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INFLUENCE OF ODONTOPREPARATION TYPE FOR METAL-CERAMIC CONSTRUCTIONS ON CYTOKINE PROFILE DYNAMICS IN ORAL AND GINGIVAL FLUID

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Cytokines are a group of polypeptide mediators involved in the formation and regulation of the body's protective reactions. The biological effects of cytokines are mediated through specific cellular receptor complexes that bind cytokines with very high affinity, and individual cytokines may use common receptor subunits.

The main sources of IL-1 in the body are monocytes and macrophages, as well as Langerhans cells, Kupffer cells in the liver, endothelial cells, fibroblasts, keratinocytes, microglia cells, neutrophils, T-lymphocytes, in addition to T-helpers, dendritic cells and others. Induction of IL-1 synthesis can be caused by a number of biologically active substances, the main of which are components of bacterial cell walls (lipopolysaccharides and peptidoglycans), as well as antigens, immune complexes, cytokines, cell breakdown products.

The study of various parts of the immune response that occurs in response to bacterial invasion, the study of the regulatory function of T-cells, cytokines in the pathogenesis of the periodontal disease, understanding the immunological mechanisms underlying destructive processes in periodontal tissues is necessary to create a rational scheme for treatment of inflammatory processes in this area. Influencing the processes and mechanisms of regeneration, regulating the balance of pro-inflammatory and anti-inflammatory cytokines, taking into account the individual characteristics of the patient, it becomes possible to influence the development of periodontal disease by suspending their progression.

Key words: proinflammatory cytokines, inflammatory regulators, IL-1α, IL-1β, TNF-α.

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Introduction. Cytokines are a group of polypeptide mediators involved in the formation and regulation of the body's protective reactions. The biological effects of cytokines are mediated through specific cellular receptor complexes that bind cytokines with very high affinity, and individual cytokines may use common receptor subunits. Depending on the nature of the impact on the inflammatory process, cytokines are divided into pro-inflammatory, which are involved in the initiation of inflammation, and anti-inflammatory. The key pro-inflammatory cytokine is IL-1, the main anti-inflammatory – IL-10. IL-1 is divided into 2 fractions: IL-1α and IL-1β. Both cytokines are encoded by different genes, but have practically the same spectrum of biological activity and compete for binding to the same receptors.

Aim of research. To analyse the literature sources with the characteristics of the level of mediators of pro-inflammatory processes in oral and gingival fluid, depending on the type of odontopreparation for metal-ceramic structures based on databases such as Scopus, Web of Science, MedLine, PubMed, NCBI, the study of which does not exceed 10 years, including literature reviews and clinical trial results.

The results of the research and their discussion. The main sources of IL-1 in the body are monocytes and macrophages, as well as Langerhans cells, Kupffer cells in the liver, endothelial cells, fibroblasts, keratinocytes, microglia cells, neutrophils, T-lymphocytes, in addition to T-helpers, dendritic cells and others. Induction of IL-1 synthesis can be caused by a number of biologically active substances, the main of which are components of bacterial cell walls (lipopolysaccharides and peptidoglycans), as well as antigens, immune complexes, cytokines, cell breakdown products. In humans, IL-1β is the major form of secretory IL-1 in the environment, due to the predominant presence of IL-1α in a membrane form. All known biological effects of IL-1 are mediated by its binding to specific membrane receptors that are expressed on different types of target cells [1].

IL-1 is characterized by the fact that the response of cells to its action develops in the presence of a minimum number of specific receptors involved and extremely low concentrations of ligand. The pleiotropic type of IL-1 biological action is manifested from the molecular intracellular level. Despite the minimal number of expressed receptors and the disappearing concentration of IL-1 itself, the cellular response is triggered, which ultimately leads to the expression of genes of about 100 cytokines, hormones, enzymes, growth factors, other biologically active substances and their receptors. Therefore, all the many biological effects of IL-1 in the body are determined at the subcellular level. Target cells for IL-1 are T- and B-lymphocytes, macrophages, neutrophils, endothelial cells, dendritic cells, basophils, fibroblasts, osteoclasts, hepatocytes and other cells, i.e. the target cells are almost all organs and tissues [2, 3].

An integral part of IL-1 biological action is its stimulating effect on connective tissue metabolism. It stimulates the proliferation of fibroblasts and increases their production of prostaglandins, growth factors and a number of cytokines. Under the influence of IL-1 connective tissue cells increase the synthesis of collagen, collagenase and other enzymes. Completion of repair may be hypertrophic or keloid scars, the formation of which is associated with increased formation of granulation tissue and is exacerbated by high concentrations of IL-1.

