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E.V. Krikun, S.L. Blashkova, I.Kh. Valeeva

CORRELATION ANALYSIS OF THE IMMUNOLOGICAL AND CLINICAL PARAMETERS OF PATIENTS WITH ENDO-PERIODONTAL LESIONS

In the practice of therapeutic dentistry, the most difficult from the point of view of diagnosis and prediction of treatment results are patients with simultaneous pulp and periodontal lesions in the same segment вdue to the fact that their anatomical, embryonic and functional relationships determine a high probability of joint participation in the pathological process. Inflammatory processes occurring in the pulp and periodontal tissues can lead to cause both auto- and heterosensitization of the body, which, in turn, leads to a decrease in its immune defense. The aim of the study was to determine the effectiveness of studying the level of cytokines in the diagnosis of endo - periodontal lesions. Materials and methods. We compared clinical and immunological parameters in 82 patients with endo-periodontal lesions and 47 periodontologically healthy individuals aged 23-54 years. The clinical examination included assessment of hygiene status using the Green–Vermillion Simplified Hygiene Index (OHI-S), as well as periodontal status determined by the bleeding index (SBI) and Russell periodontal index (PI) and PMA. The state of local immunity was determined by the level of pro-inflammatory (TNF-α, IL - 1ß , IL-6) and anti-inflammatory (IL-4, IL-10) cytokines and IgA. The result of the study revealed a correlation between the severity of inflammatory processes in periodontal tissues and the level of pro-inflammatory cytokines. We found statistically significant differences in the concentrations of TNF-α and IL-6 in the oral fluid of patients with endo - periodontal lesions depending on the severity of periodontal damage, which underlines the role of these cytokines in the progression of the disease. The study of periodontal status and its relationship with the level of cytokines in the oral fluid revealed important correlations that indicate the prospects of using immunological markers for the diagnosis and prediction of the course of periodontal diseases.

Keywords: periodontal disease, endo-periodontal lesions, cytokines, local immunity.

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Introduction. The modern scientific paradigm is based on the belief that the properties of the whole can be explained based on the properties of the parts. All sicentific research begins with the study of the function of isolated organs, cells, or molecules. It is important that an integrated approach to the interpretation of patient examination data, as well as dynamic treatment results, can provide a new understanding of the nature of the disease as a violation of harmony in a living system.

In the practice of therapeutic dentistry, patients with simultaneous pulp and periodontal lesions in the same segment are the most difficult from the point of view of diagnosis and prediction of treatment results, due to the fact that their anatomical, embryonic and functional relationships determine a high probability of joint participation in the pathological process [5,9,]. The spread of infection from pulp to periodontal and vice versa is a complex process involving several pathways, often working synergistically, which leads to a high probability of developing inflammatory diseases. There are various hypotheses about the ways and mechanisms of infection spread. One of the most studied methods is spreading through the dentinal tubules. A significant role is also assigned to the hematogenic pathway. Bacteria, due to their ability to adhere and form biofilms, spread in both apical and coronal directions. Another way is to spread through the palato-gingival furrows, which can serve as a reservoir for pathogenic microflora. Also, we should not forget about the role of lateral tubules, which often go unnoticed during endodontic treatment and significantly complicates the complete rehabilitation of the focus of infection, contributing to the relapse of the disease. The infection can also migrate through the alveolar bone, causing osteolysis. [5,9]. The mechanism of this process is related to the body's immune response to infection, including the activation of osteoclasts. Finally, the common lymphatic system, which connects all structures of the maxillofacial region, is of great importance [1,2].

Currently, it is proved that the cause of endo-periodontal lesions (EPL) is the association of microbial communities – biofilms. As a result of bacterial contamination, first of all, the epithelium is damaged, there by provoking an increase in periodontal permeability for pathogenic microorganisms and their metabolic products, which initially leads to inflammation of periodontal tissues and subsequently to bone destruction[3,4,7].

Inflammatory processes occurring in the pulp and periodontal tissues can cause both auto-and heterosensitization of the body, which, in turn, leads to a decrease in its immune defense. In the current pathogenesis of EPL, it is recognized that immune components play an important role. Studies show that assessment of the local immune status of the oral cavity in inflammatory diseases of the mouth can be useful both for diagnosis and for predicting the consequences of diseases[5,6].

Immunocompetent cells responsible for protecting the body can also initiate destructive processes. The protective function is that the lack of the immune system often leads to pulp and periodontal pathologies. The destructive function is manifested through the ability of immune cells to secrete cytokines, which causes the destruction of connective tissue and bone resorption. This suggests

Federal State Budgetary Educational Institution of Higher Education Kazan State Medical University of the Ministry of Health of the Russian Federation: **KRIKUN Elena V.** – PhD, associate professor of the Department of Therapeutic Dentistry, ORCID 0000-0002-5188-557X; **BLASHKOVA Svetlana L.** – MD, Professor, head of the Department of Therapeutic Dentistry, ORCID: https://orcid.org/0000-0003-3233-2926://orcid.org/0000-0003-3233-2926; **VALEEVA Ildaria Kh.** – Doctor of Biological Sciences, Senior Researcher of the Central Research Laboratory ORCID 0000-0003-3707-6511

that early elimination of bacterial contamination may increase the chances of developing immunological reactions that do not lead to bone loss[8, 10].

