DENTISTRY

FUNCTIONAL ACTIVITY OF THE ORAL ENDOTHELIUM IN PERSONS WITH CHRONIC PERIODONTITIS DURING TREATMENT WITH PLASMOLIFTING

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ABSTRACT

Chronic periodontitis as an osteoimmune disease of the oral cavity is accompanied by a change in the functional activity of endotheliocytes. Moreover, abnormal vascularization exacerbates periodontal inflammation, as it promotes the transmigration of a larger number of immunocompetent cells, the influx of inflammatory mediators and cytokines.

The aim of our work *was to study the functional activity of the endothelium of the vessels of the oral cavity in persons suffering from chronic periodontitis in the treatment of plasmolifting.*

Materials and methods. *Under observation were 30 patients diagnosed with chronic generalized periodontitis of moderate severity at the age of 35 (32.50; 40.00) years, with no severe somatic pathology (main group). The comparison group included 20 people aged 38 (34.00; 45.00) years with no inflammatory diseases in the oral cavity. All patients underwent local anti-inflammatory therapy and sanitation of periodontal pockets, correction of occlusal contacts, curettage, plasma lifting. Oral fluid concentration of soluble adhesion molecules ICAM-1 and VCAM-1, endothelin-1, qualitative and quantitative composition of microflora were determined.*

Results. *After the treatment with plasmolifting, a noticeable relief of the activity of the inflammatory process was observed. In patients with chronic periodontitis, Porphyromonas gingivalis was found in 100 % of cases in a titer of 5.73 (4.9; 6.7) lg (gEq/sample), in 62.5 % – Prevotella intermedia in a titer of 4.5 (3.0; 5.5) lg (gEq/sample). Against the background of therapy, decrease of the occurrence of the microorganism and of the number of microorganisms was observed. The concentration of the soluble form of VCAM-1 in the oral fluid of patients with chronic periodontitis exceeded the values of the control group by 38.3 times (p = 0.000001), and ICAM-1 – by 18.1 times (p = 0.00001). Against the background of plasmolifting therapy, the level of the studied substances decreased, but exceeded the control values by 25.2 and 6.4 times, respectively. The content of endothelin in the oral fluid in patients with periodontitis exceeded the values of healthy individuals by 40.7 % (p = 0.003), during therapy its values decreased, but did not reach the level of healthy volunteers (p = 0.04).*

Key words: *endothelial dysfunction, chronic periodontitis, plasmolifting, cell adhesion molecules, endothelin-1*

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ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ ЭНДОТЕЛИЯ ПОЛОСТИ РТА У ЛИЦ, СТРАДАЮЩИХ ХРОНИЧЕСКИМ ПАРОДОНТИТОМ, ПРИ ЛЕЧЕНИИ МЕТОДОМ ПЛАЗМОЛИФТИНГА

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РЕЗЮМЕ

Хронический пародонтит как остеоиммунное заболевание полости рта сопровождается изменением функциональной активности эндотелиоцитов. Причём аномальная васкуляризация усугубляет воспаление пародонта, так как способствует трансмиграции большего количества иммунокомпетентных клеток, притоку медиаторов воспаления и цитокинов.

***Целью нашей работы** явилось изучение функциональной активности эндотелия сосудов полости рта у лиц, страдающих хроническим пародонтитом, при лечении методом плазмолифтинга.*

***Материалы и методы**. Под наблюдением находилось 30 пациентов с диагностированным хроническим генерализованным пародонтитом средней степени тяжести (15 мужчин и 15 женщин) в возрасте 35 (32,50; 40,00) лет, с отсутствующей тяжёлой соматической патологией (основная группа). В группу сравнения были включены 20 человек, сопоставимые с основной группой по полу и возрасту, с отсутствием воспалительных заболеваний в полости рта. Всем больным проводилась местная противовоспалительная терапия и санация пародонтальных карманов, коррекция окклюзионных контактов, кюретаж, плазмолифтинг. В ротовой жидкости определяли концентрацию растворимых молекул адгезии ICAM-1 и VCAM-1, эндотелин-1, качественный и количественный состав микрофлоры.*

