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DOI 10.25789/YMJ.2023.83.21

УДК 579.61; 616.31; 616.8-092

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ENDOTHELIAL DYSFUNCTION IN THE PATHOGENESIS OF INFLAMMATORY PERIODONTAL DISEASES

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Manifestations of endothelial dysfunction that occur in response to microbial invasion in inflammatory periodontal diseases may underlie the occurrence and progression of these diseases. The aim of the study was to determine the level of secretion of adhesive molecules of the selectin family and the superfamily of immunoglobulins in the gingival/periodontal pocket and their relationship with marker periodontal pathogens.

For the study, flushes of the gingival pocket (a total of 88 samples) of patients with chronic generalized periodontitis and intact periodontitis were obtained. The content of soluble forms of the adhesion molecules sICAM-1, sVCAM, sE-selectin, and sL-selectin was determined by ELISA. Marker periodontal pathogens were isolated by real-time PCR. The study revealed changes in the adhesiveness of molecules in individuals with chronic generalized periodontitis (CGP): the concentrations of sL-and sE-selectin molecules in the gingival/periodontal pocket discharge in patients with CGP increased by an average of 80,4% (p=0.045) and 63,6% (p=0,038), respectively. While the concentrations of adhesive proteins of the superfamily of immunoglobulins sICAM-1 and sVCAM in individuals with CGP exceeded the corresponding concentrations of the control group to a greater extent: 9,7 (p=0,022) and 18,1 (p=0,023) times, respectively. The frequency of detection of periodontal pathogenic bacteria genes was 96,4% in patients with CGP and 28,6% in the group with intact periodontitis. Statistically significant correlations of moderate and high degree were found between the content of sVCAM and T. forsythia (r=0,683, p=0,02) and A. actinomycetemcomitans (r=0,621, p=0,04), as well as sICAM-1 and P. gingivalis (r=0,628, p <0,001) and A. actinomycetemcomitans (r=0,821, p=0,04) in the group of patients with CGP. In the examined patients with intact periodontitis, weak negative correlation between sL-selectin and T. denticola was found (r=-0,482, p=0,03). Thus, elevated concentrations of the soluble adhesive molecules sICAM-1, sVCAM, sE-and sL-selectin may indicate endothelial cell alteration due to persistent inflammatory process caused by virulence factors of specific subgingival bacterial flora.

Keywords: chronic generalized periodontitis, periodontal pathogenic bacteria, inflammation, adhesion molecules, endothelial dysfunction.

Introduction. Pathogenetic aspects of the onset and progression of inflammatory periodontal diseases (IPD) include an imbalance in the microbiota of oral biotopes, as well as shifts in the immune response system: changes in the secretion of inflammatory markers - cytokines, antimicrobial peptides, acute phase proteins, and secretory immunoglobulins of the gingival fluid. The main bacteria involved in the development and progression of IPD, including chronic generalized periodontitis (CGP), include gram-negative anaerobic flora: *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola,* and *Prevotella intermedia* [3, 6, 8]. Being distinguished by high adhesive, invasive and toxic properties, these representatives of the bacterial community contribute to damage to the membranes of the cell walls of endotheliocytes, penetration into the vascular bed and toxigenic effect on the vascular endothelium. Manifestations of endothelial dysfunction that occur in chronic periodontitis, accompanied by a violation of its antiplatelet, anticoagulant, and fibrinolytic properties, may underlie the occurrence and progression of this disease [4].

Thus, the study of markers of endothelial dysfunction in the pathogenesis of chronic generalized periodontitis is of particular interest. A key role in changing the adhesive properties of the vascular wall is played by a complex system of membrane proteins expressed on the surface of endotheliocytes – intercellular adhesion molecules that include integrins, adhesive receptors of the immunoglobulin superfamily, selectins, cadherins, and homing receptors of leukocytes. Thus, the intercellular adhesion molecule-1 (sICAM-1), a member of the immunoglobulin superfamily and a functional ligand for the leukocyte integrin LFA-1 (Lymphocyte Function-Associated Antigen-1), is a marker that triggers inflammatory reactions and is expressed earlier and in a larger volume than HLA-DR. Studies have shown that the vascular endothelial adhesion molecule 1 (sVCAM), also a member of the immunoglobulin superfamily, is not permanently expressed on the endothelium, but can be synthesized in response to stimulation by bacterial lipopolysaccharides, TNF-α and IL-1 [2, 9], as well as IFN-γ and IL-4. The endothelial-leukocyte adhesion molecule-1 (sE-selectin) and the leukocyte adhesion molecule-1 to endothelial cells (sL-selectin) contribute to the formation of the first, not yet strong contacts of inactivated polymorphonuclear leukocytes with the endothelium at the sites of inflammation, mediate the initial interaction of leukocytes with endothelial cells, and the level of their expression on the endothelium is associated with inflammation [2, 4, 6].