Modern studies have confirmed that a decrease in the reactivity of the immune system is associated with dystrophic changes and impaired regeneration processes in periodontal tissues. The level of cytokines in saliva can serve as an indicator of the activity of macrophages and monocytes located in the oral mucosa[1,7].

Some studies indicate that minimal amounts of pro-inflammatory cytokines are necessary for the formation of an inflammatory focus and subsequent recovery. At the same time, high levels of IL-1β and IL-6 may indicate a chronic inflammatory process. Scientists suggest that an imbalance in the level of cytokines plays a key role in the development of chronic inflammatory reactions, which gives cytokines significant diagnostic and prognostic value[4,7].

The aim of our study was to determine the effectiveness of studying the level of cytokines in the diagnosis of endo-periodontal lesions.

Materials and methods. The study was conducted on the basis of the dental clinic of the Kazan State Medical University of the Ministry of Health of the Russian Federation. The sample included 129 people aged 23-54 years, who sought dental care, who were divided into two groups depending on the presence of endo-periodontal lesions (EPL): the main group and the comparison group. The main group included 82 patients who had a combination of endodontic and periodontal lesions in one sector during clinical examination, including 30 men (36.4%) and 52 women (63.6%). The comparison group consisted of 47 patients with healthy periodontitis, including 25 men (55.6%) and 22 women (44.4%). The clinical examination included assessment of hygiene status using the Green–Vermillion Simplified Hygiene Index (OHI-S), as well as periodontal status determined by the bleeding index (SBI), Russell periodontal index (PI) and PMA. The state of local immunity was determined by the level of pro-inflammatory (TNF-α, IL - 1ß, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines and IgA, using an enzyme-linked immunosorbent assay, with the inclusion of a set of reagents from Vector-Best LLC (Russia) according to generally accepted rules in the Central Research Laboratory FEDERAL State Budgetary Educational Institution Of Higher Education Of The Ministry Of Health Of The Russian Federation. Statistical analysis was performed using the IBM SPSS Statistics 20 program To assess the diagnostic significance of quantitative features in predicting a certain outcome, the method of ROC-curve analysis was used.

Results and their discussion. Data analysis showed that the differences between the groups by gender did not reach statistical significance (p=0.198). The average age of participants in the main group was 38.5 years (Q1-Q3: 33.0-47.0 years), while in the control group it was 23 years (Q1-Q3: 22.0-25.0 years). The differences in age between the study groups were statistically significant (p<0.001), which indicates a significantly older age of patients with EPL.

Comparison of the studied groups was also carried out by the level of cytokines in saliva. The results of the analysis clearly demonstrated the presence of statistically significant differences in the levels of all studied cytokines in the oral fluid of participants, which depended on the presence of EPL (p<0.001). The study of cytokine levels in patients with EPL made it possible to identify promising markers for early diagnosis and assessment of the severity of the disease. Tumor necrosis factor-α (TNF-α) is a pleiotropic cytokine that is considered in numerous studies as a key mediator of immune inflammation in various human pathologies. Comparing the level of TNF-α in patients with EPL and healthy persons, it was found that its concentration in the oral fluid of patients with EPL was significantly higher than in the control group. Accordingly, the level of TNF-α in the oral fluid, equal to 2.0 pg/ml, can serve as a dividing value. This makes it possible to classify patients according to the presence of EPL with 100% diagnostic efficiency. (Table 1).

Analysis of interleukin-10 (IL-10) concentrations showed that values of ≤ 2.05 pc/ ml predict a high risk of developing EPL. IL-10 levels above this threshold were associated with a low probability of disease. However, IL-10 is only one of many factors involved in the pathogenesis of EPL. Its role is complex and multifaceted: IL-10, being an anti-inflammatory cytokine, can both suppress inflammation and promote its development, depending on the balance with other cytokines and the conditions of the immune response.

Table 1

Comparative analysis of cytokine content in oral fluid depending on the presence of EPL

Cytokines	of the study groups				p
	Main		Comparison		
	Me	Q_1-Q_3	Me	Q_1-Q_3	
TNF, pkg/ml	17.38	11.85-24.71	1.24	1.01-1.62	<0.001*
IL-10, pkg / ml	1.0	0.69-1.38	3.85	3.07-5.14	<0.001*
IgA, g / l	5.23	3.92-6.79	1.96	1.61-2.87	<0.001*
IL-6, pkg / ml	8.91	6.17-11.46	2.25	1.23-3.66	<0.001*
IL-1β, pkg / ml	9.86	8.34-13.28	1.85	1.21-2.92	<0.001*
IL-4, pkg / ml	12.58	8.39-19.73	2.54	1.08-3.57	<0.001*