***Результаты**. После проведённого лечения плазмолифтингом наблюдалось заметное купирование активности воспалительного процесса. У пациентов с хроническим пародонтитом в 100 % случаев обнаружена Porphyromonas gingivalis в титре 5,73 (4,9; 6,7) lg (ГЭ/образец), у 62,5 % – Prevotella intermedia в титре 4,5 (3,0; 5,5) lg (ГЭ/образец). На фоне терапии наблюдалось снижение как встречаемости микроорганизма, так и количества микроорганизмов. Концентрация растворимой формы VCAM-1 в ротовой жидкости больных хроническим пародонтитом превышала уровень контрольной группы в 38,3 раза ($p = 0,000001$), а ICAM-1 – в 18,1 раза ($p = 0,00001$). На фоне терапии плазмолифтингом концентрация изучаемых веществ снижалась, но превышала значения контроля в 25,2 и 6,4 раза соответственно. Содержание эндотелина в ротовой жидкости у больных пародонтитом увеличивалось на 40,7 % ($p = 0,003$), а на фоне терапии снижалось, но не достигало уровня здоровых добровольцев ($p = 0,04$).*

***Ключевые слова:** дисфункция эндотелия, хронический пародонтит, плазмолифтинг, молекулы клеточной адгезии, эндотелин-1*

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Chronic periodontitis is an osteoimmune oral disease affecting the periodontal apparatus, caused by a disruption of the symbiotic relationship between the oral flora and the immune system of the host, characterized by successive periods of exacerbation followed by periods of remission, causing progressive tooth destruction and loss [1].

Leukocytes recruited into the focus of inflammation cause the development of secondary alteration and modulate the functional activity of endotheliocytes [2, 3].

The physiological function of the vascular endothelium is the dynamic secretion of thrombotic substances, anticoagulants and fibrinolysis factors, vasoactive substances, growth factors, etc., as well as leukocyte chemoattractants, inflammatory cell adhesion molecules, cytokines and reactive oxygen species [4, 5].

Periodontal disease begins with the invasion of oral bacteria into the gingival tissue. Bacterial peptidoglycans in oral biofilms, lipoteichoic acid, and lipopolysaccharides penetrate into deeper tissues due to both a number of destructive proteases of microbial origin and oral cells destroying the epithelial surface and periodontal ligament. These enzymes contribute to deepening of the periodontal pocket and damage to the endothelium of the subepithelial vascular network [6].

For example, *Porphyromonas gingivalis*, by binding to endothelial cells, increases gene expression of various chemokines (e. g., CXCL8, CCL2), adhesion molecules (CD54, CD62E, PECAM-1), ICAM-1/CD54, VCAM-1/CD106, and activates the kallikrein-kinin system [7, 8].

Increased vascularization with neoangiogenesis in healthy tissues gives an advantage in pathogen elimination. However, in presence of chronic periodontitis, abnormal vascularization is likely to exacerbate periodontal inflammation as it promotes the transmigration of a larger number of immunocompetent cells, the influx of inflammatory mediators and cytokines.

Plasmolifting as a method of therapy for oral diseases was first used in 1997 [9]. The therapeutic effect of platelet-rich plasma injected into the area of dental papillae is primarily due to the degranulation of platelet α-granules containing b-thromboglobulin and platelet-nonspecific proteins (fibronectin, fibrinogen), blood clotting factors, fibrinolysin, immunoglobulins and synthesized growth factors [10].

The aim of our work was to assess the functional activity of the endothelium of the vessels of the oral cavity in persons with chronic periodontitis in the treatment of plasmolifting.