The aim of the study was to determine the level of secretion of adhesive molecules of the selectin family and the superfamily of immunoglobulins in the gingival/periodontal pocket and their relationship with marker periodontal pathogens.

Materials and methods. A dental and clinical laboratory study was conducted on 88 people aged 18 to 45 years, who were undergoing outpatient treatment by a dentist on the basis of the dental polyclinic in Severodvinsk, Arkhangelsk region. The comprehensive study included the determination of dental status, immunological, as well as molecular genetic analysis and sociological research with questionnaires. The medical study was conducted in compliance with the rules of the international standard GCP and protocol approved by the local Ethics Committee of NSMU (Protocol No. 08/11 of 28.11.2018). Two groups were formed: the first group consisted of patients with a diagnosis of "chronic periodontitis" (n=56), including mild (n=32), moderate (n=24) severity of periodontitis in accordance with ICD 10: K05. 31-chronic generalized (mild, moderate) periodontitis; the second-the control group with intact periodontitis (n=32). The main criteria for inclusion in the groups were informed consent of patients, the age category of 18-45years, the presence of chronic periodontitis of mild and moderate severity and satisfactory oral hygiene. The criteria for exclusion from the study were: other inflammatory diseases in the oral cavity, pregnancy, and the postpartum period.

During the study, the discharge of the gingival/periodontal pocket (DGP/DPP) obtained by aspiration using a sterile syringe tube, then the resulting material was centrifuged at 1500 rpm with an exposure for 20 minutes. At the same time, samples of clinical material were frozen and stored at a temperature of -80˚C for further molecular genetic and immunological analyses.

Using an enzyme-linked immunosorbent assay (ELISA) the concentration of soluble forms of adhesion molecules sICAM-1, sVCAM, sE-selectin, and sL-selectin was determined in thawed samples separated by DGP/DPP sL- selectin in accordance with the manufacturer's instructions (Hycult Biotech, the Netherlands). The optical densities and contents of the tablet cells were studied and recorded on photometric device "Multiscan EX" (Thermo Fisher Scientific, USA). Calculations were carried out according to the manufacturer's instructions using calibration curves formed on the basis of measurement standards.

Marker periodontal pathogenic microorganisms were determined in real time using the method of polymerase chain reaction (RT-PCR). Periodontal pathogenic bacteria of the first order included: *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia,* periodontal pathogenic representatives of the second order- *Treponema denticola, Prevotella intermedia, Candida albicans.* The study was conducted in accordance with the requirements presented by the manufacturer on the Dt-light detecting amplifier ("Periodontoscreen", LLC "DNA-Technology", Russia).

Statistical processing of the results of the study with the distribution of data by the studied parameters was carried out using the special software package "STATA v. 12" («Stata Corp», USA). Significant differences (p<0,05) were also determined using the Student's t-test and correlation assessment was performed using the Pearson method.

Results and discussion. Gingival fluid is an exchange medium that promotes the migration of white blood cells from blood vessels through the epithelium to the gingival groove and influenced by bacterial chemotactic factors. The process of periodontal inflammation is characterized by a number of factors: an increase in the number of migrating leukocytes, endothelial dysfunction due to increased adhesiveness, which is probably necessary to create obstacles to the penetration of periodontal pathogenic microflora into the groove epithelium and underlying periodontal tissues [7]. In our study, the content of soluble adhesion molecules sICAM-1, sVCAM, sE-selectin, and sL-selectin in patients with chronic periodontitis was significantly higher than in the control group, which confirms this assumption. Thus, the concentrations of soluble forms of adhesion molecules sICAM-1, sVCAM, sE-selectin, and sL-selectin in chronic periodontitis exceeded those in the control group. Compared with patients with intact periodontitis, the concentration of sL-and sE-selectin molecules in the periodontal pocket discharge in patients with chronic generalized periodontitis increased by an average of 80,4% and 63,6%, respectively. While the concentrations of adhesive proteins of the family of the superfamily of immunoglobulins sICAM-1 and sVCAM in individuals with CGP exceeded the corresponding concentrations of the

control group to a greater extent: by 9,7 and 18,1 times, respectively (Table 1).

