SUBGINGIVAL MICROBIAL PROFILE AND PRODUCTION OF PROINFLAMMATORY CYTOKINES IN CHRONIC PERIODONTITIS

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ABSTRACT

This review examines literature data concerning the bacterial findings in chronic periodontitis depending on pocket depth, and presents the latest published information on the presence of proinflammatory factors in periodontal environment. It has been found that chronic periodontitis affects as much as 80% of the middle-aged population; by comparison, the prevalence of aggressive periodontitis reaches up to 1-1.5%. It is accepted that this social disease is multifactorial in etiology, but the evidence in the literature suggests that the levels of specific Gram-negative organisms in subgingival plaque biofilm play a major role in the initiation and progression of the disease. Of the many bacterial species inhabiting the periodontal environment, three types - Porphyromonas gingivalis (PG), Treponema denticola (TD), Tannerella forsythia (TF) - are strongly associated with the initiation and progression of periodontitis. Microbiological studies suggest that Porphyromonas gingivalis should be considered a major etiologic agent. Currently, Porphyromonas gingivalis is strongly associated with the pathogenesis of chronic periodontitis. On the other hand, the presence of Aggregatibacter actinomycetemcomitans in patients with chronic periodontitis may be related to the severity of the disease and thus modify the therapeutic plan. The increased amount of periodontal pathogens in the subgingival area can activate a cascade of defense mechanisms of the body associated with the production of factors causing inflammation and destruction, which suggests a correlation between the bacterial findings and the body response implemented by enhancing the local cytokine expression. Studies in the literature show that the presence of certain micro-organisms in the periodontal environment is associated to increased levels of proinflammatory cytokines in the gingival fluid and gingival tissue. These levels have been associated with destructive tissues response. There is little evidence in the literature on the correlation of the levels of periodontal pathogens of sites with different pocket depth with periodontal disease activity defined by the degree of the proinflammatory cytokine expression such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6).

Key words: periodontal pathogens, microbiological diagnostics, chronic periodontitis

REZIOME

Настоящий обзор рефериует данные в литературе в связи с бактериальной нахождой при хроническом пародонтите в зависимости от глубины кармана и одновременно с этим ставит себе целью представить актуальную опубликованную информацию о присутствии проинфляматорных факторов в пародонтальной среде. Установлено, что хронический пародонтит наблюдается почти у 80% популяции среднего возраста, а данные о распространенности агрессивного пародонтита - в границах 1-1.5%. Считается, что этиология этого социального заболевания мультифакторная, однако имеющиеся в литературе данные показывают, что уровни специфических грамотрицательных микроорганизмов в сублингвальном биофильме играют основную роль в появлении и прогрессировании заболевания. Среди многочисленных видов бактерий, присутствующих в пародонтальной среде, три вида - Porphyromonas gingivalis (PG), Treponema denticola (TD), Tannerella forsythia (TF) – это основные этиологические агенты, связывающиеся тесно с патогенезом хронического пародонтита. С другой
INTRODUCTION

Chronic periodontitis is an inflammatory destructive disease of the supporting tissues of teeth associated with specific periodontal pathogens in the dental biofilm. This condition involves progressive loss of alveolar bone and the teeth supporting connective tissue, which reduces the quality of life of individuals as a result of the ineffective function, the subsequent loss of teeth, and related social and financial problems. Periodontal infection is also suggested to be associated with some systemic diseases. It is in this sense that periodontal diseases are considered a serious health problem. The high prevalence of chronic periodontitis confirms its social significance.