MATERIALS AND METHODS

The study was conducted from February 2021 to February 2022 on the basis of the Chita State Medical Academy of the Ministry of Health of Russia (Chita). Under observation were 30 patients (15 men and 15 women) diagnosed with chronic generalized periodontitis of moderate severity at the age of 35 (32.50; 40.00) years, with no severe somatic pathology (main group). The comparison group included 20 people, comparable to the main group by gender and age, with no inflammatory diseases in the oral cavity. All study participants signed a voluntary informed consent to participate in the study (Approval No. 107 of the Local Ethics Committee of the Chita State Medical Academy dated 27.01.2021).

The dental status of the subjects was assessed in accordance with the clinical recommendations (treatment protocols) approved by the Russian Dental Association (2013), as amended and supplemented [11] using standard methods: interview, examination, determination of index indicators of the state of hard dental tissues and periodontal tissues, and X-ray. All patients underwent local anti-inflammatory therapy and sanitation of periodontal pockets, correction of occlusal contacts, curettage, plasma lifting.

For plasmolifting, platelet-rich autoplasm was obtained: blood was collected into specialized Plasmolifting™ tubes, centrifuged at 1300 rpm for 10 min. The supernatant was injected with an insulin needle into the area of the dento-gingival papillae 0.1–0.2 ml and the area of the muco-gingival junction 0.3–0.5 ml. Each patient underwent the procedure 5 times: the first visit – injections were performed in two segments of the upper jaw (in the 1st and 2nd segments); the second – 3 days later in the lower jaw (in the 3rd and 4th segments); the third – after 7 days; the fourth – after 30 days and in the fifth visit, after 6 months, injections were performed in all four segments.

Oral fluid was collected from healthy human volunteers ($n = 20$) and patients with generalized moderate periodontitis ($n = 30$) after an overnight fast. The collected saliva was centrifuged at 400 g and 4 °C for 10 min to remove cells. The cell-free supernatant was then collected and centrifuged again at 1500 g and 4 °C for 20 min to remove the remaining cells and cellular detritus. Cell-free saliva samples were stored on ice until use. Saliva sampling in patients with chronic periodontitis was performed twice: before the therapy and after achieving remission of the disease.

The concentration of soluble adhesion molecules ICAM-1 and VCAM-1 was determined in oral fluid using Human Vascular Inflammation Panel 1 multiplex assay kits (Biolegend, USA). Endothelin-1 levels were performed by ELISA using the Endotelin kit (1–21) (Biomedica, Austria). Oral fluid was analyzed without dilution. All stages of the study were performed according to the instruction of the kits.

The qualitative and quantitative composition of oral fluid microflora was studied by PCR using the ParodontoScreen kit.

Non-parametric criteria were used in statistical analysis: the Mann-Whitney U test for comparing two independent subgroups, the Wilcoxon test for comparing dependent subgroups, the Spearman's rank correlation coefficient (R) for analysing the correlation between different indica-

tors. Descriptive statistics are represented by median and interquartile range (25th, 75th percentiles).

Statistical processing of the data was performed using the IBM SPSS software package. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The incidence of periodontal inflammatory diseases at outpatient appointments was more than 75 %, of which the prevalence of chronic periodontitis was 63.2 ± 2.5 % of cases. It occurred with equal frequency in individuals of both genders and different social statuses, but its prevalence increased with age.

As reported by the patients, the duration of the disease was 5.2 (4.2; 6.2) years. Oral hygiene was assessed using the OHI-S index. It was revealed that patients of the main group pay insufficient attention to oral hygiene: the index value at the initial examination was 3.02 (2.86; 3.30) points, against 0.38 (0.15; 0.51) in the comparison group. The index decreased after therapy but did not reach control values and was 1.40 (0.90; 1.90).

