CURRENT UNDERSTANDING OF THE ETIOLOGY OF CHRONIC GENERALIZED PERIODONTITIS

Alimova D.M., Fazilova L., Mukimov O.A., Eshimova P.E., Ismailova S.S.
Tashkent State Dental Institute
Tashkent, Uzbekistan.

ABSTRACT

This literature review presents the etiological factors that lead to one of the most common periodontal diseases - chronic generalized periodontitis. The main role belongs to the bacterial biofilm, it is the cause of the disease development. In addition, immune disorders can also be a cause of periodontal disease.

Keywords: chronic generalized periodontitis, bacterial biofilm, immunoglobulins, periodontal pathogens.

Periodontitis is the most common and polyethiological chronic inflammatory disease of the oral cavity.

To date, the periodontal microbiome has been more deeply studied and it has been concluded that periodontitis is associated with 50 systemic diseases. One of the main factors influencing the development of chronic generalized periodontitis is the imbalance between pathogenic and beneficial microorganisms in the oral cavity. In a healthy oral cavity the number of pathogenic microorganisms is minimal, and their growth and development is suppressed by favorable microorganisms. However, in generalized periodontitis this balance is disturbed, leading to oral dysbacteriosis and the development of periodontal inflammation.

The etiopathology of advanced periodontitis includes specific bacterial and fungal pathogens, active herpesviruses and anti-inflammatory immune responses [1].

The ecological diversity of the periodontal microenvironment can provide suitable conditions for colonization by species not normally considered to be permanent members of the oral microbiota. The subgingival biofilm of patients with periodontitis, gingivitis, generalized aggressive or chronic periodontitis may contain Neisseria spp., Streptococcaceae, Candida albicans, Enterobacteria, Pseudomonas Aeruginosa, Eubacterium saphenum, Clostridium Difficile, Olsenellauli, Hafniaalvei, Serratia marcescens and Filifactoralocis [2]. It is known from numerous literature data that A. actinomycetemcomitans, Porphyromonas gingivalis, Porphyromonas endodontalis, Prevotella intermedia, Treponema denticola, Tannerella forsythia, Fusobacterium nucleatum possess the greatest aggressiveness [2, 3]. These pathogens

have certain pathogenicity factors that affect the course of the infectious process. At the same time, each microbial pathogen has its own features that influence the immunopathogenesis of periodontitis. A number of recent studies have proposed a new model of periodontal pathogenesis, indicating a synergistic and dysbiotic interaction of the microorganisms responsible for the initiation of periodontitis, rather than the action of individual periodontal pathogens [4-6].

Bacteria called edge pathogens, found in low numbers under healthy conditions, can destabilize the community and cause the development of dysbiosis. The most studied pathogen is P. gingivalis, an anaerobic Gram-negative Coccobacillus in the family Bacteroidaceae. In the natural environment, P. gingivalis is a component of a multispecies biofilm; it penetrates the epithelial and immune cells of the gingiva, remaining viable and capable of further spreading among cells and tissues [7]. P. gingivalis is an important component of the oral microbiome and a highly adaptive colonizer. The bacterium has the ability to evade host defenses and interfere with the relationships between other oral species that make up the microflora located in the supra- and subgingival periodontal biofilm, leading to the chronic inflammation, cellular prosurvival profile and subsequent tissue damage observed in individuals with chronic periodontitis. Molecules produced by P. gingivalis play an important role in the immunopathogenesis of chronic periodontitis, acting on both innate and adaptive immunity [8]. A number of studies have shown that P. gingivalis localizes in various subcellular compartments of host cells, including cytoplasm, endosomes and autophagosomes. It has been found that the bacterium, instead of being transported to the endosomal pathway, moves to autophagosome-like vacuoles and stays in vacuoles that resemble early and late autophagosomes, which may allow it to survive by blocking fusion with lysosomes [9]. Bacterial trafficking through the autophagic pathway allows them to avoid host defense mechanisms and obtain nutrients, which is particularly advantageous for the asaccharolytic P. gingivalis. In addition, the outer membrane vesicles produced by P. gingivalis enter human cells via the lipid-dependent endocytic pathway, are directed to endosomes, and are sorted into lysosomal compartments. P. gingivalis strains 33277, 381, and A7436 can locally invade periodontal tissues and evade host defense mechanisms by using a number of virulence factors that disrupt innate immune and inflammatory responses. Various virulence factors of this bacterium, such as capsule components, lipopolysaccharides (LPS), fimbriae, proteases, and outer membrane proteins, can contribute to immunogenicity by stimulating innate and adaptive immunity mechanisms in both the humoral and cellular immune responses of the host [9]. All this indicates the ability of this pathogen to invade host cells, which may be an escape mechanism from the host’s defenses, contributing to the penetration of the microorganism into the bloodstream and thus

