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ANALYSIS OF THE RESULTS OBTAINED AND SOME FEATURES OF CYTOKINE PROFILE IN MIXED SALIVA OF PATIENTS WITH GASTROINTESTINAL TRACT DISEASE

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ANNOTATION

Objective: To study the obtained data and some features of cytokine profile in mixed saliva of patients with gastrointestinal tract disease

Methods: 140 patients with gastrointestinal tract pathology were examined, including 98 men (70%) and 42 women (30%), mean age - 51.9 years. According to endoscopic examination, the patients had lesions of different parts of the GI tract (chronic gastritis; peptic ulcer disease of the stomach and 12-peritoneum). The control group included 25 practically healthy individuals. Diagnosis of the lesion of different GIT departments was based on classical criteria and was carried out taking into account clinical-endoscopic, functional and morphological data Verification of chronic gastritis was carried out according to classification signs.

Obtained results: it was found that the spectrum of oral cavity lesions in various concomitant diseases is wide. At the same time, they develop pathological conditions in oral cavity tissues, and on their background there is a reception of various preparations for their own correction.

Conclusions. Thus, the level of interleukin-4 in the mixed saliva of patients with GI disease decreased by 23% relative to the comparison group data. At the same time, the level of IL-6 in the mixed saliva of the examined patients exceeded the initial level in 2.4 times. IL-6 is known to be an inducer of inflammatory reaction and triggers the synthesis of acute phase proteins in the liver (C-reactive protein, serum amyloid A, etc.), as well as reduces the production of fibronectin, albumin and transferrin in the liver. The key anti-inflammatory factor IL-10. is known to inhibit the production of TNFα, IL-1β and IL -6 and inhibit the expression of major histocompatibility complex class II.

Keywords:cytokine profile, gastrointestinal tract, oral cavity

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АНАЛИЗ ПОЛУЧЕННЫХ РЕЗУЛЬТАТОВ И НЕКОТОРЫЕ ОСОБЕННОСТИ ЦИТОКИНОВОГО ПРОФИЛЯ В СМЕШАННОЙ СЛЮНЕ У ПАЦИЕНТОВ С ЗАБОЛЕВАНИЕМ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

АННОТАЦИЯ

Цель: изучить полученные данные и некоторые особенности цитокинового профиля в смешанной слюне у пациентов с заболеванием желудочно-кишечного тракта

Методы: Обследовано 140 пациента с патологией желудочно-кишечного тракта, из них 98 мужчин (70%) и 42 женщин (30 %), средний возраст - 51,9 лет. Согласно эндоскопическому исследованию у пациентов выявлялись поражения различных отделов ЖКТ (хронический гастрит; ЯБЖДК - язвенная болезнь желудка и 12-перстной кишки). В контрольную группу вошли 25 практически здоровых лиц. Диагностика поражения различных отделов ЖКТ базировалась на классических критериях и осуществлялась с учетом клинико-эндоскопических, функциональных и морфологических данных Верификация хронического гастрита проводилась по классификационным признакам

Полученные результаты: обнаружено что, спектр поражений полости рта при различных сопутствующих заболеваниях широк. При этом, они развивают патологических состояний в тканях ротовой полости, и на их фоне имеет место прием различных препаратов для собственной коррекции.

Выводы. Таким образом, снижение уровня интерлейкина-4 в смешанной слюне больных заболеванием ЖКТ на 23% относительно данных группы сравнения. При этом, уровень ИЛ-6 в смешанной слюне у обследованных пациентов превысил исходный уровень в 2,4 раза. Как известно ИЛ-6 является индуктором воспалительной реакции и запускает синтез белков острой фазы в печени (С-реактивного белка, сывороточного амилоида А и др.), а также снижает продукцию фибронектина, альбумина и трансферрина в печени. Как известно, ключевой противовоспалительный фактор ИЛ-10. ингибирует продукцию TNFα, IL-1β и IL -6 и препятствует экспрессии главного комплекса гистосовместимости II класса.

