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MODERN VIEWS ON THE ETIOLOGY AND ROLE OF MICROBIAL PERSISTENCE IN THE DEVELOPMENT OF INFLAMMATORY PROCESSES IN THE PERIODONTAL COMPLEX (review)

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Key words: *periodontitis, oral mucosa, gums, dental plaque, periodontium, traumatic occlusion, microorganisms*
Ключові слова: *пародонтит, слизова оболонка порожнини рота, ясна, зубна бляшка, пародонт, травматична оклюзія, мікроорганізми*

Abstract. Modern views on the etiology and role of microbial persistence in the development of inflammatory processes in the periodontal complex (review). Marfiian O.V., Demkovych A.Ye., Bondarenko Yu.I., Yaremchuk O.Z. *Alveolar tissue diseases cause the appearance of dentition defects, thereby reducing the patients' work capacity and quality of life. The purpose of this research was to investigate, modern views on the etiology of periodontitis and the role of microbial persistence in the development of inflammatory processes of periodontal complex basing on a review of literary sources. Literature review was conducted using PubMed, Web of Science, Scopus, Google Scholar from 2018 to March 2024. There were no restrictions on the date of publication or the language of scientific sources. Searches were conducted according to MeSH (Medical Subject Headings) with using the following search terms: "periodontitis", "oral mucosa", "gums", "dental plaque", "periodontium", "traumatic occlusion", "microorganisms". In total, during the initial analysis 82 literary sources were selected and processed, after further systematization of the selected information using general scientific methods, 70 of them remained. Used methods: bibliographic and analytical. Generalized periodontitis is a chronic inflammatory-dystrophic process that occurs as a result of various factors. In the pathogenesis of this disease, the key role is played by the inflammatory process, which is a complex interaction of microcirculatory, hematological and connective tissue reactions to the lesion. Local (exogenic) and general (endogenic) causative factors are distinguished. The main factors that cause pathological changes in periodontium are bacterial biofilm, traumatic occlusion and various anatomical anomalies. Dental plaque occupies a special and main place among the causes of periodontitis. At present, leading pathogenetic links in the development of the inflammation in the periodontium, in particular, the disruption of free radical oxidation, the processes of peroxide oxidation of lipids and proteins, the disorder of the functional state of the antioxidant system, the formation of oxidative stress, as well as the humoral link of adaptive immune protection and cytokinesis, have not been sufficiently studied. There is no doubt about the role of the microbial factor in the etiology of periodontal diseases, but the penetration of microbes into the periodontium does not always lead to the development of the disease, because the organism has a number of protective mechanisms that counteract the development of inflammation.*

Реферат. Сучасні погляди на етіологію та роль мікробної персистенції в розвитку запальних процесів пародонтального комплексу (огляд літератури). Марфіян О.В., Демкович А.Є., Бондаренко Ю.І., Яремчук О.З. *Захворювання пародонтальних тканин спричиняють появу дефектів зубних рядів, чим знижують працездатність та якість життя пацієнтів. Метою цієї роботи було дослідити на підставі огляду літературних джерел сучасні погляди на етіологію пародонтиту та роль мікробної персистенції в розвитку запальних процесів пародонтального комплексу. Огляд літератури проводився за допомогою PubMed, Web of Science, Scopus, Google Scholar з 2018 року до березня 2024 року. Не було обмежень щодо дати публікації чи мови наукових джерел. Пошуки проводилися за термінами MeSH (Medical Subject Headings) з використанням таких пошукових термінів: «пародонтит», «слизова оболонка порожнини рота», «ясна», «зубна бляшка», «пародонт», «травматична оклюзія», «мікроорганізми». Усього при первинному аналізі було відібрано та оброблено 82 літературних джерела, після подальшої систематизації відібраної інформації за допомогою загальнонаукових методів із них залишилось 70. Використані методи: бібліографічний та аналітичний. Генералізований пародонтит є хронічним запально-дистрофічним процесом, який виникає внаслідок різноманітних факторів.*