IL-1 can indirectly induce hyperalgesia by stimulating the synthesis of prostaglandins and thromboxanes, modulation of sympathetic fibres by increasing the expression of receptors to nerve growth factor and bradykinin. IL-1 is involved in the regulation of endothelial and coagulation functions, inducing procoagulant activity, and acts on blood vessels, causing vasodilation. In neutrophils under the action of IL-1 there is an oxygen

explosion. One of the most important biological effects of IL-1 is the activation of lymphocytes, and especially the activation of T-helpers.

IL-10 is the most important anti-inflammatory cytokine, which has mainly anti-inflammatory and anti-cytokine effects. Sources of IL-10 are T-helper-2-lymphocytes, B-lymphocytes, monocytes/macrophages, keratinocytes, mast cells, thymocytes. Macrophages produce IL-10 under the influence of exogenous and endogenous factors such as endotoxins, catecholamines, etc. [4].

This cytokine exerts its effect through a receptor complex that is expressed on the surface of many cells. Target cells for IL-10 are mast cells, B-lymphocytes, neutrophils, monocytes/macrophages, but the main targets for it are antigen-presenting cells and lymphocytes [5].

IL-10 is an inhibitor of inflammation and the cytokine cascade. It inhibits the synthesis of T-helpers 1, chemokines, adhesive molecules, monocyte-macrophage tumour necrosis factor TNF-α, IL-1, IL-6, IL-12, granulocyte colony-stimulating factor cytokines. Thus, the main function of IL-10 is to limit and inhibit the inflammatory process [6, 7, 8].

At the clinical stages of preparation of abutment teeth for prosthetics with fixed orthopaedic structures in the marginal periodontium there is a local immune response to an acute stimulus in the process of gum retraction. Laboratorially this is confirmed by preclinical manifestations of inflammation signs by the development of cytokine background imbalance. Thus, the concentration of IL-1β increases several times, while the level of anti-inflammatory cytokines is in a state in which the restoration of balance by the body itself is impossible [9].

The study of the composition of the gingival pocket's contents has allowed over the past few years to form a cytokine concept of inflammation in the periodontium. According to this concept, the activation of monocytes and macrophages by periodontopathogenic microorganisms at the level of the gingival junction increases the production of pro-inflammatory cytokines by these cells, causing an imbalance between their pro- and anti-inflammatory pools. This is one of the main causes of periodontal tissue damage, which can lead to the resorption of alveolar bone [10].

It is believed that one of the key mechanisms of osteoporosis formation in the course of periodontitis is an increase in the level of major pro-inflammatory gingival cytokines due to the switching of the immune response to Th1-type response and reducing B-lymphocyte activity. This imbalance between pro- and anti-inflammatory pools of cytokines in the course of periodontal disease is considered to be a consequence of inadequate local immune response to the microflora. High concentrations of intercellular mediators of inflammation in the gingival fluid in patients with inflammatory periodontal disease cause gingival pocket, bone dystrophy of alveolar processes, changes in the composition and properties of oral fluid [11, 12].

Cytokines regulate immune mechanisms aimed at eliminating any genetic invasion (the infectious agent) of damaged structures and restoring the stability of the internal environment [13, 14].

The biological action of cytokines is carried out through specific cellular receptor complexes. Cytokines regulate the development of local protective reactions in tissues involving different types of blood cells, endothelium, connective tissue and epithelium. Local defence mechanisms are carried out through the effects of a number of cytokines (TNF-α, IL-2, IL-4, IL-6, γ-interferon) by forming a typical inflammatory response. Inflammation is developed as a response to tissue damage by pathogens involving pro-inflammatory cytokines, which include IL-1, TNF, IL-6, chemokines and some other cytokines [15].

The onset of inflammation in the gums is characterized by an increase in the volume of circulating blood, resulting in an increase in the number of functioning capillaries; they become dilated and blood-filled. Structural changes in the capillary endothelium lead to increased permeability of their wall as a result of increased microvesicular transport in endothelial cells. This causes intercellular oedema in the gum epithelium and leads to a decrease in the differentiation of epithelial cells and barrier properties, accumulation of microorganisms not only in the gingival sulcus, but also between epithelial cells, increased aggression of anaerobic microorganisms [16]. Thus, the optimal balance of anti-inflammatory interleukins and IL-1 provides an adequate reaction of the body in response to the introduction of a foreign agent, and its change inevitably leads to dysfunction of the cytokine network and, consequently, the immune system as a whole. Under the conditions of the inflammatory process in the periodontium, the epithelial barrier is inevitably damaged, which in combination with microbial aggression leads to the activation of epithelial cells. In this case, epitheliocytes acquire the properties of immunocompetent cells and begin to secrete cytokines (IL-1, IL-6, INF-γ), as well as chemokines responsible for attracting circulating T-lymphocytes into the mucous membrane. Violation of the integrity of the epithelium due to the increase in intercellular spaces is the most important factor in the development of gingivitis [17, 18].

