# Immune system of periodontium and identification of professional conditions in limestone quarry workers

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Abstract. In our article, we studied the concentration of immunoglobulins, the interleukin system and observed their changes before and after our patented treatment with a dressing based on "Placentol". The study material was the oral fluid of the patients. We observed 67 patients with a diagnosis of chronic generalized periodontitis of mild severity from 214 employees. The patients are workers of the limestone quarry. We revealed the occupational dependence of the disease by chronic generalized periodontitis in workers of the limestone quarry, which turned out to be highly conditioned (that is, working conditions affect the state of the periodontal). The results of the treatment pleased us, we achieved clinical improvement on the fourth visit.

The work of the periodontal immune system is partly determined by the direction of the development of pathological processes in chronic inflammation. The main cause in the pathogenesis of chronic immunological inflammation can be a local disorder at the level of the mucosal system or small abnormalities at the systemic level. This task is complex and it is studied both from the immunological position and from the position of general pathology, taking into account the functioning of other homeostatic systems of the body. The article also provides information on the role of cytokines in the pathogenetic mechanisms of the development of chronic inflammation in the periodontal tissues, and how, with the help of our patented treatment, the immune system of the oral cavity can be increased. Also, to carry out early diagnosis, prevention and treatment of periodontitis diseases in limestone quarry workers, identifying their relative risk index and the etiological proportion of periodontitis incidence. The

aim of our work is to study the changes in the parameters of the immune system of the oral cavity, under the influence of the treatment of the "Placentol" dressing, in the workers of the limestone quarry, and in the future to offer them our treatment.

Keywords: chronic generalized periodontitis, occupational conditioning, cytokines, periodontal disease, local immunity.

## Introduction

For many years, specialists have been interested in the problems of assessing the damage to the health of workers from exposure to unfavorable production factors. The occupational risk assessment is carried out for individual occupational groups with similar working conditions and its result is an assessment of the group risk. It has been proven that one of the main roles in the development of the immune response is the activation of the Th2-type cytokine system, and interleukins like IL-4, IL-5, IL-9, IL-13 (they are produced by Th2) enhance the formation of immunoglobulin E (IgE) [1]. This chain of immunity leads to immune inflammation, tissue destruction with the simultaneous involvement of the effector cells of the immune system. Despite the large amount of data concerning the issues of inflammation of periodontal tissues, there is still no consensus in the scientific world about the direction, mutual determination and depth of immune disorders in periodontitis. At the same time, most scientists explain the state of the immune system, which we consider as secondary immunodeficiency. According to V.S. Shirinsky, secondary immunodeficiency is a clinical and immunological syndrome, which is based on quantitative and functional disorders of various populations and subpopulations of cells of the monocytic-macrophage system, nonspecific defense factors associated with the development of autoimmune, allergic, infectious and tumor diseases [2]. Indeed, the state of local barriers is determined by the level of proliferation and differentiation of immunocompetent cells in the central organs of immunogenesis [3]. It is also important that the peculiarities of the functioning of the mucosal immune system (MIS) largely determines the direction of the development of pathological processes in chronic immunological inflammation (CII). At the same time, what is primary in the pathogenesis of CII, or a local disturbance at the MIS level, or minor anomalies at the systemic level, is a rather complicated question and is still discussed from both immunological positions and the positions of general pathology, taking into account the functioning of other homeostatic systems of the body [4.5].

A large number of studies are aimed at studying the role of cytokines in the development and formation of periodontal disease. According to numerous literary sources, it can be seen that the mucous membrane of the intraoral cavity is normally in a state of "controlled" inflammation, regulated by a complex balance of inflammatory and anti-inflammatory cytokines. Cytokines

trigger a complex of integrative-adaptive reactions, involving all types of effector cells in the elimination of the pathogen [1,7]. The initial phases of the inflammatory process to chemical and other genital malformations proceed with the release of pro-inflammatory cytokines. The phase nature of cytokine regulation is manifested by a natural adaptive-compensatory increase in the production of pro-inflammatory cytokines that contribute to the relief of inflammatory processes [2]. With the development of the inflammatory process in the periodontal tissues, the level of pro-inflammatory cytokines in most cases increases significantly [3]. Also, biological media are actively involved in the inflammatory process of the oral cavity as an indicator of an integral assessment of the state of the intraoral cavity, which have been little studied in the light of the cytokine homeostasis of the oral and gingival fluid [4,5,6].