LEVELS OF SUBGINGIVAL PERIODONTAL PATHOGENS ASSOCIATED WITH CHRONIC PERIODONTITIS

There is substantial evidence in the literature that subgingival plaque microorganisms are capable of triggering destructive processes in periodontal tissues.\(^1\)\(^-\)\(^4\) It has been demonstrated by clinical studies that longterm and effective control of the subgingival bacteria is critical for arresting the progression of periodontal disease.\(^5\) Some gram-negative bacteria have been consistently detected as regular constituents of the microbial flora in periodontal lesions and these, among others, include Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Prevotella intermedia, Tannerella forsythia, Spirochetes (Treponema denticola) Capnocytophaga sp.\(^1\)\(^,\)\(^3\)\(^-\)\(^6\)\(^,\)\(^11\)

Salari et al. found a high concentration of anaerobic bacteria in patients with periodontal disease, especially in deep periodontal pockets.\(^12\) The correlation between pocket depth (PD) and microbial findings is widely discussed in the literature. There is sufficient evidence that the periodontal pathogens Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia are detected more frequently in deep periodontal pockets (> 5 mm) than in shallow ones (< 4 mm).\(^8\)

Haffajee et al. carried out a comparative study in healthy subjects and patients with periodontitis, covering more than 40 bacterial species. The results showed a prevalence of Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia and Selenomonas noxia in periodontally affected individuals.\(^8\)

Many researchers have suggested that the persistence in the subgingival biofilm of Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia, whether singly or in combination, is related to high risk for progression of periodontal disease.\(^3\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^11\)\(^,\)\(^13\) These microorganisms were detected less frequently in shallow pockets (up to 4 mm); they were found to increase in quantity in pockets of 4 to 6 mm depth and were in the highest levels in pockets of over 6 mm depth. The presence of these periodontal pathogens in shallow pockets is believed to be a sign of infection and activity of the disease in deep periodontal sites (pockets). Socransky et al. reported of frequent co-occurrence of Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia in the subgingival plaque in periodontitis.\(^14\) Hence, the authors suggest that these three bacterial species, which form such a tightly related group, should be termed “red complex”. Table 1 presents the periodontal pathogens that are most closely associated with periodontal destruction.\(^14\)

The literature shows that the classical periodontal
pathogens, such as those of red and orange complexes plus *Aggregatibacter actinomycetemcomitans*, are the main microorganisms responsible for the pathogenesis of periodontitis. Evidence for this comes from the fact that any reduction of their levels and concentrations (in the course of the treatment) can be effective in controlling the progression of the disease and lead to long-standing stabilization of the periodontium. Besides this, it is a well-known fact that the combined scaling and root planning and systemic antibiotics have greater effectiveness against pathogenic oral microflora. There is evidence, however, that this approach may not be as effective against poorly-identified microbial species such as some putative periodontopathogenic microbial species (viruses, *Escherichia coli*, *Candida* sp., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacteroides* sp.). In some cases it can lead to excessively developed species of this kind and to the persistence of periodontal destruction. In this sense, additional studies on the specific microbiological profiles of sites at different depth of the pocket in periodontitis would be useful in the planning of therapeutic strategies and in the identification of the sites at risk of destruction. On the other hand, microbiological control after therapy can identify microbiological findings in relation to the successful healing response or the occurrence of refractory periodontitis. The characterization of subgingival microflora after therapy would be a valid criterion for the effectiveness of therapy. Successful supportive treatment for patients with periodontitis after active therapy and predicting the progression and recurrence in patients treated for periodontitis would be successfully carried out by monitoring the levels of subgingival periodontal pathogens.

The gram-negative anaerobes (mainly red complex pathogens), which are the major etiological factors of chronic and aggressive periodontitis, are well characterized:

*Aggregatibacter actinomycetemcomitans* (*Actinobacillus*) – a G(-) small rod-shaped capnophilic facultative anaerobe. It produces many virulence factors such as endotoxin, leukotoxin, collagenase, protease, and possesses the ability to invade periodontal tissues.

*Tannerella forsythia* – a nonpigmented saccharolytic G(-) rod-shaped obligate anaerobe. It can be isolated from periodontal pockets, tonsils, and the back of the tongue and the saliva of patients with periodontitis. Pathogenicity: proteolytic enzymes that lead to the destruction of immunoglobulin and the complement system. It can induce apoptosis and cell death.