Ключевые слова:цитокиновый профиль, желудочно- кишечный тракт, ротовая полость

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tibbiyot fanlari nomzodi, dotsent
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OSHQOZON-ICHAK TRAKTI KASALLIGI BO'LGAN BEMORLARDA OLINGAN NATIJALARNI TAHLIL QILISH VA ARALASH TUPURIKDAGI SITOKIN PROFILINING BA'ZI XUSUSIYATLARI

ANNOTATSIYA

Maqsad: oshqozon-ichak trakti kasalligi bo'lgan bemorlarda aralash tupurikdagi sitokin profilining topilmalari va ba'zi xususiyatlarini o'rganish.

Material va metodlar: Oshqozon-ichak trakti patologiyasi bo'lgan 140 bemor tekshirildi, ulardan 98 nafari erkaklar (70%) va 42 nafari ayollar (30 %), o'rtacha yoshi 51,9 yosh. Endoskopik tekshiruvga ko'ra, bemorlarda oshqozon - ichak traktining turli qismlarining shikastlanishi aniqlandi (surunkali gastrit,shqozon va o'n ikki barmoqli ichakning oshqozon yarasi). Nazorat guruhiga 25 nafar sog'lom shaxs kirdi. Oshqozon-ichak traktining turli bo'limlariga zarar etkazish diagnostikasi klassik mezonlarga asoslangan va klinik-endoskopik, funktsional va morfologik ma'lumotlarni hisobga olgan holda amalga oshirilgan surunkali gastritni tekshirish tasniflash xususiyatlariga muvofiq amalga oshirildi.

Natijalar: turli xil qo'shma kasalliklarda og'iz bo'shlig'ining shikastlanish spektri keng ekanligi aniqlandi. Shu bilan birga, ular og'iz bo'shlig'i to'qimalarida patologik sharoitlarni rivojlantiradilar va ularning fonida o'zlarining tuzatishlari uchun turli xil dorilar qabul qilinadi.

Xulosa. Shunday qilib, oshqozon-ichak trakti kasalligi bilan og'rigan bemorlarning aralash tupurigidagi interleykin-4 darajasining taqqoslash guruhi ma'lumotlariga nisbatan 23% ga kamayishi.

Shu bilan birga, tekshirilgan bemorlarda aralash tupurikdagi il-6 darajasi boshlang'ich darajadan 2,4 baravar oshdi. Ma'lumki, il - 6 yallig'lanish reaktsiyasining induktori bo'lib, jigarda o'tkir fazali oqsillarning sintezini boshlaydi (C-reaktiv oqsil, sarum amiloid a va boshqalar), shuningdek jigarda fibronektin, albumin va transferrin ishlab chiqarishni kamaytiradi. Ma'lumki, il-10 ning asosiy yallig'lanishga qarshi omili. Tnfa, IL-1b va IL -6 ishlab chiqarishni inhibe qiladi va II darajali asosiy gistokompatibillik kompleksining ifodalanishiga to'sqinlik qiladi.
Kalit so'zlar: sitokin profili, oshqozon-ichak trakti, og'iz bo'shlig'i