Revealing the occupational causation of periodontal diseases in a limestone quarry gives us the opportunity for early prevention of periodontal diseases. [7] There were 214 employees under our supervision, aged from 22-58 years. In 67 patients, chronic generalized periodontitis (CGP) of mild severity was revealed. Among 67 patients with mild CGP, occupational conditioning was calculated. To determine the effectiveness of the treatment carried out by randomization, the patients were divided into the following groups:

1- main group of 34 patients with CGP who were prescribed the treatment we recommended;

2 - comparison group of 33 patients with CGP who received basic therapy.

The control group consisted of 20 people, without signs of periodontal disease, to clarify the parameters of the norm. All groups were comparable in terms of age and experience.

At the dental appointment, anamnesis was collected, the dental formula, complaints, the presence of dental deposits, bleeding gums, and bone resorption were recorded. Informed voluntary consent was signed by all patients. The material of the research was the oral fluid, where the concentration of immunoglobulins (Ig) was studied as sIgA, IgA, IgM, IgG, IgE and lysozyme. The quantitative determination of immunoglobulins (IgA, IgM, IgG, IgE) in the oral fluid was carried out by an automatic immunoturbidimetric method in a Turbox Plus immunochemical protein analyzer (Finland). As immunological reagents used kits for the determination of Ig "Turbox Plus" manufactured by "Orion Diagnostica" (Finland). The sIgA and lysozyme levels were studied by ELISA diagnostics. The spectrum of cytokines in the oral fluid was investigated to reveal their role in the pathogenetic mechanisms of the development of chronic inflammation in the periodontal tissues. To study cytokines, special modern equipment was used, including a Bio-Plex installation with a set of reagents for the analysis of cytokines (Bio-Plex ProTM Rat Cytokine Th1/Th2 Assay). The system of interleukins IL-6 and IL-10 was assessed using enzyme-linked immunosorbent assay of commercial diagnostic kits from ZAO Vector-Best

(Novosibirsk, Russia); IL-1β, TNFα (tumor necrosis factor α) - by the enzyme immunoassay using ProCon reagents on the Stat-Fax 2100 enzyme immunoassay analyzer, TGF-1β (transforming osta factor β1) from Quintikin (USA); IL-4 and IL-8 - using reagents of LLC "Cytokin" (St. Petersburg, Russia) according to the attached instructions, the results were expressed in pg/ml. The studies were carried out before and after treatment. Statistical processing of the obtained research results was carried out using the statistical software package STATISTICA v.6.0 (StatSoft Inc., USA). The comparison group was prescribed basic therapy: removal of dental plaque with ultrasound, rinsing with an antiseptic solution "Chlorhexidine", application of gel "Metrogyl Denta".

In addition to the basic therapy, the main group was prescribed dressings with Placentol balm, which was prepared as follows: Placentol balm and water dentin in a ratio of 5: 1, respectively, were mixed until the consistency of thick sour cream and on a dried gum isolated with cotton swabs in a thin layer mixture. Exposure time 15 minutes. Courses with treatment 10 daily procedures. The active ingredients of the Placentol balm are: purified water, biologically active substances: 20 amino acids (including all irreplaceable ones), low molecular weight peptides, glutathione, acetylcholine, choline, DMAE, Q10, hyaluronic acid, chondroitin sulfate, succinic acid, lecithin, polyunsaturated fatty acids, cytokines (interleukins, interferons, osta factors), alpha-fetoprotein, vitamins (A, B1, B2, B3, B4, B5, B6, B9, B10, B12, C, D, E, H), macro- and microelements (magnesium, silicon, potassium, sodium, calcium, iron, manganese, zinc, copper, selenium). When applied topically, it has an immunocorrective, reparative, anti-inflammatory, regenerating effect, increases the immunity of the oral cavity. Determination of professional conditionality, establishing the connection between diseases and work, was carried out in accordance with the principles of evidence-based medicine - determining the degree of causal relationship between health disorders and work, in accordance with R 2.2.1766-03. [3,4,5]. The relative risk of morbidity was calculated using the formula: RR= Ji%/Jo%. Further, having found the indicator of the relative risk, we calculated the etiological proportion of the incidence of periodontitis by the formula: EF=(RR-1)/RR×100, where EF is the etiological proportion; RR is an indicator of relative risk.