When assessing the level of expression of adhesive molecules depending on the severity of chronic periodontitis, it was found that in the subgroup with a mild course (n=32), the concentrations of sL-selectin and sE-selectin were lower by 55,9% (p=0,048) and 28% (p=0,032) than in the subgroup with a moderate course (n = 32). The results of the study showed a high degree of severity (n=24) and were 6,0 ng/ml [5,8; 6,3] and 4,3 ng/ml [4,0; 4,8], respectively. Concentrations of soluble forms of adhesion molecules of the immunoglobulin superfamily were also lower in patients with mild severity CGP: the concentration of sICAM-1 was 72,5 [69,7; 73,1] ng/ml, which is 27% (p=0,05) lower than in the group with moderate severity, while the concentration of sVCAM was 62,7 [56,4; 68,0] ng/ml, which is 24,6% (p=0,036) lower than in the group with moderate severity of chronic periodontitis.

The shifts in the secretion of adhesion molecules in the gingival/periodontal pocket secreted in our study correlate with the data on the study of serum concentrations of adhesive molecules in chronic periodontitis [6]. Thus, the results of the conducted studies indicate that patients with chronic generalized periodontitis develop systemic disorders associated with the violation of the adhesive properties of the vessel wall, manifested in an increase in serum concentrations of sICAM-1, sVCAM, sE-and sL-selectin caused by endotheliocyte alteration [2].

To determine the application points of intercellular adhesion molecules in the pathogenesis of endothelial dysfunction in the development of inflammatory and destructive changes in periodontal tissues, we evaluated markers of periodontal pathogenic microorganisms of the gingival/periodontal pocket. In patients, with chronic periodontitis, periodontal pathogenic bacterial flora was detected in 96,4% of cases. The oral microbiome is in constant dynamic balance: normal microbial flora provides processes of colonization resistance and reparative regeneration, while the appearance of periodontal pathogenic bacteria contributes to the formation of shifts in the homeostasis of the oral ecosystem and the formation of an inflammatory and destructive process. It is the microbial factor that underlies the occurrence and progression of IPD: an inflammatory reaction from the connective tissue and endothelium leads to a violation of the integrity of the gingival epithelium, subsequently causing the formation of deep periodontal pockets

Table 1

Expression level of adhesion molecules of the secreted DGP/DPP in patients with chronic periodontitis and in patients with intact periodontitis M [Q1; Q3]

Adhesion molecules, (ng/ml)	Group 1 (chronic periodontitis)	Group 2 (intact periodontal disease)	Statistical significance level
sL-selectin	9.2 [5.8; 14.7]	5.1 [2.9; 10.1]	p=0.045
sE-selectin	5.4 [4.0; 6.7]	3.3 [0.4; 4.8]	p=0.038
sICAM-1	83.0 [69.7; 98.5]	8.6 [2.5; 11.4]	p=0.022
sVCAM	76.2 [56.4; 82.8]	4.2 [2.1; 8.3]	p=0.023

Table 2

Correlation matrix of soluble adhesion molecules in DGP/DPP washes and markers of periodontal pathogenic microorganisms of the gingival pocket

Indicators	sL-selectin	sE-selectin	sICAM-1	sVCAM
Periodontitis				
P. gingivalis	r=0.289 (p=0.04)	r=0.322 (p=0.034)	**r=0.628** (p<0.001)	**r=0.542** (p=0.05)
T. forsythia	r=0.263 (p=0.03)	r=0.434 (p=0.03)	r=0.142 (p=0.03)	**r=0.683** (p=0.02)
A. actinomycetemcomitans	r=0.371 (p=0.02)	r=0.283 (p=0.006)	**r=0.821** (p=0.04)	**r=0.621** (p=0.04)
Associations of periodontal pathogens	r=0.388 (p=0.31)	r=0.189 (p=0.05)	r=0.112 (p=0.02)	r=0.311 (p=0.04)
Control				
T. denticola	**r=-0.482** (p=0.03)	r=0.134 (p=0.36)	r=0.179 (p=0.2)	r=0.212 (p=0.4)
P. intermedia	r=0.424 (p=0.33)	r=0.017 (p=0.26)	r=0.122 (p=0.08)	r=0.165 (p=0.3)