У патогенезі цього захворювання ключову роль відіграє запальний процес, який представляє собою складну взаємодію мікроциркуляторних, гематологічних і сполучнотканинних реакцій на ураження. Серед причинних факторів розвитку пародонтиту розрізняють місцеві (екзогенні) та загальні (ендогенні). Головними факторами, які спричиняють виникнення патологічних змін у тканинах пародонта, є бактеріальна біоплівка, травматична оклюзія та різноманітні анатомічні аномалії. Особливе та основне місце серед цих причин, безумовно, посідають мікроорганізми зубної бляшки. На сьогоднішній день ще недостатньо вивчено провідні патогенетичні ланки розвитку запального процесу в пародонті, зокрема порушення вільнорадикального окиснення, процесів пероксидного окиснення ліпідів, білків, порушення функціонального стану антиоксидантної системи, формування оксидативного стресу, а також гуморальної ланки адаптивного імунного захисту та цитокіногенезу. Роль мікробного фактора в етіології захворювань пародонта не викликає сумнівів, проте проникнення мікроорганізмів у тканини пародонта не завжди призводить до розвитку захворювання, адже в організмі існує низка захисних механізмів, які протидіють розвитку запалення.

Diseases of the alveolar tissues cause the appearance of dentition defects, thereby reducing the working capacity and quality of life of patients. Periodontitis affects the development of pathological processes in other organs and systems. The widespread prevalence of periodontal diseases and their progressive course lead to tooth extraction, aesthetic discomfort, the appearance of tooth hyperesthesia, gum recession, periodontal abscess, as well as an increase in the risk of diseases of the cardiovascular system and gastrointestinal tract [1]. The importance of this problem is emphasized by the long-duration treatment of periodontal diseases, therefore it is very important to start treatment as early as possible before the development of inflammatory periodontal diseases into a dystrophic-inflammatory process – generalized periodontitis [2]. In recent years, there has been a trend towards an increase in the incidence of generalized periodontitis, especially among young people. The study of the epidemiology of periodontal diseases, in particular inflammatory diseases, is of significant scientific and practical interest [3], and can serve as a basis for the purposeful prevention of generalized periodontitis, its complicated forms and chronicity of the pathological process of periodontal complex tissues.

The purpose of this work was to investigate, modern views on the etiology of periodontitis and the role of microbial persistence in the development of inflammatory processes of the periodontal complex basing on a review of literary sources.

MATERIALS AND METHODS OF RESEARCH

The literature review was based on the analysis of a significant volume of digital publications, which were found as a result of a literature search in global databases, such as PubMed (https://pubmed.ncbi.nlm.nih.gov), Web of Science Core Collection (https://www.webofscience.com/wos/woscc/basic-search), Scopus (https://www.scopus.com) and Google Scholar (https://scholar.google.com.ua). A review of literary sources was conducted in order to identify and process publications in which the etiological factors of inflammatory processes of the periodontal complex were studied, as well as the influence of the microbial factor and dental plaque on the development of generalized periodontitis. The literature review analyzing the most recent evidence covered the period of the year 2018 to March, 2024. Searches were conducted using MeSH (Medical Subject Headings) terms with using synonyms and combinations of the following search terms: "periodontitis", "oral mucosa", "gingiva", "dental plaque", "periodontal", "traumatic occlusion", "microorganisms ". In addition to the electronic search, a similar search was conducted in the bibliographic references of the selected articles. A total of 82 sources of literature were selected and processed during the primary analysis, which included evidence-based randomized trials, systematic reviews, and others. After further systematization of the selected information using general scientific methods (analysis, synthesis, generalization, critical evaluation of the collected data), 70 most relevant sources remained. Exclusion criteria: publications that did not meet the purpose of this review, results, publication language other than English and Ukrainian. Methods used for design and writing of the article: bibliographic and analytical. The study was approved by the Bioethics Commission of Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine (protocol No. 77 dated April 18, 2024).

