Global Science Research Journals

Available online at
www.globalscienceresearchjournals.org

Global Journal of Medicine and Medical Sciences

ISSN: 2449-1888, Vol. 7 (9). Pp. 541-545
December, 2019
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Full Length Research Paper | Open Access

Modern ideas about the etiopathogenetic mechanisms of the occurrence of inflammatory and dystrophic lesions of the periodontium

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Accepted 22 December, 2019

Annotation

In this article, in the light of recent data, a detailed analysis is given on the etiopathogenetic mechanisms of the occurrence of inflammatory-dystrophic periodontal lesions. The role of microbes in the development of periodontal diseases is proved. It has been established that the osteosorbing role of periodontal bacteria is associated with the RANK-RANKL-ORG system, which leads to osteolysis of bone tissue, which in turn leads to atrophy of bone tissue. An impressive amount of literature is analyzed, the corresponding conclusions are made.

Keywords: Matrix metalloproteinases; RANK-RANKL-ORG system; bone osteolysis; periodontium

RELEVANCE

According to a report by the WHO research team (2019), based on a population survey of 53 countries, there is a high incidence of periodontal disease in the world. In people aged 15-19 years, periodontal disease occurs in 55 - 89%, at the age of 35 -44 years - in 65 - 98%. In people of older age groups, they reach 98% [8, 14, 18].

Inflammatory changes in periodontal disease in recent years is an urgent problem of dentistry. The current state of this problem stems from their high prevalence among the population, an increase in the intensity and severity of the inflammatory process, the formation of a chronic focus of odontogenic infection, as well as its adverse effect on the body.

In recent years, several monographs of leading Russian dentists have been published, edited by A. G. Shargorodsky (2002) and T. G. Robustova (2006), L. Yu. Tsepov, A. I. Nikolaev (2002), A. I. Grudyanov(2009), L.A. Dmitrieva (2013), devoted to the course of the inflammatory process in periodontal tissues. Inflammatory processes in periodontal tissues affect the quality of life of patients [145]. The connection of inflammatory processes in periodontal disease with other diseases has been shown [11]. Unfortunately, despite the presence of a large number of works in this direction, the unresolved issues related to the study of the inflammatory process in various tissues of the body do not become smaller [23]. In recent years, acute inflammatory processes in the maxillofacial region are increasingly taking a protracted course, and the number of truly chronic inflammatory diseases is not reduced [16].

The most common and periodontal pathology, as well as severe, is chronic generalized periodontitis (CGP), it lasts a long time - for years, with periods of remissions and exacerbations, which leads to a significant violation of the functions of the dentition due to destruction of bone tissue and tooth loss.

A high tendency to progression, the prevalence of periodontal inflammation, difficulties in achieving stable remission, their polyetiologicity, as well as an increase in prevalence in young people with atrophic and severe destructive periodontal changes, low availability of periodontic care to a larger population create the urgency of this problem.

The leading etiological factor in inflammatory periodontal diseases is currently recognized as a microbial plaque (plaque), which contains microorganisms with high pathogenicity, the ability to adhere to tooth tissues and the release of invasive enzymes (endotoxins). WHO defines such a group of

microorganisms as periodontopathogenic flora (Porphiromonasgingivalis, Prevotellamelanogenica, Veillonellaparvula, Fusobacteriumnucleatum, Peptostreptococcus micros, etc.) [13].