The results of the study of periodontal tissue condition of the subjects are presented in Table 1. Objective examination of patients with chronic periodontitis revealed gingival hyperemia and swelling, periodontal pockets and bleeding on probing, soft dental plaque and mineralized dental deposits. Tooth mobility in all included in the study was within the physiological range. Resorption of interalveolar septa up to 1/3 was determined radiologically in the main group. After the treatment with plasmolifting there was a noticeable relief of the activity of the inflammatory process, which was expressed in the reduction of PMA, bleeding index, gingival recession, depth of periodontal pocket.

Tannerella forsythia (2.9 (1.6; 4.1) lg (gEq/sample)) and *Treponema denticola* (3.0 (1.1; 4.0) lg (gEq/sample)) were most common in control group. The titre of these microorganisms was 4.73 (4.2; 5.1) and 4.26 (3.8; 5.2) lg (gEq/sample) among patients with chronic periodontitis. In addition, *Porphyromonas gingivalis* was detected in 100 % of cases at a titre of 5.73 (4.9; 6.7) and *Prevotella intermedia* was found in 62.5 % of patients at a titre of 4.5 (3.0; 5.5) lg (gEq/sample). Against the background of therapy, both a decrease in the occurrence and num-

TABLE 1

INDICATORS OF THE STUDY OF THE STATE OF THE ORAL CAVITY IN PATIENTS OF THE MAIN GROUP, ME (25th; 75th PERCENTILES)

Indicators	Control group (*n* = 20)	Patients with periodontitis (*n* = 30)	
		initial examination	after plasmolifting
Bleeding index	0.00 (0.00; 0.00)	2.30 (2.10; 2.80) $p_1 = 0.00001$	0.68 (0.62; 0.73) $p_1 = 0.0001$ $p_2 = 0.0001$
PMA	0.00 (0.00; 0.00)	40.6 (30.85; 50.00) $p_1 = 0.00001$	12.89 (10.21; 13.99) $p_1 = 0.00001$ $p_2 = 0.0001$
Gingival recession, mm	0.00 (0.00; 0.00)	1.39 (1.26; 1.53) $p_1 = 0.00001$	0.75 (0.63; 0.88) $p_1 = 0.00001$ $p_2 = 0.361$
Plaque index	0.00 (0.00; 0.00)	3.50 (1.98; 3.85) $p_1 = 0.00001$	2.42 (2.30; 2.50) $p_1 = 0.00001$ $p_2 = 0.0001$
Periodontal pocket depth, mm	2.00 (2.00; 3.00)	6.10 (4.40; 6.60) $p_1 = 0.00001$	3.7 (3.2; 4.2) $p_1 = 0.002$ $p_2 = 0.0001$

Note. p_1 – level of statistical significance of differences compared to the control group; p_2 – compared to the group of patients receiving plasmolifting.

ber of microorganisms was observed. For example, *Porphyromonas gingivalis* was found only in 30 % of the subjects, and its number decreased by 2.5 times ($p = 0.003$).

The level of soluble adhesion molecules and endothelin-1 was determined in order to confirm the involvement of vascular endothelium in the pathological process.

Cell adhesion molecules (CAMs) are cell surface proteins involved in the binding of cells to each other, to endothelial cells or to the extracellular matrix. VCAM-1 (CD106) is predominantly expressed on the membrane of endothelial cells. However, in case of severe or chronic inflammation it is also expressed on the surface of other cells including tissue macrophages, dendritic cells, bone marrow fibroblasts, myoblasts, oocytes, Kupffer cells, Sertoli cells and cancer cells [12]. This protein is a major regulator of leukocyte adhesion and transendothelial migration through interaction with α4β1 integrin [13].

Soluble intercellular adhesion molecule-1 (sICAM-1) is a circulating form of ICAM-1 that is constitutively expressed or induced on the cell surface of various tissues. It serves as a counter-receptor for lymphocyte function-associated antigen (LFA-1). The interaction between ICAM-1 present on endothelial cells promotes leukocyte adhesion and their migration across the endothelium, while its soluble form blocks this process [14].