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Introduction: Immunological mechanisms play a leading role in the pathogenesis of inflammatory-destructive processes in the periodontium. That is why clinical manifestations of chronic generalised periodontitis depend not so much on the pathogenicity and virulence of the corresponding microflora as on the nature of bacterial-gostal relationships, i.e. largely on the degree of reactivity of the macroorganism, determined by the functional state of the immune system. Therefore, an important stage in understanding the nature of inflammatory periodontal diseases is the study of those immunological factors (cytokines and antibodies), as well as enzymes that can cause shifts in the morpho-functional state of the supporting apparatus of the tooth, as well as cause the corresponding clinic of this pathology. Cytokines are protein-peptide factors produced by cells and carrying out short-range regulation of intercellular and intersystem interactions. Not only immunocompetent but also endothelial cells can be cytokine producers. It has been established that the same cytokine can be produced by cell types of different histogenetic origin in different organs [1] The functions of cytokines include regulation of immune response, inflammatory reactions, haemopoiesis, participation in apoptosis, angiogenesis, chemotaxis [3]. To date, the cytokine system consists of more than 300 polypeptide substances. The most well studied are cytokines of the immune system, which are secreted during the realisation of mechanisms of general and local immunity, showing their activity at extremely low concentrations. These molecules can be considered as mediators of inflammatory reactions, possessing, at the same time, endocrine, paracrine and autocrine types of regulation[5]. In the work of cytokines, the phenomena of antagonism and synergism, their interchangeability, as well as pleiotropy, i.e. the ability of the same mediator to influence different processes, act on many types of cells, causing different effects, are noted [4]. Interleukins are of the greatest clinical and immunological interest. According to the mechanism of action, these polypeptides can be divided into proinflammatory (inducing inflammatory response); anti-inflammatory (limiting the development of inflammatory response); and regulators with their own effector functions (cytotoxic, antiviral, etc.) [2]. Since cytokines are mediators of local action, the most indicative and reliable is the assessment of their concentration in the corresponding tissues and natural fluids (e.g., gingival fluid). The diagnostic value of cytokines lies in the fact that the study of their level makes it possible to judge the functional activity of different types of immunocompetent cells, the severity and severity of the inflammatory process, the probability of its chronicity, transition to the systemic level, as well as the prognosis [4]. Cytokine synthesis increases dramatically as a result of "tissue stress", i.e. it is an inducible process and is practically absent outside the inflammatory reaction and immune response [2]. For example, when exposed to an infectious agent, in particular - molecules of lipopolysaccharides, peptidoglycans and muramyl dipeptides, which are part of the cell wall of Gram-negative periodontopathogenic bacteria, there is an activation of macrophages, increasing the production of proinflammatory cytokines (IL-1β, TNF-α, etc.). These cytokines circulating in the blood stimulate the secretion of acute phase proteins [6]. In case of late elimination of a proinflammatory agent (antigen) and transition of the process into a chronic form (with increased activity of negative regulators inhibiting inflammation, e.g. IL-10) - there will be significant destructive processes. Thus, monocytes and macrophages activated by pathogens 20 synthesise a whole cascade of cytokines, causing an imbalance between the pro- and anti-inflammatory pool, which, as mentioned above, leads to resorptive phenomena. The study of these processes formed the basis of the cytokine concept of the development of chronic inflammation, including in the periodontal complex[8]. The most pronounced, damaging effect on periodontal tissues is characteristic of proinflammatory IL-1β and TNF-α. In particular, there is a direct

correlation between the severity of periodontitis and the level of TNF-α in venous blood [2]. In turn, IL-1β is one of the main mediators of pathological process generalisation in the periodontium [9]. IL-1β producers are macrophages, to a lesser extent dendritic cells, endothelium, and fibroblasts. IL-1β stimulates the emigration of PMNL from bone marrow, causes exocytosis of lysosomal enzymes and free radicals by phagocytes, stimulates mast cell degranulation, activates prostacyclin production, and the formation of acute phase proteins by hepatocytes, which is the reason for its pyrogenic effect[8]. IL-1β and TNF-α stimulate bone tissue resorption (activate osteoclasts); adversely affect tissue repair by inhibiting the process of resynthesis of collagen fibres by fibroblasts; stimulate collagenase synthesis. Moreover, the above activity is manifested at insignificant concentrations of these polypeptides [11]. It has been established that during the progression of generalised periodontitis there is a significant increase in the level of these cytokines both in gingival tissues and gingival fluid [14]. Moreover, the formed cytokines not only adversely affect the surrounding tissues, but also stimulate further activation of the cells synthesising them, which shows their paracrine regulation[13]. With chronicity of inflammatory processes in the periodontium (which is especially characteristic of the elderly), there is an imbalance between cytokines, which leads to hyperactivation of osteoclasts. Accordingly, the degree of degenerative and destructive lesions of alveolar bone in generalised periodontitis is directly related to the level of accumulated cytokines [12]. IL-8 belongs to the chemokine family and is a low molecular weight proinflammatory cytokine. Its production is carried out under the influence of bacterial endotoxins, as well as some cytokines (TNF and IL-1). IL-8 has the ability to activate neutrophils and monocytes, initiating their chemotaxis to the focus of inflammation, and can have a destructive effect on bone tissue. Increased level of this cytokine correlates with acute and chronic inflammatory conditions, tissue neutrophil infiltration. When studying the cytokine profile of periodontitis patients, an increase in IL-8 in venous blood and gingival fluid was also found [7]. In addition, increased secretion of anti-inflammatory IL-10 plays a special role in the pathogenesis of periodontitis and bone resorption, which does not allow the development of a full-fledged inflammatory response, the main task of which is the elimination of the pathogen. As a result, a sluggish course of periodontitis is clinically observed against the background of pronounced destructive processes in the periodontal complex [12]. Factors of humoral immunity, primarily antibodies - immunoglobulins produced by plasma cells (activated B-lymphocytes), which are specific for a particular antigen, play an important role in the pathogenesis of chronic generalised periodontitis. Immunoglobulins of three classes are most associated with periodontal tissues: IgA, IgG and IgM [15]. It has been established that immunoglobulins enter the gingival fluid from the bloodstream. Thus, the factors of local immunity determined in the gingival fluid are a reflection of the general humoral immunity and correlate with it. In its turn, the gingival sulcus can be positioned as a kind of "representative" of the general immunity in the periodontal complex [16]. At the same time, a certain share of immunoglobulins is formed locally, in the tissues of marginal periodontium, so the origin of these antibodies determined during inflammation has both systemic and local character[10]. It is established that with the progression of periodontal pathology there is a gradual decrease in the level of nonspecific defence and an increase in the activity of specific factors. In particular, in inflammatory destructive processes in the periodontal complex there is an increase in the level of immunoglobulins, which is the result of pronounced antigenic stimulation as bacterial invasion spreads under the gingiva. There is an active synthesis of antibodies, with their subsequent transudation into the gingival fluid[9]. Elevated IgA levels indicate the presence of acute or chronic infection (including bacterial origin). Immunoglobulins of class M carry out antibacterial immunity and are produced first in response to an infectious factor. Immunoglobulins of class G are the leading effectors of humoral immunity. It has been established that the bulk of antibodies to bacteria belong to IgG [11]. High levels of sIgA, IgG, and complement fractions are found in the contents of periodontal pockets. In case of direct reaction of 23 antibodies with antigens - cytotoxic reactions are observed, which leads to the destruction of tissue structures. It is established that the most frequent cytotoxic antibodies are represented by immunoglobulins of G and M classes [13]. High activity of enzymes, primarily lactate dehydrogenase (LDH) and alkaline phosphatase (ALP), plays an important role in the development and progression of inflammatory and destructive processes