Periodontal bacteria produce enzymes that stimulate the activity of various immunocompetent cells - macrophages, white blood cells. Proteolytic enzymes of periodontal bacteria are one of the most important virulent factors: Actinobacillusactinomycetecomitans and Porphyromonasgingivalis, which have a wide range of virulence factors, in particular proteolytic and osteoresorbing activities. Actinobacillusactinomycetecomitans produce collagenase (collagenolytic activity); Porphyromonasgingivalis - metalloproteinases, cysteine proteinases, asparagin proteinases that cause degradation of non-specific Ig A and Ig G (by splitting them into small peptides) [10]. The presence of such virulent bacteria in the gingival sulcus and periodontal tissues cause an immune response from the body (cellular and humoral immunity). The main antibacterial mechanism includes proteolytic enzymes produced by monocytes, polymorphonuclear leukocytes [21]. Inflammatory periodontal diseases are one of the main problems of theoretical and practical dentistry. Its solution is significantly complicated due to a constant change in the etiological structure and an increase in the specific gravity of conditionally pathogenic representatives of normal microflora, the pathogenetic capabilities of which are not precisely determined [18]. Gingivitis usually begins with an increase in the number of actinomycetes in dental plaques along the edge of the gums, where bacteroids and coca flora are also present. In chronic gingivitis, fusobacteria, veyllonella and campylobacter are secreted [7]. Periodontitis is an inflammatory-dystrophic process in the alveolar processes. Damage to periodontal tissues can be caused directly by infection, sensitization by a non-infectious allergen, impaired lipid or other metabolism, impaired neurohumoralcorrelations [5, 14]. CDW leads to destruction of the connective tissue of the gums, periodontal ligaments and alveolar bone. Periodontal inflammation is a local protective reaction of the body that develops in response to trauma or the introduction of an infectious agent. A series of biochemical reactions is launched, as a result of which the vessels expand and the permeability of the vascular wall increases, which leads to an increase in blood flow, accompanied by the release of plasma and blood cells into the extracellular matrix. This stimulates the complement system, contributes to the violation of microcirculation and activation of kinins. The final stage of VP is a return to normal function due to the regeneration of affected tissues. However, in the absence of preventive and therapeutic measures, CAP can continue for a long period of time, which is fraught not only with severe damage to the involved tissues, but also of the whole organism [4].

The study of the etiology and pathogenesis of chronic generalized periodontitis remains relevant today. Despite the large number of studies conducted, the development of new methods of diagnosis and treatment, the incidence of periodontitis tends to increase steadily [14]. Despite the fact that the role of periodontopathogenic microflora in the development of this pathology is not in doubt [18, 22], it is not possible to explain all aspects of the etiopathogenesis of periodontitis in the light of microbiological theory. Periodontitis is characterized by the specific nature of microflora with a predominance of anaerobic forms. The most virulent are communities of periodontogenic strains, such as Aggregatibacteractinomycetemcomitans, Porphyromonasgingivalis, Prevotella intermedia, Bacteroidesforsythus, Tneponemadenticola, Weilonella recta [11,14]. Campylobacter rectus, Tannerella forsythia, Prevotellanigrescens, Eikenellacorrodens, Peptostreptococcus micros, Eubacteriumnodatu also have periodontopathogenic activity [19]. The formation of periodontal microbial complexes is associated with the interaction of microorganisms within the community on mutually beneficial conditions, when the vital products of some strains serve as a source of nutrition for others, and the exchange of genetic material is possible in order to increase resistance to antibacterial drugs. The altering effect of bacteria on periodontal tissues is mediated through endo- and exotoxins and proteolytic enzymes that can increase the permeability of the gingival epithelium, disrupt collagen synthesis by fibroblasts, inhibit the activity of immune system cells, stimulate the formation of immunoglobulins and, thus, provoke an inflammatory reaction in the periodontal complex [22]. However, the presence of periodontopathogenic strains and the species composition of their associations do not always correlate with the clinical picture of the disease [11, 19]. It is known that poor patient oral hygiene is not always leading to the development of pronounced inflammatory and destructive changes in the periodontal complex [14], and periodontal pathogens are often detected in patients with clinically healthy periodontal disease [15]. Thus, the view on bacterial invasion as a trigger mechanism in the development of periodontal pathology remains modern [9]. The initial part of the inflammatory process is the release of endotoxins by gram-negative bacteria of dental plaque. Endotoxins, being lipopolysaccharides (LPS), trigger a whole chain of immunological reactions: they stimulate the synthesis of cytokines by macrophages, activate the complement system, and have antigenic and cytotoxic properties. Moreover, the response of a macroorganism to bacterial lipopolysaccharides can vary greatly depending on the state of the immune system, which largely determines the risk of periodontal disease [12]. So begins the first stage of inflammation - an acute phase response. Macrophages begin the release of a large number of biologically active substances, such as