* - differences in indicators are statistically significant (p<0.05)

Table 2

Data from ROC analysis of the relationship between the level of cytokines in the oral fluid and the presence of EPL

Cytokines	cut-off	Area under the ROCcurve (S_{xy})		Diagnostic efficacy	
		S_{xy}±m	95% ДИ	Se, %	Sp, %
TNF, pkg / ml	2.0	1.0	1.0-1.0	100.0	100.0
IL-10, pkg / ml	2.05	0.95±0.03	0.89-1.0	99.1	88.9
IgA, g / l	3.18	0.92±0.03	0.87-0.98	84.5	83.3
IL-6, pkg / ml	4.69	0.95±0.02	0.91-0.99	91.8	83.3
IL-1β, pkg / ml	4.08	0.98±0.01	0.95-1.0	93.6	94.4
IL-4, pkg / ml	4.86	0.98±0.01	0.96-1.0	94.5	94.4

Further analysis expanded the range of markers studied to include IL-6, IL-4, IL-1β, and IgA. Evaluation of the prognostic value of these indicators showed that TNF-α shows the greatest correlation with the development of EPL, followed by IL-10, IL-4, and IL-1β. This indicates an important role of pro-inflammatory cytokines in the development and progression of the disease. It is important to note that high levels of IgA in saliva do not always correlate with the severity of the disease, which may be due to its diversity of isotypes and its role in various immune mechanisms. (Table 2).

For a more in-depth study of the pathophysiological mechanisms of EPL, a correlation analysis of the relationship between cytokine levels and dental indices was performed: periodontal Russell index (PI), gum bleeding index (SBI), and PMA. The results of the analysis revealed statistically significant direct correlations between PI values and TNF-α, IL-6, IL-1β, and IL-4 concentrations in patients suffering from EPL. This indicates a strong relationship between the severity of inflammatory processes in periodontal tissues and the level of pro-inflammatory cytokines.

Correlations between SBI and cytokine concentrations (TNF-α, IL-10, IL-6, IL-1β, IL-4) were also statistically significant, but were characterized by a low density. This may indicate that gum bleeding is only one indicator of the inflammatory process, while a comprehensive analysis should take into account a wide range of different biomarkers.

An increase in the PI, PMA, and SBI indices significantly correlated with high levels of TNF-α, IL-6, and IL-1β, as well as with lower levels of IL-4 and IgA. These results confirm the multifactorial nature of periodontal inflammation, which includes both pro-and anti-inflammatory cytokines. The levels of TNF-α, IL-10, IL-4, and IL-1β demonstrated the greatest prognostic significance for assessing the risk of developing chronic inflammation. (Table 3). In particular, TNF-α occupies a leading position in the ranking of prognostic markers.

Moreover, there were statistically significant differences in the concentrations of TNF-α and IL-6 in the oral fluid of patients with EPL, depending on the severity of periodontal damage (PI), which emphasizes the role of these cytokines in the progression of the disease. TNF-α, being a powerful pro-inflammatory cytokine, stimulates the production of other inflammatory mediators, and IL-6 plays a key role in regulating the inflammatory response and the body's systemic response to infection. Understanding this relationship opens up new opportunities for developing personalized therapies focused on controlling the levels of these cytokines.

Table 3

Data of correlation analysis of the relationship between the level of cytokines in the oral fluid and dental indices

Cytokines	Dental indexes							
	OHI-S		PI		PMA		SBI	
	ρ_{xy}	p	ρ_{xy}	p	ρ_{xy}	p	ρ_{xy}	P
TNF	0.027	0.779	0.286	0.002*	0.093	0.334	0.251	0.008*
IL-10	-0.085	0.376	0.034	0.728	-0.074	0.444	0.188	0.049*
IgA	0.006	0.953	-0.009	0.928	-0.012	0.902	-0.006	0.949
IL-6	-0.084	0.383	0.332	<0.001*	0.058	0.545	0.235	0.014*
IL-1β	0.039	0.684	0.274	0.004*	0.077	0.422	0.221	0.02*
IL-4	-0.06	0.536	0.224	0.019*	0.118	0.219	0.211	0.027*

* - the correlation is statistically significant ($p<0.05$)

Conclusion. The study of periodontal status and its relationship with the level of cytokines in the oral fluid revealed important correlations that indicate the prospects of using immunological markers for the diagnosis and prediction of the course of periodontal diseases. The obtained data confirm the high informative value of the analysis of cytokines in the oral fluid for the diagnosis and monitoring of the treatment of periodontal diseases. Determination of TNF-α, IL-1β, IL-6, IL-10, and IL-4 levels in mixed saliva can serve as an additional tool for evaluating the effectiveness of therapy and predicting the risk of complications. It is important to note that using only the applied indices may not be sufficient to fully assess the severity of periodontitis and predict its course. An integrative approach that combines clinical assessment with laboratory methods for determining cytokine levels allows you to get a more complete and reliable picture of the periodontal condition and make more informed treatment decisions.

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