acting systemically in the host organism. Some researchers consider P. gingivalis to be key in the development of immunopathological events in periodontitis with predominantly pro-inflammatory-directed macroorganism reactions. The ability of P. gingivalis to evade the immune response in the host proinflammatory process and gain access to nutrients in the microenvironment is directly related to its survival, proliferation and infection. Important features of P. gingivalis-mediated chronic periodontitis include the ability of the bacterium to adhere to and engulf host cells, to spread through host cells and tissues, and to disrupt host immunological surveillance and defense mechanisms. However, the virulence determinants of periodontal pathogens that provide effective infectivity and contribute to synergism in increasing virulence are still unclear.

Another periodontal pathogen, A. actinomycetemcomitans, is able to bind to IgM class antibodies using the HSP60 protein. This pathogen is not only responsible for maintaining the conformation of the cellular proteins, it also functions as a powerful virulence factor causing bone resorption in periodontitis [10]. A. actinomycetemcomitans is associated with the development of aggressive periodontitis and may contribute to chronic periodontitis. This bacterium expresses complex operons for two cytotoxins: leukotoxin (Lkt) and cytophosphate-toxin (Cdt) [11].

Recent studies have shown a syntrophy between different bacterial species within the oral biofilm through mutual cooperation/competition for nutrients, especially between P. gingivalis, T. denticola, P. intermedia and T. forsythia, which form a polymicrobial community and dominate the periodontal biofilm. Biofilms modulate the epithelial-cell immune response in different ways depending on their properties and composition. Keratinocytes of the gingival epithelium form a barrier against bacterial infection and invasion. They are bound together by a number of specialized transmembrane molecular complexes, including intercellular junctions including tight junctions, adhesive junctions and gap junctions [12].

Candida albicans may be involved in the pathogenesis of chronic periodontitis. Taxonomic profiling combined with functional expression analysis has shown that Candida albicans, Streptococcus mutans and other periodontopathogens are not always present or numerically important in foci of candidiasis, caries or periodontitis. However, Candida albicans combines with Streptococcus spp. and their increased virulence will co-colonize in invasive candidiasis, early childhood caries or periimplantitis [13].

The etiopathogenesis of severe forms of periodontitis includes herpesvirus-bacterial co-infection. Evaluation of the pathogenicity of herpesviruses (cytomegalovirus and Epstein-Barr virus), periodontopathogenic bacteria (A. actinomycetemcomitans and P. gingivalis) and coinfection of these infectious agents

showed their role in the initiation and progression of periodontitis. Cytomegalovirus and A. actinomycetemcomitans/P. gingivalis exhibit synergistic pathogenicity in the development of localized (aggressive) juvenile periodontitis. Cytomegalovirus and Epstein-Barr virus are associated with P. gingivalis in periodontitis. Periodontal herpesviruses entering the general bloodstream may also contribute to disease in various organ systems. There is the possibility of a bilateral interaction between periodontal - and periodontopathic bacteria, with herpesviruses promoting bacterial growth and bacterial factors reactivating latent herpesviruses. Bacterial gingivitis can promote herpesvirus colonization of the periodontium, and herpesvirus infections can interfere with the host's antibacterial defense and alter periodontal cells to predispose to bacterial adhesion and invasion. Herpesvirus-bacterial synergistic interactions probably constitute an important pathogenic determinant of aggressive periodontitis. However, mechanistic studies of molecular and cellular interactions between periodontal herpesviruses and bacteria are still scarce [14, 15].

Periodontal herpesviruses, which are spread through the systemic circulation, may represent an important link between periodontitis and systemic diseases. Periodontal therapy targeting both herpesviruses and bacterial pathogens can provide long-term clinical improvement and potentially reduce the risk of systemic disease. Molecular diagnostic tests for periodontal pathogens may allow early microbial identification and preventive therapy [16].

If we look at the etiopathogenesis of periodontitis from other points of view, it is worth noting that in chronic generalized periodontitis a decrease in the amount of Ig G in saliva and gingival fluid was recorded. It is characteristic for catarrhal gingivitis there is the activation of local protective factors, mainly of non-specific character. As the pathological process progresses in the periodontal tissues (with the formation of periodontal pockets) the situation changes: the level of non-specific protection decreases, and functional activity of the specific factors (sIg A) increases that, probably, is caused by the antigenic stimulus increase as the result of bacterial plaque spreading under the gum [17].