in the periodontal complex [12]. The sources of enzymes in the periodontal complex are host cells (macrophages, PMNL, fibroblasts and osteoclasts), as well as microorganisms of dental plaque. The appearance of active forms of enzymes in gingival fluid initiates tissue destruction processes [10]. Lactate dehydrogenase (LDH) is an intracellular, cytoplasmic, glycolytic enzyme that catalyses the reversible hydrogen splitting from the lactic acid molecule. The extracellular localisation of this enzyme indicates cell death and, consequently, tissue damage, which is observed when gingival epitheliocytes are destroyed and the enzyme is released into the interstitium, which leads to an increase in the level of this enzyme in gingival and oral fluids [6]. When LDH concentration increases, there is a disruption of the functional activity of a number of immunocompetent cells, in particular neutrophils, as well as a decrease in synthetic activity in tissues [5]. In the presence of periodontal pockets, as well as the progression of destructive processes in the periodontium, there is a significant increase in LDH activity, and its increase correlates with the severity of periodontitis [3]. One of the most reliable indicators of bone metabolism is the determination of alkaline phosphatase, which catalyses the detachment of phosphoric acid from its organic compounds. The enzyme is located on the surface of the cell membrane and takes part in phosphorus transport [14]. Numerous histochemical studies confirm the active participation of alkaline phosphatase in bone tissue metabolism. In particular, a significant increase in the content as well as activity of alkaline phosphatase is determined during bone tissue destruction [8]. In addition to osteoblasts, this enzyme is found in lysosomes of neutrophils, as well as in gingival epithelial cells. Moreover, the increase of alkaline phosphatase activity in gingival fluid can be an indicator of destructive processes observed in periodontitis. A direct correlation between the activity of alkaline phosphatase, the level of bone tissue resorption, and the nature of the course of inflammatory processes in the periodontium has been established [7]. Thus, the analysis of cytokine profile, determination of antibody levels and enzyme activity in gingival fluid and venous blood of individuals suffering from chronic generalised periodontitis is a necessary stage of diagnosis, allowing to assess the degree and severity of inflammatory-destructive processes in the periodontium, as well as to choose the most optimal, etiopathogenetically justified treatment.