RESULTS AND DISCUSSION

In the pathogenesis of periodontitis, the inflammatory process plays a key role, which is a complex interaction of microcirculatory, hematological and connective tissue reactions to the lesion [4]. These reactions can vary in intensity, but basically remain similar in nature. Damage to cells and microvessels can be the initial trigger for the development of an inflammatory response [5].

Local (exogenous) and general (endogenous) factors are distinguished between the causative factors of the development of inflammatory periodontal diseases [6]. Local etiological factors usually include the following: traumatic impact of orthopedic prostheses, defects in tooth filling, presence of carious

lesions, dentition defects, anomalies of the bite, problems with prosthetics, improper attachment of labial frenulums, minor anomalies of the oral cavity, insufficient oral hygiene, as well as bad habits and other factors [7, 8, 9].

Among the common reasons for the development of inflammatory periodontal diseases, the most important are: general polymorbidity of the body, impaired immunological reactivity, taking certain medications, negative environmental effects, extreme conditions such as stress, etc. [10]. According to the results of research by the scientific community, a third of the world's population has some genetic predisposition to periodontal diseases [11]. A low socioeconomic standard of living [12], the nature of nutrition, which results in insufficient intake of vitamins, macro- and microelements [1], hypo- and vitamin deficiency, metabolic disorders, metabolic diseases, endocrinopathy, diseases of the gastrointestinal tract and blood systems are common risk factors for periodontitis, and recently the role of elemental deficiency of phytoadaptogens and polyphenols [13], stress and chronic psycho-emotional stress, some physical factors – radiation and chemotherapy, industrial hazards [14] has been considered. The relationship between the occurrence of pathological changes in the periodontal tissues and excess body weight, bad habits, among which the main place is given to tobacco smoking, as well as the use of alcohol and narcotic drugs [15] has been proven. These factors can contribute to the development of more severe forms of periodontal disease.

One of the most frequent reasons for the resistance of generalized periodontitis to local treatment is the presence of an undiagnosed concomitant pathology in the patient, which significantly reduces the effectiveness of periodontal treatment [16]. The relationship between the occurrence of the inflammatory process in the periodontal complex and systemic diseases, namely: cardiovascular diseases [17], rheumatoid arthritis and atherosclerosis, as well as systemic osteoporosis, endocrine disorders, etc., has been proven [18, 19]. The impact of endocrine pathology on dental diseases is reflected in a number of scientific studies, which established a close relationship between the state of the periodontium and disorders of the endocrine system [20]. A number of studies have demonstrated a higher prevalence of periodontal disease among patients with diabetes than among healthy individuals [21]. In the etiology and pathogenesis of chronic periodontitis, the role of diabetes mellitus, including bacterial invasion, reparative processes, blood circulation, and metabolism in the tissues of the periodontal complex is discussed. It should be noted that an important role in the pathogenesis of periodontal pathology is played by diabetic microangiopathy, which leads to hypoxia of periodontal tissues and their damage by microorganisms. According to a number of authors, periodontitis in patients with diabetes occurs in almost 100% of cases [22].

Currently, more and more publications testify to the relationship between diabetes and periodontal diseases, this allows dentists to take a specialized approach to treatment, taking into account both pathologies. Inflammatory periodontal diseases, according to scientific studies, are one of the most common complications of diabetes, along with neuropathy, nephropathy, retinopathy, and micro- and macrovascular diseases [23].

Hypothyroidism is also considered one of the most common diseases of the endocrine system. A number of authors testify to the high prevalence of chronic generalized periodontitis in patients with hypothyroidism [24]. In a number of works devoted to this pathology, it was found that the depth of periodontal pockets is significantly less in patients with a subclinical form of primary hypothyroidism in all groups of teeth of the upper and lower jaws, compared to patients with clinical manifestations [25].

According to modern views on the etiology and pathogenesis of chronic generalized periodontitis, great importance is given to the systemic damage of bone tissue, in particular osteoporosis. The works of Twardowski S. and co-authors proved the clinical and pathogenetic relationships between generalized periodontitis and osteoporosis [26]. Prots H. and co-authors (2021) established a correlation between the degree of bone mineralization of the jaws and the severity of generalized periodontitis. The more severe the process of periodontitis, the lower the density of bone structures in the maxillofacial region [27].