In early progressive forms of generalized periodontitis, an increase in the potential of polymorphonuclear leukocytes for nonspecific activation by cytokines with a decrease in their antibacterial properties is revealed, which makes them dangerous for periodontal tissues [18, 19].

According to L.Yu. Orekhova et al. (1997) [20], in patients with chronic generalized periodontitis there is an interdependence between the levels of immunoglobulins and lysozyme activity in oral fluid, indicating the compensation of lysozyme deficiency in oral fluid by strengthening the immunoglobulin supply. Disturbance of mechanisms of mutual compensation for deficiency of protective

humoral substrates in inflammatory periodontal diseases can be referred to the factors of disease pathogenesis. Intensification of lipid peroxidation (LPO) processes in chronic generalized periodontitis has been reliably established [21, 22]. It is believed that reactive oxygen species play an important role in the pathogenesis of the disease both through direct damage of periodontal tissues and indirectly through changes in saliva properties due to salivary gland dysfunction [23].

In recent years, the balance between the levels of pro-oxidants and antioxidants, the balance between the reactions of free-radical oxidation of lipids and the state of antioxidant protection of the organism, which are in inseparable unity and determine the course of tissue cellular metabolism [24, 25], has been given fundamental importance.

Taking into account the presence of immunological changes when the organism is exposed to various factors: endocrine system diseases, psychoneurological features, hemocirculatory disorders, gastrointestinal pathology, etc, (2004) [23], who attribute system reactions of free-radical oxidation and immunological misbalances to the universal processes of cellular alteration and apoptosis and emphasize the significance of cytokine regulation in these processes. These organism-wide mechanisms unite the pathogenesis of many diseases, explain their association and connection to the same risk factors and peculiarity of inflammatory periodontal diseases is the uniformity of reactions of its structural formations in the form of non-specific inflammatory-degenerative process in response to various changes in various organ systems.

To conclude, it is worth noting that understanding the processes of immune response, formation and progression of periodontitis, as well as identifying biomarkers of inflammation can contribute to expanding knowledge about the pathogenetic mechanisms, improve diagnosis and support various therapeutic strategies. Research on viral, fungal and bacterial periodontal infections will help to understand the clinical and biological characteristics of periodontitis, the response mechanisms and the severity of the immune system response and to form new strategies to combat the disease. Identification and quantification of periodontal pathogens may have prognostic value. In the future, the development of new diagnostic methods for viral, fungal and bacterial pathogens at the early stage of periodontal disease is necessary, as well as the development of new vaccines against periodontal viruses, which may be a promising direction and a hope for inexpensive periodontitis prevention in a large group of people.

REFERENCES:

1. Slots J. Focal infection of periodontal origin. - Periodontol 2000. - 2019; 79 (1): 233-5. PMID: 30892771.

2 Slots J. Focal infection of periodontal origin. - Periodontol 2000. - 2019; 79 (1): 233-5. PMID: 30892771.
3. Colombo A.P.V., Magalhães C.B., Hartenbach F.A.R.R., Souto R.M., da Silva-Boghossian C.M. Periodontaldisease-associated biofilm: A reservoir for pathogens of medical importance. - Microb Pathog. - 2016; 94: 27-34. PMID: 26416306.
4. Chevalier M., Ranque S., Prêcheur I. Oral fungal-bacterial biofilm models in vitro: a review. - Med Mycol. - 2018; 56 (6): 653-67. PMID: 29228383.
5. Ippolitov E.V. Monitoring of microbial biofilm formation and optimization of diagnosis of inflammatory periodontal diseases: ABSTRACTof Ph. D. - Moscow: I.M. Sechenov First Moscow State Medical University, 2016. - 49 c. [Ippolitov E.V. Monitoring of microbial biofilm formation and optimization of periodontal inflammatory diseases diagnostics: dissertation ABSTRACT. - Moscow: Sechenov University, 2016. - 49 p. (In Russ.)] eLIBRARY ID: 30437271
6. Chen C., Feng P., Slots J. Herpesvirus-bacteria synergistic interaction in periodontitis. - Periodontol 2000. - 2020; 82 (1): 42-64. PMID: 31850623.
7. Olsen I., Progulske-Fox A. Invasion of Porphyromonas gingivalis strains into vascular cells and tissue. - J Oral Microbiol. - 2015; 7: 28788. PMID: 26329158.
8. Carvalho-Filho P.C., Gomes-Filho I.S., Meyer R., Olczak T., Xavier M.T., Trindade S.C. Role of Porphyromonas gingivalis HmuY in immunopathogenesis of chronic periodontitis. - Mediators Inflamm. - 2016; 2016: 7465852. PMID: 27403039.
9. Zenobia C., Hajishengallis G. Porphyromonas gingivalis virulence factors involved in subversion of leukocytes and microbial dysbiosis. - Virulence. - 2015; 6 (3): 236-43. PMID: 25654623.
10. Wang C., Hörkkö S. Natural Monoclonal Antibody to Oxidized Low-Density Lipoprotein and Aggregatibacter actinomycetemcomitans. - Methods Mol Biol. - 2017; 1643: 155-67. PMID: 28667536.
11. Konig M.F., Abusleme L., Reinholdt J., Palmer R.J., Teles R.P., Sampson K., Rosen A., Nigrovic P.A., Sokolove J., Giles J.T., Moutsopoulos N.M., Andrade F. Aggregatibacter actinomycetemcomitans-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. - Sci Transl Med. - 2016; 8 (369): 369ra176. PMID: 27974664.
12. Groeger S, Meyle J. Oral Mucosal Epithelial Cells. - Front Immunol. - 2019; 10: 208. PMID: 30837987.
13. de Cássia Negrini T., Koo H., Arthur R.A. Candida-bacterial biofilms and host-microbe interactions in oral diseases. - Adv Exp Med Biol. - 2019; 1197: 119-41. PMID: 31732939.

14. Makino K., Takeichi O., Imai K., Inoue H., Hatori K., Himi K., Saito I., Ochiai K., Ogiso B. Porphyromonas endodontalis reactivates latent Epstein-Barr virus. - Int Endod J. - 2018; 51 (12): 1410-1419. PMID: 29858508.
15. Akram Z., Al-Aali K.A., Alrabiah M., Alonaizan F.A., Abduljabbar T., AlAhmari F., Javed F., Vohra F. Current weight of evidence of viruses associated with peri-implantitis and peri-implant health: A systematic review and meta-analysis. - Rev Med Virol. - 2019; 29 (3): e2042. PMID: 30901504.
16. de Sousa Rodrigues P.M., Teixeira A.L., Kustner E.C., Medeiros R. Are herpes viruses associated with aggressive periodontitis? A review of literature. - J Oral Maxillofac Pathol. - 2015; 19 (3): 348-55. PMID: 26980964.
17. Krechina E.K. State of nonspecific oral cavity resistance in adolescents / E.K. Krechina, V.V. Khazanova, E.A. Zemskaya // Dentistry. - 1991. - №2. - C. 29-31.
18. Bezrukova I.V. Antimicrobial activity of the drug "Imudon" in the treatment of inflammatory periodontal diseases / I.V. Bezrukova // Periodontology. - 2000. - №3. - C. 46-47
19. Bezrukova I.V. Disorder of the functional activity of polymorphonuclear leukocytes in atypical forms of inflammatory periodontal diseases / I.V. Bezrukova // Periodontology. - 2000. - №4(18). - C. 12-15.
20. Orekhova L.Y., Levin M.Y., Sofronov B.N. Features of local immunity in inflammatory periodontal diseases // Periodontology. - 1997. - №2. - C. 7-12.
21. Simakova T.G. Application of antioxidants in treatment of periodontal diseases (review) / T.G. Simakova, M.M. Pozharitskaya // Institute of Stomatology. - 2007. - №1. - C. 105-109.
22. Tarasenko L.M. The role of lipid peroxidation in the pathogenesis of periodontal damage under stress / L.M. Tarasenko, O.N. Voskresensky // Pat. - 1986. - №6. - C. 12-14.
23. Orekhova L.Yu. (Ed. by Prof. L.Yu. Orekhova)-Moscow: Poly Media Press, 2004. - 432 c.
24. Galiullina E.F. New approaches to the etiology of periodontal diseases in the light of the modern concept of their pathogenesis / E.F. Galiullina // Periodontology. - 2017. - T.22, №2(83). - C. 21-24.
25. Sazontova T.G. Antioxidants and pro-oxidants - two sides of one whole (Part I) / T.G. Sazontova // Prevention Today. - September 2007. - C. 18-23.