Derived the incidence of CGP among limestone workers. The prevalence of mild chronic generalized periodontitis in limestone quarry workers in the main group was 31.3±1.5%, and in the control group - 9.3±1.3%.

We calculated the relative risk of chronic generalized periodontitis morbidity = 3.4. The degree of production conditionality at RR>2 and EF>50% is high.

Thus, CGP is an occupational disease among limestone quarry workers, the etiological proportion of the disease is 70.6% EF>50% RR>2, and the relative risk index is 3.4.

Before the treatment, the immunological parameters of the oral fluid significantly differed from those of the norm, which indicated the presence of an inflammatory process in the periodontal tissues.

After the treatment, the results of studies of the level of pro-inflammatory (IL-1β, IL-6, IL-8, TNFα) and anti-inflammatory (IL-4, IL-10, TGF-1β) interleukins in the oral fluid in patients with mild CGP of the main group showed a significant quantitative increase in the level of immunopeptide mediators such as IL-1β, IL-6, IL-8, TNFα and a decrease in the concentration of IL-4, TGF-1β. Thanks to the proposed treatment, in the main group, the shifts in the concentration of interleukins are statistically significant, and the degree of change in their level correlates with the severity of the disease. However, an imbalance with pro- and anti-inflammatory cytokines - an increase in the content of IL1β and IL-8, which are chemoctants against the background of a decrease in the level of IL-4 and IL-10, leads to the inevitable progression of inflammatory and destructive processes in the periodontal tissues. The established correlation between the concentration of IL-1β, IL-6, IL-8 and TNFα from the severity of damage to the periodontal tissues is presented for IL-1β as an inverse average relationship ($r=-0.20$; $p=0.08$); for IL-6 as a direct mean relationship ($r=0.41$; $p\leq0.001$); for IL-8 as a direct mean relationship ($r=0.44$; $p\leq0.001$) and for TNFα as a strong direct correlation ($r=0.82$; $p\leq0.001$).

The content of IL-10, which is an inhibitor of IL-1β and IL-8, decreases. This fact reflects the simultaneous triggering of the inflammatory response and repair mechanisms. Apparently, damage to the periodontal tissues, as well as the processes of self-cleaning of the oral cavity lead to the activation of the inflammatory process at the level of the periodontal junction, as a result, immune cells such as neutrophilic and eosinophilic granulocytes, mononuclear phagocytes are concentrated in the lesion focus, and their activation causes an increase in the synthesis of interleukins. This increases the production of pro-inflammatory cytokines such as IL-1β, IL-6 and IL-8, associated with dysfunction of cell-mediated immune responses at the level of the periodontal junction. Lymphocytes, as participants in immune responses at the level of the gingival junction, activate the Th1 immune response, however, insufficient production of IL-10 reduces anti-infectious protection, which leads to an exacerbation of periodontal disease.

The results of the study of the concentration of immunoglobulins sIgA, IgA, IgM, IgG, IgE and lysozyme in the oral fluid of patients with chronic generalized periodontitis (CGP) show their ambiguous changes after treatment with basic therapy and the dressing "Placentol". The sIgA

content in the group of CGP patients of the main group exceeds the initial value by 1.5 times, while in patients from the comparison group of the disease, on the contrary, a decrease in its level is determined by 1.5 times in comparison with persons belonging to the control group. The ambiguous change in the level of sIgA in the oral fluid can be explained by the fact that it is the predominant immunoglobulin in the secretions of the mucous membranes, including the oral fluid; performs an effector function, consisting in the aggregation of microbes and the sorption of these aggregates on the surface of epithelial cells with a simultaneous suppression of the reproduction of microbes, which is facilitated to a greater extent by lysozyme. Some predominance of IgA and IgG in patients of the main group in comparison with other immunological parameters (IgM, IgE), although they were statistically significantly lower than the initial parameters, can be explained by the fact that these immunoglobulins are more actively involved in the primary reaction to the presence of an acute phase of inflammation. Further study of the dynamics of changes in the immunological parameters of the oral fluid, characterizing the local immunity of the intraoral cavity, shows their decrease, which is very significantly manifested in patients of the comparison group. The established fact indicates the presence of local immunodeficiency in the oral fluid of CGP patients in the comparison group.