The role of antioxidants in the development of periodontal pathology has been determined [28]. Research conducted in recent years has made it possible to expand and supplement the current understanding of the role of vitamin D in the regulation of many physiological processes of the body [29]. It has been proven that vitamin D deficiency contributes to the development of not only skeletal, but also some extraskeletal diseases. A wide range of biological effects of active metabolites of vitamin D and publications on the relationship between the state of the oral cavity and the status of vitamin D in the body make it possible to evaluate its role in the development of dental pathology in a new way, as well as to develop the most effective approaches to their diagnosis and treatment [29].

The main local factors that cause pathological changes in periodontal tissues are bacterial biofilm,

traumatic occlusion, and various anatomical anomalies (shortening of the frenulum of the upper, lower lip, and tongue, the presence of dense mucous cords, a fine lining of the oral cavity, etc.) [30]. Additional factors that can worsen the condition of the periodontium are nutritional disorders, deficiency of macro- and microelements, hypo- and vitamin deficiency, metabolic disorders, metabolic diseases, endocrinopathy, diseases of the gastrointestinal tract [1] and blood systems. These factors can contribute to the development of more severe forms of periodontal diseases [31].

Traumatic occlusion, and even disharmony of the prosthetic relationships of the dentitions, plays a major role in the pathology of the periodontal complex [32]. Occlusive trauma leads to ischemia of the periodontium and the development of dystrophic processes in it. The destruction of the dental ligamentous apparatus of some teeth determines the functional load of others, which can also activate dystrophic-destructive processes, including in bone tissue, increasing osteoclastic resorption [33].

Researchers believe that a disruption of the systemic and local antioxidant balance has a significant impact on the development of dystrophic-inflammatory periodontal diseases [34]. In many scientific studies, significant changes in the biochemical indicators of the composition of oral fluid in gingivitis and periodontitis were found [35]. According to scientists, in the formation of dystrophic-inflammatory diseases of the periodontium, disruptions in the systemic and local antioxidant balance play an important role [36]. Many studies have revealed significant biochemical changes in saliva in gingivitis and periodontitis [37]. An important role in the development and progression of inflammatory and destructive processes in the periodontal complex is played by the high activity of enzymes, in particular lactate dehydrogenase and alkaline phosphatase [38].

Enzymes in the periodontal complex have their sources both in the cells of the host organism (such as macrophages, polymorphonuclear leukocytes, fibroblasts and osteoclasts), and in the microorganisms of dental plaque. The appearance of active forms of enzymes in the gingival fluid causes the start of tissue destruction processes [39].

Lactate dehydrogenase (LDH) is an intracellular, cytoplasmic enzyme involved in the glycolytic process [40]. Its extracellular localization indicates cell death and tissue damage, as this enzyme is released into the intercellular space and can be detected in gingival and oral fluids. An increase in the concentration of lactate dehydrogenase often indicates a disorder of the functional activity of a number of immunocompetent cells, in particular neutrophils, and a decrease in synthetic activity in tissues [41]. In the presence of periodontal pockets and the progression of destructive processes in the periodontium, a significant increase in LDH activity is observed. At the same time, the growth of LDH activity correlates with the severity of periodontitis [42].

One of the most reliable indicators of bone metabolism is the assessment of alkaline phosphatase (ALP) activity [43]. This enzyme accelerates the separation of phosphate from organic compounds, which allows us to assess the state of the bone remodeling process and the activity of osteoblasts [44]. The enzyme is located on the surface of the cell membrane and is involved in the transport of phosphorus [45]. Numerous histochemical studies confirm the active participation of ALP in the metabolism of bone tissue. At the same time, an increase in the activity of this enzyme in the gingival fluid can be an indicator of the destructive processes observed in periodontitis. A direct correlation between the activity of ALP and the level of bone tissue resorption, as well as the course of inflammatory processes in the periodontium was established [46].