cytokines, prostaglandins, free radicals. Currently, more than 200 substances belonging to the class of cytokines have been isolated. In the focus of inflammation, they have an effect on almost all types of cells: granulocytes, macrophages, fibroblasts, epithelial cells, and then on T and B lymphocytes. An important role of cytokines is the interconnection between nonspecific defense reactions and specific immunity [20]. So, under the influence of LPS, monocytes, macrophages and epithelial cells secrete a large number of cytokines of the first wave, the main of which are tumor necrosis factor (TNF), interleukin -1β (IL-1β), interleukin-6 (IL-6), and they are secreted it is in this sequence, increasing the secretion of each other [11, 20]. The release of these cytokines in high concentrations can stimulate the secretion of the remaining pro-inflammatory cytokines, as well as matrix metalloproteinases (MMPs) and prostoglandin E2. IL-1β and TNF also induce bone resorption and inhibit the bone formation, acting indirectly through osteoclast precursors and the RANK-RANKL-OPG system. Receptors for IL-1β are located on osteoblasts [9]. Many studies have shown an increase in the content of IL-1β in the gingival fluid in patients with periodontitis compared with patients with gingivitis and healthy control [18]. A decrease in the content of IL-1β in the gingival fluid after periodontal treatment has also been repeatedly reported [23]. In addition, the antagonists of IL-1β and TNF are able to reduce the loss of clinical attachment and alveolar bone in primates [20]. If the protective mechanisms of the macroorganism were not able to suppress bacterial invasion, the destruction of periodontal tissues is aggravated. 19]. It is known that poor patient oral hygiene is not always leading to the development of pronounced inflammatory and destructive changes in the periodontal complex [14], and periodontal pathogens are often detected in patients with clinically healthy periodontal disease [15]. Thus, the view on bacterial invasion as a trigger mechanism in the development of periodontal pathology remains modern [9]. The initial part of the inflammatory process is the release of endotoxins by gram-negative bacteria of dental plaque. Endotoxins, being lipopolysaccharides (LPS), trigger a whole chain of immunological reactions: they stimulate the synthesis of cytokines by macrophages, activate the complement system, and have antigenic and cytotoxic properties. Moreover, the response of a macroorganism to bacterial lipopolysaccharides can vary greatly depending on the state of the immune system, which largely determines the risk of periodontal disease [12]. So begins the first stage of inflammation - an acute phase response. Macrophages begin the release of a large number of biologically active substances, such as cytokines, prostaglandins, free radicals. Currently, more than 200 substances belonging to the class of cytokines have been isolated. In the focus of inflammation, they have an effect on almost all types of cells: granulocytes, macrophages, fibroblasts, epithelial cells, and then on T and B lymphocytes. An important role of cytokines is the interconnection between nonspecific defense reactions and specific immunity [20]. So, under the influence of LPS, monocytes, macrophages and epithelial cells secrete a large number of cytokines of the first wave, the main of which are tumor necrosis factor (TNF), interleukin -1β (IL-1β), interleukin-6 (IL-6), and they are secreted it is in this sequence, increasing the secretion of each other [11, 20]. The release of these cytokines in high concentrations can stimulate the secretion of the remaining pro-inflammatory cytokines, as well as matrix metalloproteinases (MMPs) and prostoglandin E2. IL-1β and TNF also induce bone resorption and inhibit the bone formation, acting indirectly through osteoclast precursors and the RANK-RANKL-OPG system. Receptors for IL-1β are located on osteoblasts [9]. Many studies have shown an increase in the content of IL-1β in the gingival fluid in patients with periodontitis compared with patients with gingivitis and healthy control [18]. A decrease in the content of IL-1β in the gingival fluid after periodontal treatment has also been repeatedly reported [23]. In addition, the antagonists of IL-1β and TNF are able to reduce the loss of clinical attachment and alveolar bone in primates [20]. If the protective mechanisms of the macroorganism were not able to suppress bacterial invasion, the destruction of periodontal tissues is aggravated.