Thus, in patients with CGP of all groups, in general, there is a local humoral immunodeficiency. According to the results of the correlation analysis in the group of CGP patients of the main group, moderate connections within the block of secretory immunological parameters of the oral fluid were revealed. In the local immunity system, moderate correlations were found between: lysozyme and sIgA ($r=0.31$; $p\leq0.04$); lysozyme and IgA ($r=0.38$; $p\leq0.05$); lysozyme and IgM ($r=0.33$; $p\leq0.04$); lysozyme and IgG ($r=0.30$; $p\leq0.05$); lysozyme and IgE ($r=0.35$; $p\leq0.05$); between sIgA and IgA ($r=0.60$; $p\leq0.01$); sIgA and IgM ($r=0.27$; $p\leq0.05$); sIgA and IgG ($r=0.22$; $p\leq0.05$); sIgA and IgE ($r=0.24$; $p\leq0.05$); IgA and IgM ($r=0.52$; $p\leq0.01$); IgA and IgG ($r=0.45$; $p\leq0.05$); between IgA and IgE ($r=0.49$; $p\leq0.01$); IgM and IgG ($r=0.42$; $p\leq0.05$); IgM and IgE ($r=0.47$; $p\leq0.05$); IgE and IgG ($r=0.39$; $p\leq0.05$). The value of the pair correlation coefficients varied from 0.26 to 0.61, which is typical for a moderate correlation strength. Evaluating the structure of the correlation network in the group of CGP patients in the comparison group, we found that it has a much more complex structure in comparison with the group of control individuals. Correlation interactions in this group of patients are characterized by an increase in the correlation between the blocks of local immunity:

Within the block of local immunity parameters, links of moderate strength are observed in sIgA with IgA of the oral fluid ($r=0.62$; $p\leq0.01$); sIgA with IgG ($r=0.39$; $p\leq0.05$); sIgA with lysozyme ($r=0.31$; $p\leq0.05$); sIgA with IgM ($r=0.42$; $p\leq0.05$); sIgA with IgE ($r=0.32$; $p\leq0.05$).

The number of correlations between the indices of local immunity was maximum in comparison with the main and the comparison group. Within the block of local immunity parameters, links of moderate strength are observed in sIgA with IgA (r=0.68; p≤0.01); sIgA with IgG (r=0.53; p≤0.01); sIgA with lysozyme (r=0.49; p≤0.01); sIgA with IgM (r=0.42; p≤0.01); sIgA with IgE (r=0.50; p≤0.01); in lysozyme with IgA (r=0.48; p≤0.01); in lysozyme with IgM (r=0.45; p≤0.01); in lysozyme with IgG (r=0.41; p≤0.01); in lysozyme with IgE (r=0.46; p≤0.01); for IgA and IgE (r=0.56; p≤0.01); in IgM with IgG (r=0.48; p≤0.01); in IgM with IgE (r=0.51; p≤0.01) and in IgE with IgG (r=0.44; p≤0.01). In patients with chronic generalized periodontitis working in a limestone quarry, a statistically significant imbalance with pro- and anti-inflammatory cytokines was revealed. Changes in the state in their cytokine status made it possible to determine informative criteria with predictive value in the oral fluid, contributing to the relief of inflammatory processes. The revealed changes indicate the disruption of adaptation processes and the development of clinical symptoms of periodontal disease. Thus, based on the data obtained, we conclude that the significant role of MIS indicators in maintaining homeostasis in CGP is confirmed by the results of mathematical and statistical analysis. Consequently, with CGP in the studied groups, the oral cavity immune system operates in a mode of functional tension. Proof of this fact is the results of correlation analysis, which revealed an increase in intrasystemic interactions of protective factors in CGP.

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