Most researchers believe that the disruption of microcirculation plays a primary role in the development of periodontitis. This disruption causes tissue hypoxia, activates free radical oxidation and leads to disorganization of biomembranes, which is accompanied by the release of physiologically active pro-inflammatory substances, such as eicosanoids and cytokines [47]. The importance of free radical oxidation processes, especially lipid peroxidation, in the occurrence of chronic inflammatory processes of the periodontal complex has been established [34].

Despite the essential importance of each of the factors listed above, it is worth recognizing that dental plaque microorganisms occupy a special and main place among the causes of inflammatory periodontal diseases, although one of the necessary conditions for activating the virulence of periodontopathogenic microflora is a predisposition to it [48]. Microbial plaque is considered the leading etiological factor in the formation of inflammatory and dystrophic-inflammatory diseases of the periodontal complex [49]. Traditionally, in periodontology, special attention is paid to this factor, as the leading and most important one. The involvement of microorganisms in the development of alveolar tissue inflammation is a widely recognized phenomenon both in the national and international scientific community [50].

One of the most important factors in the development of inflammatory and dystrophic-inflammatory diseases of periodontal tissues is the formation of dental plaque, which is formed due to the transformation of soft dental plaque into it [51]. Dental plaque contains food residues, microorganisms,

exfoliated epithelial cells, leukocytes, and a mixture of proteins and lipids from saliva [52].

Plaque collects in those areas of the oral cavity that do not receive proper cleaning during meals or hygienic procedures. These sites, known as retention sites, include the cervical region, tooth contact surfaces, periodontal pockets, filling surfaces, dentures, orthodontic prostheses, etc. [53].

Dental plaque leads to inflammation of the gums due to the influence of products of microbial metabolism, enzymes and toxins contained in it [54]. Microorganisms make up about two-thirds of the dry mass of this bacterial film, while the intercellular matrix makes up one-third [55]. The latter includes various components, such as glycosaminoglycans, lipids, metabolic products of microorganisms and various inorganic components, including iron, copper, zinc, potassium, calcium, phosphorus, etc. [56]. Under such conditions, the species composition of the microbiota changes, which is accompanied by an increase in the number of gram-negative strains of cocci, spirochetes, and bacilli. It is known that streptococci account for about half of plaque bacterial persistence [57].

Inside the dental plaque (biofilm), biocenotic relationships and the exchange of genetic information between microorganisms are realized, which leads to the appearance of new properties of bacteria (increases their virulence, tolerance to antibiotics, antiseptics, antibodies, and phagocytes), which were not noted before [55]. This is especially evident in the elderly in case of chronic inflammation in the periodontium, when the microflora has time to acquire resistance to many drugs, which often causes treatment failures [58].

Today, the specific periodontopathogenic microflora, according to various authors, includes from three to twenty species of bacteria [59]. There can be noted 12 the most associated with periodontitis "marker" species of microorganisms, among them *Actinobacillus actinomycetemcomitans* (now known as *Aggregatibacter actinomycetemcomitans*), *Porphyromonas gingivalis, Treponema denticola, and Bacteroides forsythus* (now known as *Parabacteroides*) [48, 60]. These first three are often called "first order pathogens" or "triad" of periodontopathogenic microorganisms [54]. Also, the main microorganisms that contribute to the destruction of alveolar tissues include a number of types of streptococci, such as *Str. sobrinus, Str. salivarius, Str. oralis, Str. mutans, Str. mitis* [61]. They, in turn, contribute to the formation of dental plaque and trigger the infectious process [62], which causes the loss of collagen fibers and their connection with tooth cementum, the increase of periodontal pockets and the resorption of alveolar bone [63]. Although the bacterial factor is of the essence, it is obvious that the development of a full-fledged inflammatory process in the tissues of the periodontal complex requires not only the presence of microbial invasion. Decline of the body's protective factors is also important [64]. That is why the bacterial model of the occurrence and course of periodontitis must be considered in conjunction with the individual reaction of the human body and the influence of external factors [65].