*Porphyromonas gingivalis* – a black-pigmented, non-motile, non-saccharolytic *coccobacillus*, a G(-) obligate anaerobe. It possesses many of the virulence factors which help it to overcome the body defences and facilitate its colonization in the oral cavity. Among the virulence factors are: lipopolysaccharides, polysaccharide capsule, fimbria, hemagglutinins, extracellular proteolytic enzymes and adhesins. According to some researchers *Porphyromonas gingivalis* may have a suppressive effect on the response of the organism in periodontitis. It is claimed to be the principal etiological agent in chronic periodontitis and is categorized as aggressive periodontal pathogen. It has been detected in 85.75% of the subgingival plaque samples taken from patients with chronic periodontitis and is rarely found in patients and in sites without periodontal destruction. The reduction in the levels of *Porphyromonas gingivalis* is related

<table>
<thead>
<tr>
<th>Complex</th>
<th>Pathogen Strain</th>
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<tbody>
<tr>
<td>Aa-complex</td>
<td><em>Aggregatibacter actinomycetemcomitans</em></td>
</tr>
<tr>
<td>Red complex</td>
<td><em>Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia</em></td>
</tr>
<tr>
<td>Orange complex</td>
<td><em>Prevotella intermedia, Peptostreptococcus (Micromonas) micros, Fusobacterium nucleatum</em></td>
</tr>
<tr>
<td>Orange-associated complex</td>
<td><em>Eubacterium nodatum</em></td>
</tr>
<tr>
<td>Green complex</td>
<td><em>Capnocytophaga gingivalis</em></td>
</tr>
</tbody>
</table>

- Very highly pathogenic - Aa-complex;
- Highly pathogenic - red complex;
- Highly to moderately pathogenic - orange and orange-associated complexes;
- Moderately pathogenic - green complex.
with establishing control of the disease and the periodontal site (periodontal pockets). According to contemporary data the level of that periodontopathogen in samples of subgingival plaque may be used for periodontal disease progression prediction in specific sites (pockets).

*Treponema denticola* – it is a spiral-shaped motile microorganism with gram-negative cellular wall. It possesses proteolytic enzymes which may destroy immunoglobulins (IgA, IgM, IgG) and the complement factors.

**INDICATIONS FOR MICROBIOLOGICAL DIAGNOSTIC TESTS IN CHRONIC PERIODONTITIS**

The usefulness of microbiological diagnostic tests in different periodontitis forms diagnosis and for identifying periodontal diseases progression is fairly well debated in the literature. Many authors view microbial identification more in the light of being an additional tool in the treatment planning of patients with more severe periodontal lesions and/or poor response to treatment. However, most publications refer to situations that are clinical cases presentations and aim to lead to the accurate choice of additional and target antimicrobial therapy based on microbiological data.

Most articles in the literature, referenced by Listgarten & Loomer, concerning the use of microbial identification as treatment plan base for patients with periodontitis, are only descriptions of clinical cases. Only one publication contains a control group of 10 periodontal specialists not using microbiological data against 13 periodontal specialists who use such data in routine practice. The study shows that these specialists change 69% of their treatment plans after receiving the microbiological results, their patients have more visits, more procedures with scaling and root planning, 79% more courses of treatment with antibiotic agents and less periodontal surgery.

The use of microbiological tests as an additional diagnostic tool in differentiating the various forms of periodontitis, as well as an indicator of healing or progression of periodontal disease is recommended by a number of researchers. In many studies the presence of putative periodontal pathogens in subgingival biofilm is significantly associated with ineffective response to therapy, while the lack of subgingivally established periodontal pathogens is a criterion for a good response to therapy. Moreover, it is believed that the absence of pathogens in periodontal pockets is a favourable predictor of periodontal disease compared with their presence, which is considered as a disease progression predictor. Authors suggest that detection of periodontal pathogens (Aa, Pg, Pi, Cr) above certain “critical” levels after active treatment show an increased risk of recurrence. Chaves et al. have found that the presence of *P gingivalis* is indicative of the progression of periodontitis and bone loss, and Tran et al. have found a significant correlation between the presence of *Tannerella forsythia* and attachment loss (5.3 times more than in the cases without *Tannerella forsythia*).