Aim of the study: Study of immunological features of mixed saliva in patients with gastrointestinal tract disease**.**

Material and methods of research: We have investigated 140 patients with pathology of gastrointestinal tract, including 98 men (70%) and 42 women (30%), average age - 51.9 years in outpatient conditions of Tashkent State Dental Institute for the period 2020-2023. According to endoscopic examination, the patients had lesions of different parts of the GI tract (chronic gastritis; peptic ulcer disease of the stomach and 12-peritoneum). The control group included 25 practically healthy individuals. Diagnosis of the lesions of various GI tract sections was based on classical criteria and was carried out taking into account clinical-endoscopic, functional and morphological data Verification of chronic gastritis was carried out according to classification signs proposed by the International Association of Gastroenterologists on the basis of endoscopic and morphological criteria. Patients and healthy controls were monitored according to a unified programme including general clinical examination, esophagogastroduodenoscopy (EGDS). Biomaterial was collected in the morning hours, on an empty stomach into graduated tubes. In all patients, collection of mixed saliva samples was performed initially before drug administration. Before starting the procedure, the patient rinsed the mouth with distilled water for 30 seconds, followed by 5 minutes of rest. The patient then swallowed all accumulated saliva, after which direct collection of material began for 15 minutes. When finished, the tube was tightly capped, placed in an ice container and transported to the laboratory within an hour and a half. In the laboratory, the tubes were centrifuged at 3000 rpm for 10 minutes at 4°C, after which the saliva sample was frozen and stored at -80°C until examination. Pro- and anti-inflammatory cytokines (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-a), as well as alpha-defensin 1-3, were determined in blood and oral fluid by solid-phase enzyme-linked immunosorbent assay using test systems produced by Vector-Best CJSC (Novosibirsk, Russia). Statistical processing of the data was performed on a personal computer using a standard software package for applied

statistical analysis (Statistica for Windows v. 7.0). The value of $p<0.05$ was used to assess the reliability of differences.

RESULTS: It is known that the spectrum of oral cavity lesions in various concomitant diseases is wide. At the same time, concomitant diseases contribute to the development of pathological conditions in the tissues of the oral cavity, and on their background there is the use of various drugs for their correction. Gerontological population, which is the main consumer of medicines, should not be ignored. When analysing the nosologies of gastrointestinal tract diseases, atrophic and chronic gastritis prevailed. According to the data obtained, 63% of patients with gastrointestinal pathology noted the presence of bad breath (halitosis). Dryness of the oral cavity was reported by 28% of the respondents. Colour change of tongue and gingiva was noted by 52% of respondents. Burning sensation in the oral cavity was noted by 8% of respondents, and 12% of patients indicated the presence of hypersalivation. To determine the intensity of the carious process in patients with GI pathology, the CPP index was used. The KPU index in patients was 8.48+0.91, which corresponds to the average level of caries intensity. The number of filled teeth ranged from 1 to 6. The number of extracted teeth was insignificantly lower than the number of filled teeth, it ranged from 1 to 24 teeth. The values of the KPU index were significantly positively dependent on the diagnosis of GI nosology. The lowest values of the CPU index were present in patients with chronic gastritis, and the highest in patients with CJD. In addition to clinical examination of oral tissues, in patients with GI pathology, a study of mixed saliva, which reflects the changes occurring in the oral cavity, was performed. It is known that cytokines, possessing the ability to regulate the processes of proliferation, differentiation, functional activity of cells, apoptosis, haemopoiesis, angiogenesis, as well as the ability to carry out intercellular and intersystem interactions, determine the type, strength and duration of the immune response, can have both pro- and anti-oncogenic effects. Their mechanism of action is realised in an extra- and/or intracellular way through binding to specific receptors located on the cytoplasmic membrane of cells or circulating in soluble form. IL-1a and IL-1p are produced by activated macrophages, keratinocytes as inactive precursor protein molecules and are converted into active cytokines by the action of either caspase-1 protease or IL-1-converting enzyme (1CE). The ability of IL-1p to inhibit gastric acid formation is realised both directly, through its effect on receptors of parietal cells, and indirectly, through stimulation of synthesis of PG E2, which is a strong inhibitor of hydrochloric acid secretion, and through activation of receptors in the central nervous system, located in the anterior hypothalamic region in the paraventricular nucleus.