Mediators of the immune system at different stages of inflammation have different activity. Their family includes mediators of pre-immune inflammation: TNF-α, IFN-α, IFN-β, IL-1, IL-6, IL-12, chemokines. Their main producers are monocytes/macrophages, fibroblasts, endotheliocytes. Regulators of activation, proliferation and differentiation of lymphocytes – IL-2, IL-4, IL-13, TGF-β – are produced by interepithelial lymphocytes. The main subpopulations of T-lymphocytes produce regulators of immune inflammation IFN-γ (activator of monocytes/macrophages, NK-cells), IFN-β (activator of neutrophils), IL-5 (inducer and activator of eosinophils and B-cells), IL-9 (activator of mast cells), IL-10 (inhibitor of monocyte/macrophage activity), IL-12 (activator of T-killers, NK-cells). Their main producers are mature T-helpers, T-killers and some types of accessory cells [19].

Chemokines enhance the directed migration of leukocytes into the site of inflammation, together with other cytokines increase their functional activity by stimulating phagocytosis, the production of oxygen radicals, which together are aimed at eliminating pathogens. At the same time, anti-inflammatory cytokines activate connective tissue metabolism, stimulate the proliferation of fibroblasts and epithelial cells, filling tissue defects and restoring their integrity.

It has been found that IL-1 is a pathogenetic marker of severe forms of chronic periodontitis; it stimulates the synthesis of collagenase in fibroblasts and promotes their transformation into osteoblasts. The combination of these two mechanisms can cause tissue destruction of the mucous membrane of the oral cavity [20].

TNF-α is a major regulator of early immune responses, a leading activator of the inflammatory process and an obligatory marker of autoimmune diseases. It has been found that TNF-α is most intensely inhibited by cortisol. Therefore, the assessment of the mechanisms of regulation of this cytokine creates some difficulties. The level of cytokines in saliva varies in a normal state and changes significantly in the conditions of pathology. The change in the concentration of cytokines is due not only to the severity of the pathological process, but also its duration.

A number of studies indicate changes in the concentrations of a number of cytokines (IL-4, IL-8, IF-γ, IL-1β, etc.) and some indicators of local immunity of the oral cavity in the process of orthopaedic treatment. At the same time, the mechanisms of influencing the local and systemic immunity of the prosthetic process itself are still unexplored. So far, no criteria have been formulated to assess the risk of the impaired immune status of patients after orthopaedic treatment [21, 22, 23].

In most publications on the study of local immunity in dental patients, the main object of study is saliva as well as capillary blood of the gums. The studies mainly deal with such markers as CD3+, CD4+, CD8+, CD4+ / CD8+, CD19+; information on the phenotyping of NK-cells is almost absent.

Isolated studies have shown the great practical importance of the response of the general and local immune systems to elucidate the complex mechanisms of prostheses and prosthetic materials impact on the condition of oral tissues and the ability to predict the effectiveness of various orthopaedic treatments [24].

It has been established that the conditions that contribute to the violation of immune homeostasis of the body are changes in the subpopulation composition of lymphocytes, decreased immunoregulatory coefficient, increased number of cytolytic killer T-lymphocytes and changes in the number of NK-cells in human blood. In the peripheral blood, depending on the severity of pathological processes in the oral cavity, there is a decrease in the relative and absolute content of T-lymphocytes. Inflammation of the oral mucosa is accompanied by an increase in the content of B1-cells, which is often combined with an imbalance in the ratio of CD4+ and CD8+ cells. Studies confirm that there is a strong correlation between oral soft tissue damage and peripheral blood levels of T-lymphocytes as well as their regulatory subpopulations. This allows, as the phenotypic lymphocytes decrease, to assess and predict the severity of the pathological process. The content of immunoglobulins (G, A, M, D, E) in peripheral blood differs from their concentration in saliva. Depending on the duration and severity of the disease, the level of immunoglobulins in saliva can exceed serum concentrations by 3-5 times [25, 26, 27, 28].

Conclusions. Studies of the body's protective forces in the course of inflammatory periodontal disease allow us to draw a conclusion that the main clinical manifestations of the periodontal disease depend more on the activity of immune cells than on the direct exposure of oral microorganisms. Inadequate immune response determines pathological changes in the periodontium – the destruction of connective tissue, destruction of bone tissue, i.e. the severity of the disease.

The study of various parts of the immune response that occurs in response to bacterial invasion, the study of the regulatory function of T-cells, cytokines in the pathogenesis of the periodontal disease, understanding the immunological mechanisms underlying destructive processes in periodontal tissues is necessary to create a rational scheme for treatment of inflammatory processes in this area. Influencing the processes and mechanisms of regeneration, regulating the balance of pro-inflammatory and anti-inflammatory cytokines, taking into account the individual characteristics of the patient, it becomes possible to influence the development of periodontal disease by suspending their progression.