The microflora of periodontal pockets differs significantly in different patients. Predominance of certain opportunistic and pathogenic microorganisms probably determines the course and severity of the disease. At the same time, the most important importance is attached to non-specific and immune resistance - local immunity of the oral cavity, the state of which is largely related to the number and functions of normal (indigenous) microflora [66, 67]. Microorganisms that make up the normal microflora of the oral cavity play a multifaceted role in providing protective, adaptive, and exchange-trophic mechanisms aimed at preserving the stability of the internal environment and supporting its functioning [68].

It is important that the periodontopathogenic microflora is an association of several types of microorganisms, the "flourishing" of which is impossible under monoculture conditions. They always present complexes, "consortia", symbioses and in them bacteria cease to act alone [62]. Nevertheless, these mechanisms are initiated by bacterial components that trigger the body's cascading inflammatory reactions to plaque antigens. The result is the synthesis of pro-inflammatory cytokines (IL-1, TNF, IL-8, etc.), prostaglandin E2 and other mediators [69].

With an insufficient immune response, pathogenic microorganisms continue to penetrate the attachment epithelium and adjacent connective tissue, maintaining their viability in it for a fairly long period of time [48]. At the same time, periodontopathogenic bacteria secrete virulence factors that suppress the chemotactic regulation of phagocytes (mainly polymorphonuclear leukocytes (PML)), or completely destroy them [70].

Along with the bacterial flora, representatives of yeast-like fungi, simple viruses and the simplest microorganisms are also found in dental plaque. An increase in insemination by opportunistic bacteria and yeast fungi of the genus Candida is also noted [61].

Analysis of scientific sources of information indicates that disturbances in the microbiocenosis or dysbacteriosis of the oral cavity play a significant role in the pathogenesis of many dental diseases. Modern studies indicate that generalized periodontitis is a chronic inflammatory-dystrophic process that occurs as a result of various factors. The study of the mechanisms of the development of inflammatory

processes of the periodontal complex and their relationship with various etiological and pathogenetic factors is currently one of the most relevant directions in the world scientific community.

The results of numerous studies show that inflammatory and dystrophic-inflammatory diseases of the periodontium often occur against the background of dysbacteriosis of the oral cavity. The severity of dysbacteriosis usually depends on the degree of periodontal tissue damage. In patients, there is a decrease in the quantitative content of endogenous (normal) microflora, which ensures colonization resistance of the mucous membrane.

As mentioned, the main etiological factor in the development of periodontitis is considered to be a microbial factor, which usually occurs at the initial stage of the disease. However, in order to activate the virulence of microorganisms that contribute to the development of periodontitis, it is necessary to have a certain predisposition to it. According to modern ideas, gingivitis and periodontitis are considered as two different stages of the same inflammatory-destructive process in the periodontal complex. Therefore, it is important to understand that periodontitis cannot be considered in isolation from previous stages, such as gingivitis, because they are interconnected and are parts of the same pathological process.

CONCLUSION

1. Inflammatory diseases of alveolar tissues tend to increase significantly, which leads to the development of various complications that are dangerous for the body and increases the period of incapacity for work.
2. To date, the leading pathogenetic links of the development of the inflammatory process in the periodontium, in particular, the disruption of free radical oxidation, the processes of peroxidation of lipids and proteins, the disorder of the functional state of the antioxidant system, the formation of oxidative stress, as well as the humoral link of adaptive immune defense and cytokinesis, have not been sufficiently studied.
3. The key role of the microbial factor in the etiology of periodontal diseases in modern dentistry is beyond doubt, but it should be noted that the penetration of microorganisms into the alveolar tissue does not always lead to the development of the disease, because the body has a number of protective mechanisms that counteract the development of inflammation.

Contributors:

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Demkovych A.Ye. – data curation, methodology, conceptualization;

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Yaremchuk O.Z. – conceptualization, resources.

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