There are various additional methods available for accurate diagnosis and treatment of periodontal diseases, some of which are microbiological. They are based on anaerobic culture examination, species-specific serological tests, DNA-DNA hybridization with species-specific DNA probes, enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR). Two of the key pathogenic bacterial species (*Porphyromonas gingivalis* and *Tannerella forsythia*), related to the etiology, pathogenesis and progression of chronic periodontitis, are found not to yield good growth in cultural technique.

Loesche et al. compared ELISA, the immunofluorescence assay, the DNA probes and culturing techniques in detecting these two organisms and concluded that the DNA probes and the immunofluorescence method are much more efficient and more sensitive than the cultural procedure.

**PROINFLAMMATORY CYTOKINES WITH RESPECT TO THE DESTRUCTIVE PROCESSES IN CHRONIC PERIODONTITIS**

Periodontal pathogens, present in high levels in supragingival biofilm and subgingival space, have the ability to cause activation of the protective mechanisms of the host and the immune system. In recent decades, it has been established that the host inflammatory response against bacteria and their virulence factors is the basis for understanding the pathogenesis of chronic periodontitis. The destructive response of the organism is associated with an extremely increased expression of inflammatory cytokines in the tissue.

It has been shown that the gingival tissue and the gingival fluid in patients with chronic periodontitis contain larger amounts of proinflammatory factors - RANKL (receptor activator of NF-kB ligand), pro-inflammatory cytokines, such as interleukins 1 and 6 (IL-1 and IL-6), tumor necrosis factor alpha (TNF-α), chemokines such as interleukin-8 (IL-8)
and other mediators of inflammation by comparison to those of healthy individuals. Elevated levels of expression of these products in tissues in response to pathogenic bacteria from the subgingival space is considered a key factor in alveolar bone resorption and loss of connective tissue in chronic periodontitis.

Cytokines are a large group of small proteins with certain features of biological activity, whose main function is to regulate host response in periodontitis. The group includes interleukins, interferons and TNF (tumor necrosis factor) family. Chemokines form a distinct group with their activity similar to that of interleukins, of which 35 are known. Table 2 and Table 3 address the main activities of key periodontal destruction cytokines.

It has been established that IL-1 and TNF-α are involved in the induction of bone resorption by promoting the differentiation of osteoclast precursors and subsequent activation of osteoclasts. IL-1 and TNF-α cause tissue damage by stimulating the release of prostaglandin E$_2$ from the monocytes and fibroblasts and matrix metalloproteinases degrading extracellular matrix proteins.

Another proinflammatory cytokine with a significant role in the pathogenesis of chronic periodontitis is interleukin 6 (IL-6), which contributes to the secretion of B cells which mature into immunoglobulin-producing plasma cells. This finding has been associated with the presence of more plasma cells in the periodontal lesions and with the detection of specific antibodies against Porphyromonas gingivalis. In recent studies IL-6, produced by osteoblasts, shows an ability to induce bone resorption. It is believed that IL-6 is also involved in tissue destruction through inducing production of anti-collagen type I antibody of CD5 + B cells, which, unlike the B cells in healthy subjects, are upregulated in the tissue of patients with chronic periodontitis.