Prospects for further research. Further research should focus on study the level of cytokines in the oral fluid in the dynamics of the use of fixed prostheses.

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ВПЛИВ ВИДУ ОДОНТОПРЕПАРУВАННЯ ПІД МЕТАЛОКЕРАМІЧНІ КОНСТРУКЦІЇ НА ДИНАМІКУ ЦИТОКІНОВОГО ПРОФІЛЮ В РОТОВІЙ ТА ЯСЕННІЙ РІДИНІ

Попович І. Ю.

Резюме. *Вступ.* У статті наведено огляд наукової літератури за результатами цитологічного дослідження рівня прозапальних цитокінів у ротовій та ясенній рідині залежно від виду одонтопрепарування під ортопедичні незнімні конструкції.

Мета дослідження. Проаналізувати літературні джерела з характеристикою рівня медіаторів прозапальних процесів у ротовій та ясенній рідині залежно від виду препарування зубів під незнімні конструкції на основі таких баз даних, як Scopus, Web of Science, MedLine, PubMed, NCBI, вивчення якого не перевищує 10 років, включаючи огляди літератури та результати клінічних випробувань.

Результати дослідження. На клінічних етапах підготовки зубів для протезування незнімними ортопедичними конструкціями, у маргінальному пародонті виникає локальна імунна відповідь на гострий подразник. Лабораторно це підтверджується доклінічними проявами ознак запального процесу шляхом розвитку дисбалансу цитокінового фону.

Ключовим прозапальним цитокіном є IL-1, основним протизапальним – IL-10. IL-1 ділиться на 2 фракції – IL-1α та IL-1β. Індукція синтезу IL-1 може бути викликана цілою низкою біологічно активних речовин, головними з яких є компоненти клітинних стінок бактерій, а також антигени, імунні комплекси, цитокіни, продукти розпаду клітин. При наявності подразнюючого фактора концентрація IL-1β підвищується в кілька разів, при цьому рівень протизапальних цитокінів знаходиться в стані, при якому відновлення балансу власними силами організму неможливе.

IL-10 є інгібітором запалення та цитокінового каскаду. Він пригнічує синтез цитокінів Т-хелперів 1, хемокінів, адгезивних молекул, пригнічує синтез моноцитарно-макрофагального фактора некрозу пухлини TNF-α, IL-1, IL-6, IL-12, гранулоцитарного колонієстимулюючого фактора. Таким чином, головною функцією IL-10 є обмеження та пригнічення запального процесу.

Висновки. Основні клінічні прояви захворювань пародонту залежать від активності клітин імунітету. Впливаючи на процеси та механізми регенерації, регулюючи баланс прозапальних та протизапальних цитокінів, стає можливим вплив на розвиток захворювань пародонту шляхом зупинення їх прогресування.

Ключові слова: прозапальні цитокіни, регулятори запального процесу, IL-1α, IL-1β, TNF-α.

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Popovich I. Yu.

Abstract. Introduction. The article gives an overview of the scientific literature on the results of a cytological study of the level of proinflammatory cytokines in the oral and gingival fluid, depending on the type of odontopreparation for cermet structures.

Purpose. Analyze literature sources with a characteristic of the level of mediators of proinflammatory processes in the oral and gingival fluid, depending on the type of odontopreparation for cermet structures.

Results. At the clinical stages of the preparation of teeth for prosthetics with non-removable orthopedic structures, a local immune response to the acute stimulus appears in the marginal periodontium.This is confirmed in laboratory by preclinical manifestations of signs of the inflammatory process by developing an imbalance in the cytokine background.

The main pro-inflammatory cytokine is IL-1, the main anti-inflammatory cytokine is IL-10. IL-1 is divided into 2 fractions – IL-1α and IL-1β. The induction of IL-1 synthesis can be caused by a number of biologically active substances, the main of which are the components of the cell walls of bacteria, as well as antigens, immune complexes, cytokines, cell-decay products. In the presence of an irritating factor, the concentration of IL-1β increases several times, while the level of anti-inflammatory cytokines is in a state where the balance of the body's own forces can not be restored.

IL-10 is an inhibitor of inflammation and a cytokine cascade. It inhibits the synthesis of cytokines of T-helpers 1, chemokines, adhesion molecules, suppresses the synthesis of monocyte-macrophage tumor necrosis factor TNF-α, IL-1, IL-6, IL-12, granulocyte colony-stimulating factor. Thus, the main function of IL-10 is the restriction and suppression of the inflammatory process.

Conclusions. The main clinical manifestations of periodontal diseases directly depend on the activity of immunity cells. By influencing the processes and mechanisms of regeneration, regulating the balance of proinflammatory and anti-inflammatory cytokines, it becomes possible to influence the development of periodontal diseases by suspending their progression.

Key words: proinflammatory cytokines, inflammatory regulators, IL-1α, IL-1β, TNF-α.

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