writing, editing approval, or decision to publish.

Consent for publication

Informed consent was obtained from every participant for documentation and examination.

Competing interests

The authors declare no competing interests.

Ethical approval

Ethical approval was granted by the Institutional Human Ethical Committee

Informed patient consent

All patients' clinical records were obtained with informed consent.

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