**Tumor Necrosis Factor-Alpha**
Similar to IL-1β, TNF-α can be considered as an essential mediator of the immune response in periodontitis as it is produced directly by a number of cells and generally activates the immune response through the secondary mediator molecules, induces

Table 2. The main group of cytokines (Taylor, 2010)

<table>
<thead>
<tr>
<th>Cytokine group</th>
<th>Function</th>
<th>Mediators</th>
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<tbody>
<tr>
<td>Proinflammatory cytokines</td>
<td>Primary immune response and activation of the inflammation</td>
<td>IL-1, TNF-α, IL-12, IL-23, IL-32</td>
</tr>
<tr>
<td>Glycoprotein 130 signalling cytokines</td>
<td>Differentiation and growth of leukocytes, acute-phase reactions</td>
<td>IL-6, IL-11, leukemia inhibitory factor, oncostatin M</td>
</tr>
<tr>
<td>T-cell regulators</td>
<td>Balance of T-cells, regulation of acquired immunity, impact on inflammatory response</td>
<td>IFN-γ, IL-12, IL-15, IL-18, IL-6, IL-17, IL-23, IL-4, IL-5, TGF-β and the like</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Down-regulation of immune response and inflammation</td>
<td>TGF-β, IL-10, IL-13</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Activation of neutrophil chemotaxis</td>
<td>IL-8 and others.</td>
</tr>
<tr>
<td>Type 1 interferon</td>
<td>Antiviral immune response</td>
<td>IFN-α, IFN-β</td>
</tr>
<tr>
<td>Activators of bone cells</td>
<td>Development and function of bone cells</td>
<td>RANKL</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Regulation of tissue function, fibrosis, repair</td>
<td>TGF-β, vascular endothelial growth factor, hepatocyte growth factor, epidermal growth factor, fibroblast growth factor</td>
</tr>
<tr>
<td>Factors stimulating colonization</td>
<td>Hematopoiesis, localized differentiation of immune cells</td>
<td>IL-3, IL-7 and the like</td>
</tr>
<tr>
<td>Adipokines</td>
<td>Metabolic regulation, immune regulation</td>
<td>IL-6, leptin, adiponectin, visfatin</td>
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chemokines, adhesion molecules and prostaglandin E_2. TNF-α elevates phagocytic and neutrophil activity, induces the secretion of matrix metalloproteinases, stimulates the differentiation of osteoclasts and causes apoptosis in fibroblasts. In plaque-induced inflammation (such as the one associated with chronic periodontitis) the levels of TNF-α are increased. It has been found that both IL-1β and TNF-α are present in higher levels and have a distinctive expression in inflamed gingival tissue in periodontitis.

**INTERLEUKIN 6**

It is considered as a pleiotropic cytokine which, like IL-1β and TNF-α, appears early in the immune response development in periodontitis. Activated by other cytokines (IL-1β and TNF-α), it produces a wide spectrum of cells - activated T-cells, B-cells, macrophages, dendritic cells, and the so-called non-immune cells (keratinocytes, fibroblasts and endothelial cells). It is active in the immune system, the cardiovascular and nervous systems, and hematopoiesis; it signals the proteins of the acute phase response (C-reactive protein) in hepatocytes and the localized immune response (periodontal disease). It regulates the proliferation and differentiation of B cells, the differentiation of dendritic cells, stimulates bone resorption and osteoclast development. IL-6 has been found in elevated levels in the gingival fluid and tissue in patients with periodontitis. It is assumed that it may affect the differentiation of monocytes into osteoclasts and may also affect the development of the localized B-cells in the periodontium. Taylor believes that IL-6 has the power to “overturn” the course of the disease (localized bone turnover).4