Pathological processes in this case are mainly due to the reaction of the body, which enhances the destruction initiated by microbes. Toxic bacteria and enzymes such as hyaluronidases, collagenases and proteases destroy the components of the extracellular matrix, creating nutrients for bacterial growth [17]. The arginine and lysine-specific cysteine proteases produced by P. gingivalis are key virulence factors leading to invasion of the host tissue. After the start of immuno-inflammatory processes, leukocytes and fibroblasts secrete various molecules (for example, proteases, MMP, cytokines, prostaglandins and various enzymes). The disease is accompanied by an imbalance between activated tissue-depleting MMPs and their endogenous inhibitors (TIMP). As a result, the connective tissue attachment and the bone of the alveolar ridge are destroyed, and the attachment epithelium and inflammatory infiltrate are displaced in the direction of the apex of the tooth root [22]. In addition, osteoclasts are activated, which, both directly and indirectly, through the RANK / RANKL / OPG system, continue bone destruction. In the presence of periodontal pathogens, CD4 + T cells show increased RANKL expression [20]. With the development of the destructive process, the density of microorganisms increases, which leads to even greater damage to the periodontal. Microflora gradually becomes anaerobic, and the reaction of the body becomes more destructive and

chronic. Ultimately, the destruction of the musculoskeletal system reaches a scale that threatens tooth loss [12]. Bacterial virulence factors can themselves cause bone resorption. Endotoxin secreted by the cell walls of gram-negative microorganisms induces CD4 + T cells to stimulate resorption through interaction with macrophages. P. gingivalis bacteria produce a fibril protein, which has a powerful stimulating effect on osteoclasts using tyrosine kinase [17], the antibodies to which prevent bone loss in infected animals. The bacteria Aggregatibacteractinomycetemcomitans secrete heat shock protein of 62 kDa, in picomolar concentrations, showing the ability to stimulate bone resorption, as well as a peptide that acts as a powerful inducer of IL-6 in fibroblasts and monocytes [18]. Other virulent factors of T. denticola and T. forsythia include binding of the negative complement regulator FH to spirochete surface proteins, which correlates with complement resistance [16]. Recently, T. which is responsible for hemolytic and oxidative activity and destruction of gingival and periodontal tissues. In addition, sulfide creates an ecological niche selectively favorable for T. Denticola [21]. T. forsythia bacteria express a unique glycosylated surface S layer, which plays an immunomodulatory role in influencing the immune response [23]. Recently, it was demonstrated that in vitro this S layer plays an important role in delaying the cytokine response of monocytes and macrophages [11]. Thus, the important etiological role of periodontopathogenic microflora in the development of inflammatory periodontal diseases should be recognized, however, it is only the trigger for the main destructive process - resorption of the alveolar bone.

However, to date, there is insufficient information on the role of bacteria in the development of periodontal diseases, the mechanisms of recognition and response of the host organism to the introduction of bacteria from the initial section of the digestive tract (oral cavity), and the intricacies of the defense mechanism of nonspecific and specific innate and acquired human immunity, in connection with what we consider it relevant to conduct such a study.

CONCLUSIONS

Today, the influence of bacteria (Porphiromonasgingi-valis, Prevotellamelanogenica, Veillonellaparvula, Fusobacteriumnucleatum, Peptostreptococcus micros) is undeniable in the occurrence and development of inflammatory and dystrophic lesions of periodontal disease. To date, the number and species composition of microflora is not always correlated with the development of the clinical picture of the disease. Therefore, the presence of peculiar biomarkers in the development and course of inflammatory-dystrophic periodontal lesions is currently considered unexplored.

The osteoresorbing property of periodontopathogenic bacteria is associated with the influence of a specific RANK-RANKL-ORG system, which directly or indirectly acts on the compact and spongy plate of the alveolar bone, causing lysis of osteoblasts, which ultimately leads to atrophy.

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How to cite this paper::
Gaybullaev E and Rizaev.J. (2019). Modern ideas about the etiopathogenetic mechanisms of the occurrence of inflammatory and dystrophic lesions of the periodontium. Glob. J. Med. Med. Sci. 7(9). Pp. 541-545 http://www.globalscienceresearchjournals.org/gjmms/