Our studies have shown an average 3.6-fold increase in IL-1a concentrations in mixed saliva in patients with gastrointestinal tract disease compared to healthy patients. High values of IL-1a in blood in patients with gastrointestinal tract disease most likely indicate the development of chronic inflammatory process. This condition is characterised by increased production of cytokines with proinflammatory effects, i.e. cytokines in these pathological processes play the role of both aggression and protection factors. Their content depends on the etiological factor, variant of course, stage, duration of chronic inflammatory and destructive disease. In response to chronic inflammation of the gastrointestinal mucosa, there is an induction of interleukin-8 secretion by macrophages. As is known, activating neutrophils, IL-8 leads to their degranulation, release of lysosomal enzymes, leukotrienes, which have a damaging effect on the gastrointestinal mucosa. In addition, increased IL-8 levels are also found in peripheral blood regardless of localisation. In our studies, we observed an increase in the level of IL-8 in mixed saliva in patients with gastrointestinal tract disease on average 3 times relative to the indicators of healthy individuals. The pro-inflammatory cytokine tumour necrotising factor α (TNF-α) plays an important role in the formation of the inflammatory response. TNF-α is considered the strongest stimulus for IL-1β production and is synthesised by T-lymphocytes and macrophages. This cytokine is multifunctional and plays a predominant role in the formation of local and general pathological processes, in particular, it activates the synthesis of pro-inflammatory interleukins, stimulates T- and B-lymphocytes, regulates the intensity of inflammation, increases the phagocytic activity of monocytes, nitric oxide formation, which also takes part in the implementation of physiological processes and inflammatory response in the mucosa of the gastroduodenal region. As can be seen from the presented results of studies, the level of tumour necrotising factor α was

increased relative to the indicators of the comparison group by 1.6 times. Prolonged and pronounced increase of TNF-a in mixed saliva in patients with GIT disease may contribute to the imbalance between the osteoforming function of osteoblasts and osteo-destructive function of osteoclasts towards hyperactivation of the latter in the dentoalveolar system.

Conclusions: Thus, the increase in IL-4 level in this situation probably has a compensatory character in relation to pro-inflammatory cytokines and acts as a factor stabilising the course of the disease. In addition, it is indicated that the level of TNF-α and IL-6 can indirectly judge the activity of the inflammatory process in the gastroduodenal zone. The analysis of the obtained results of the study, presented in Table 1, indicates a decrease in the level of interleukin-4 in the mixed saliva of patients with GIT disease by 23% relative to the data of the comparison group. At the same time, the level of IL-6 in the mixed saliva of the examined patients exceeded the initial level by 2.4 times. IL-6 is known to be an inducer of inflammatory reaction and triggers the synthesis of acute phase proteins in the liver (C-reactive protein, serum amyloid A, etc.), as well as reduces the production of fibronectin, albumin and transferrin in the liver. The key anti-inflammatory factor IL-10. is known to inhibit the production of TNFα, IL-1β and IL -6 and inhibit the expression of major histocompatibility complex class II. One of the markers of activation of the inflammatory process is considered to be the level of antibacterial proteins defensins. We studied the content of a-defensins (HNP1-3) in the saliva of patients with GI diseases. As can be seen from the presented research results, the content of a-defensins 1-3 in the oral fluid of the patients of the main group and healthy individuals presented in Table 1 indicates a reduced secretion of a-defensins 1-3 in the oral fluid of the main group relative to the indicators of the comparison group. The identified evidence suggests inactivation of a-defensins, which may lead to increased microbial colonisation and increase the risk of viral and bacterial infections in the oral cavity. Low levels of diphensins in the mixed saliva of patients with GI disease contribute to decreased IL-8 secretion and progression of the inflammation process in the oral mucosa. Thus, when studying the content of cytokines and antimicrobial peptide in mixed saliva of patients with GI disease, the predominance of pro-inflammatory cytokines over anti-inflammatory cytokines and a decrease in the level of antimicrobial peptide were noted, which may activate bone resorption. In general, the identified changes may lead to an imbalance in the local immune response of mucous membranes and the development of both autoimmune and inflammatory diseases of the oral cavity.

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