**ASSOCIATION BETWEEN INCREASED LEVELS OF PERIODONTAL PATHOGENS AND THE EXPRESSION OF PROINFLAMMATORY CYTOKINES**

Many authors have focused their research on such association and have obtained results in accordance with the view that the presence of certain organisms is positively correlated with cytokine gene expression in gingival fluid and in gingival tissue. Overall, however, there is almost no information in the literature regarding the above in conjunction with the severity of periodontal disease, as well as with periodontal pockets depth. Most often, such attempts at finding correlation between biomarkers and microbiological data obtained from the same regions (periodontal sites) are limited in the number of tested bacterial strains and the number of the tested cytokines. Teles et al. investigated the relationship between the biomarkers of gingival fluid (IL-1β, IL-8, MMP-8), the levels of 40 bacterial strains and the clinical parameters of periodontal disease. They found a positive correlation between these three main clinical and biomarker criteria, as well as the proportions of bacteria from the red and orange complexes. The authors found that the bacteria of the red complex were positively associated with the expression of the tested cytokines. They associated their research with the depth of periodontal pockets, but went no further than to compare only shallow pockets in the studied groups - periodontally healthy subjects and subjects with periodontitis. Some authors have found a statistically significant increase of IL-1β and IL-8 in patients with periodontitis. The few reports in the literature include the study of Engebretson et al., who concluded that in patients with severe periodontitis there were elevated levels of IL-1β compared to patients with mild

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**Table 3. Effects of the major cytokines in periodontal diseases (Liu et al, 2010)**

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<th>Cytokines</th>
<th>Bone resorption</th>
<th>Osteoclast formation, stimulated (+) or inhibited (-) by immune cells or osteoblasts</th>
<th>Osteoclast formation, stimulated (+) or inhibited (-) by mature osteoclasts or osteoclast precursors</th>
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<tr>
<td>Interleukin 1</td>
<td>Yes</td>
<td>+ (direct)</td>
<td>+ (direct-osteoclasts)</td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>Yes</td>
<td>+ (direct)</td>
<td>+ (osteoclasts)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Yes</td>
<td>+ (direct)</td>
<td>- (osteoclast precursors)</td>
</tr>
<tr>
<td>Prostaglandin E2</td>
<td>Yes</td>
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and moderate periodontitis\textsuperscript{10}, and Rescala et al.\textsuperscript{41}, establishing also elevated levels of IL-1β in deep periodontal pockets as compared to shallow ones dominated by bacteria of the red complex. Studies of IL-6 and its involvement in the processes of periodontal destruction are few but strong on its role as mediator of the body’s response on the scale of IL-1β and TNF-α.

Baqui et al. studied and proved the relationship between the presence of the pathogens \textit{Porphyromonas gingivalis} and \textit{Fusobacterium nucleatum} and the production of IL-6 from human monocytes.\textsuperscript{42} This is in agreement with the findings of Roberts et al.\textsuperscript{33} who found that the mononuclear cells derived from the periodontal ligament have the capacity to respond to the periodontal pathogens and their virulence factors and induce the expression of pro- and anti-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, IL-12, IL-13, TNF-α, IFN-γ) in tissues affected by periodontal disease. These authors suggest that TNF-α play an essential role in the processes of periodontal destruction.

**CYTOKINES AND PERIODONTAL DISEASE**

On the basis of certain well-studied and known properties of the various cytokines and evidence from studies of periodontal diseases, it is known that pro-inflammatory cytokines such as IL -1, TNF-α and IL-6 are the first signalling cytokines which are also prevalent in periodontal lesion.

Are cytokines a part of target treatment rationale for periodontal disease?

The description of cytokine action from the group consisting of IL-1 and IL-6 with their expression and biological activity is considered by some authors as a future opportunity for therapeutic interventions - i.e. an anti-cytokine therapy or host response modulation.

**CONCLUSIONS**

Cytokines are an important component in the regulation of host inflammatory response as a whole. Based on literature reports for periodontal infection and systemic diseases such as cardiovascular disease, osteoporosis, rheumatoid arthritis and others relations, chronic periodontitis is increasingly perceived as a polygenic disease with a complex etiology and interrelationships with other chronic inflammatory diseases. Tissue destruction in chronic periodontitis can be linked to the localized level of destructive cytokines such as IL-1, TNF-α and IL-6. Most studies aim at achieving a holistic understanding of the idea that this complex system could be used for predicting the destructive effects in periodontitis. Therefore, additional data on the effect of key proinflammatory factors in the pathogenesis of periodontal disease would result in a better understanding of periodontitis and a differentiated control of the disease.

**REFERENCES**