Two mechanisms for the formation of soluble forms of adhesion molecules have been suggested: proteolytic cleavage of the molecule [15], which characterizes ICAM-1 expression on cells, and transcription of the matrix RNA encoding their formation [16].

We found a 38.3-fold increase in the concentration of the soluble form of VCAM-1 in oral fluid and an 18.1-fold increase was noted in the concentration of ICAM-1 (Table 2). Against the background of plasmolifting therapy, the level of the studied substances decreased, but exceeded the control values by 25.2 and 6.4 times, respectively.

High levels of soluble forms of adhesion molecules indicate an actively ongoing inflammatory process despite a clinically achievable state of remission.

The next stage of the work was to assess the level of developed endothelial dysfunction by endothelin-1 concentration. It is synthesized mainly by endotheliocytes in response to damaging stimuli and is immediately secreted into the external environment [17]. Endothelin-1 is classically considered a potent vasoconstrictor peptide. However, in addition to its effects on vascular smooth muscle cells, this substance is increasingly recognized as a pro-inflammatory cytokine. Endothelin-1 causes platelet aggregation and is involved in increased expression of leukocyte adhesion molecules, synthesis of inflammatory mediators, and mechanisms contributing to vascular dysfunction [18]. We found an increase of endothelin content in oral fluid among patients with periodontitis by 40.7 % ($p = 0.003$), a decrease in its concentration in treated patients to 16.55 % ($p = 0.04$).

The homeostatic dynamics of the oral cavity are constantly changing depending on the composition of the microflora. The oral dissemination of pathogens is hindered by the immune system, which, in addition to destroying pathogens, is responsible for repairing damaged tissues. Tissue alteration and vascular changes become the determining factors in the focus of the host-pathogen relationship. We have determined that even when clinical remission is achieved, an active inflammatory process continues in the periodontal tissues. This is confirmed by the presence of correlations. Thus, papillary-marginal-alveolar index has a high positive correlation with soluble form of ICAM-1 ($r = 0.764$), VCAM-1 ($r = 0.825$) and endothelin-1 ($r = 0.729$).

TABLE 2

THE LEVEL OF SOLUBLE FORMS OF INTERCELLULAR ADHESION MOLECULES IN PATIENTS WITH CHRONIC PERIODONTITIS, ME (25th; 75th PERCENTILES)

Parameters	Control group ($n = 20$)	Patients with periodontitis ($n = 30$)	
		initial examination	after plasmolifting
ICAM-1, pg/ml	0.99 (0.45; 1.34)	17.89 (14.99; 22.97) $p_1 = 0.000001$	6.34 (2.36; 10.82) $p_1 = 0.00001$ $p_2 = 0.01$
VCAM-1, pg/ml	0.30 (0.20; 0.40)	11.48 (8.99; 16.89) $p_1 = 0.000002$	7.56 (5.36; 9.54) $p_1 = 0.000001$ $p_2 = 0.000001$

Note. p_1 – level of statistical significance of differences compared to the control group; p_2 – compared to the group of patients receiving plasmolifting.

Autoplasm contains a large number of activated platelets, which, adhering to the exposed collagen of the damaged vessel, improve its barrier function, reduce thrombogenicity and enhance the growth of smooth muscle cells surrounding the endothelium [19]. All this leads to normalization of endotheliocyte function and is manifested by a decrease in the levels of both adhesion molecules and endothelin-1.

Based on the above, it can be concluded that the use of plasmolifting in chronic periodontitis is a pathogenetically justified method of therapy.

Thus, patients suffering from chronic periodontitis have increased levels of soluble forms of adhesion molecules and endothelin-1, which reflects the ongoing inflammatory process in periodontal tissues. In this case, the course of chronic periodontitis is accompanied by the development of endothelial dysfunction, manifested by an increase in the concentration of endothelin-1. The use of plasmolifting method leads to a decrease in the levels of adhesive and vasoactive molecules, reduction of bacterial load, and promotes clinical remission of the pathological process, which may be promising for further research in periodontology.

Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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