[1, 4, 8]. Among the isolated periodontal pathogens in the group with CGP, the highest frequency of occurrence was found in periodontal pathogenic bacteria of the first order: *A. actinomycetemcomitans* in 85,7% of cases, *P. gingivalis* in 78,6% of cases, *T. forsythia* in 57,1% of cases. Periodontal pathogens of the second order were also identified: *P. intermedia* in 53,6% of cases, *T. denticola* in 46,4% of cases. *C. albicans* was detected in 4,5% of cases. Associations of periodontal pathogens were found in 16 people (28,6%) in the subgroup with moderate chronic periodontitis: the most common association *was A. actinomycetemcomitans* and *P. gingivalis* in 14,3% of cases. Associations of *P. gingivalis* with *T. forsythia* were found in 8,9% of cases. The periodontal pathogenic microflora identified in patients is characterized by high adhesive, invasive, and toxic properties; these representatives of the bacterial community contribute to damage to cell wall membranes, penetration into the vascular bed, and toxigenic effects on the vascular endothelium [9]. Thus, the leukotoxin *A. actinomycetemcomitans* causes destruction of the phagocytosis object due to the interaction of polymorphonuclear leukocytes and CD11a/CD18 monocytes, accelerates monocyte lysis by activating caspase-1 [3]. The virulence of *P. gingivalis* has a damaging effect on the vascular endothelium: the adhesion and invasion of this periodontal pathogen leads to the generation of reactive oxygen species in endotheliocytes, causing oxidative stress that damages cells [2]. Also, according to some authors, *P. gingivalis* aggression factors lead to the destruction of alpha-tubulin and beta-1-integrin, as well as a decrease in ERK1/2 activation, which probably can contribute to pro-apoptotic effects. Proteo- and glycolytic enzymes *of T. forsythia* binde microorganisms to red blood cells, polymorphonuclear leukocytes and fibroblasts.

At the same time, the *T. forsythia* BspA surface antigen stimulates the production of proinflammatory cytokines in mononuclear cells when interacting with CD14 and TLR4 [3, 8].

Studies conducted in patients with intact periodontitis showed that the frequency of detection of markers of periodontal pathogenic species was 28.5%: *T. denticola* was isolated in 9,4%, *P.intermedia* in 6,3% of cases. At the same time, periodontal pathogenic bacteria of the first order and periodontal pathogens were not identified in the associations.

To conduct a deep pathogenetic assessment of the relationship between the identified types of periodontal pathogens and the content of soluble forms of gingival fluid adhesion molecules, a correlation analysis of the results obtained during the study was performed (Table 2).

Molecules of the superfamily of immunoglobulins sVCAM and sICAM-1 perform selective leukocyte adhesion, promoting the accumulation of mononuclear cells during the transition of the acute phase to the chronic stage with leukocyte endothelial reaction. ICAM-1 and the LFA-1 receptor ensure the production of T-lymphocytes, and the combined action of T-cell receptor and CD2 affects the change in the state of LFA-1 with a further increase in binding to ICAM-1. At the same time, such increase in molecules in the gingival fluid indicates a persistent inflammatory process caused by microbial flora, which is reflected in the revealed correlations of sVCAM and sICAM-1 with first-order periodontal pathogens *P. gingivalis, T. forsythia* and *A. actinomycetemcomitans* [2, 5].

It should be noted that the permeability of the epithelium contributes to the rapid entry of external molecules and cells of the immune system into the gum, and also ensures the delivery of various substances in both directions [7]. A number of researchers indicate that sL-selectin creates conditions for the formation of the phenomenon of "rolling" neutrophils inside vessels with leukocyte adhesion to the endothelium, which, in turn, leads to their accumulation in the inflammatory zone. In this case, metalloproteinases promote the cleavage of sL-selectin with a further decrease in the control of sL-selectin-mediated adhesion. The inducible adhesive molecule sE-selectin is synthesized and expressed by endothelial cells after stimulation with proinflammatory cytokines or bacterial endotoxins [4, 5, 6]. Probably, an increase in the expression of adhesive molecules of the selectin family may reflect their significant expenditure during immune reactions aimed at periodontal pathogen eradication, which is reflected in the revealed negative correlation of the average strength of sL-selectin and *T. denticola* in the control group.

Conclusion. The detected elevated concentrations of the soluble adhesive molecules sICAM-1, sVCAM, sE- and sL-selectin, to a greater extent in moderate CGP, may indicate endothelial cell alteration and endothelial dysfunction, accompanied by a violation of its antiplatelet, anticoagulant, and fibrinolytic properties due to a persistent inflammatory process caused by virulence factors of a specific subgingival periodontal pathogenic flora, mostly of the 1st order.

Thus, the soluble cell adhesion molecules sVCAM and sICAM-1, sE-selectin and sL-selectin are additional laboratory markers for determining the severity of the inflammatory process in periodontal tissues in patients with chronic periodontitis.

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