

REVIEWS

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Biochemical, Microbiological and Molecular Characteristics of Chronic and Aggressive Periodontitis

Przewlekłe i agresywne zapalenie przyzębia – porównanie w aspekcie mikrobiologicznym, biochemicznym i molekularnym

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

In 1999, a novel classification of periodontal diseases was advocated by International Workshop for a Classification of Periodontal Diseases. It clearly demarcates the nomenclature and diagnostic criteria of periodontal diseases, emphasizing generalized aggressive periodontitis and Generalized chronic periodontitis. Although periodontal disease has been subdivided into two entities, its classification and diagnosis still presents an issue. It is obvious that with the advent of technological advancement a new system ought to be created, enabling clinicians to pinpoint the diagnosis. Research teams are utilizing various forms of assays in order to develop a more lucid understanding on how to differentiate between the two forms of the disease.

The aim of our review was to show whether there are any differences and/or similarities between the two forms of periodontitis at the biochemical, microbiological and molecular level. Although future prospects in the field of molecular biology may assist clinicians through the development of a innovative “intrinsic” classification we still have to develop a better understanding of the etiological factors, pathogenesis, genetics and how microorganisms are linked with various types of periodontal disease (*Dent. Med. Probl.* 2015, 52, 3, 330–335).

Key words: chronic periodontitis, aggressive periodontitis, classification.

Słowa kluczowe: przewlekłe zapalenie przyzębia, agresywne zapalenie przyzębia, klasyfikacja.

For many years clinicians have been trying to establish a system of periodontal disease classification. In retrospect, a breakthrough would enable us to establish specific structures for easier identification of periodontal lesions in terms of etiology, virulence and treatment [1].

To briefly summarize both forms of periodontitis it is crucial to point out several characteristics of chronic periodontitis. It has been described as the most commonly detected inflammatory reaction to an infectious bacterial flora in the oral cavity, leading to a gradual attachment apparatus deterioration and alveolar bone loss [2].

Frequent occurrence of abscesses and pocket formation has also been reported. It could be localized in the case when 30% or less sites are affected and generalized being more than 30 percent of sites affected [2].

In 1999, the international workshop has postulated that this form of periodontitis, although mostly found in adults, has a potential of occurrence in children and adolescents. As it was stated earlier, local factors such as bacterial biofilm, subgingival calculus could play a role in its rate of progression. The rate of disease advancement varies from slow to moderate, although periods of rapid

progression could occur. Mucogingival deformities conditions on edentulous ridges as well as occlusal trauma are amongst the other factors [3, 4].

It is important to emphasize that systemic factors such as diabetes mellitus and an HIV infection may also have an impact on the rate of the disease progression [5–7]. The list of factors is quite extensive as developmental or acquired deformities, smoking, emotional stress could lead to development of chronic periodontitis [2, 8].

An aggressive form of periodontitis is characterized by familial aggregation, rapid alveolar bone and clinical attachment loss. The severity of the disease is incompatible with the amount of plaque. Some of the features which are not exclusively present in all patients experiencing this form of the disease are increased proportions of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, phagocyte abnormalities, elevated levels of PGE2 and IL-1 beta due to hyperactive macrophages. In certain cases disease progression can undergo self-arrest [4].

Localized form commences around the time of puberty and tends to affect first molar/incisor with proximal attachment loss present on at least two permanent teeth. There is also an increased production of antibodies due to an infectious agent [2].

Generalized form usually affects individuals around 30 years of age. Proximal attachment loss is spared in molars and incisors, but it could affect at least three other teeth [2]. The production of an antibody is not as pronounced as in localized form and destruction of alveolar bone and attachment is sporadic [2, 9].

Host susceptibility and presence of bacterial biofilm are found in both forms of periodontitis. In addition, the loss of the periodontal apparatus and alveolar supporting bone are primarily due to the reaction of the immune system to a cornucopia of indigenous microorganisms. Pharmaceutical treatment is usually effective and could potentially arrest the eventual loss of dentition [4].

An interesting feature, which is shared by both forms of periodontitis, is that most of these patients do not show any signs of general health issues. On the other hand, there is a group of those affected individuals who exhibit periodontitis due to a manifestation of a systemic disease experiencing an inhibition of an innate and adaptive immune system such as inherited neutrophil functions, viral infections, plaque-induced periodontitis associated with immunosuppression as a result of a chemotherapy. Such malfunction has a dramatic effect on the host's ability to grapple with the microbial attack [4].

To develop a better understanding of how these two entities differ, research teams through-

out the world have been trying to utilize various forms of techniques in order to correctly diagnose and treat those affected by periodontal disease. Our literature review encompasses information on how chronic and aggressive periodontitis could be differentiated on a biochemical, microbiological and molecular level.

Neutrophil Functions in Aggressive and Chronic Periodontitis

Alteration of neutrophil function plays a significant role in the pathogenesis of chronic and aggressive periodontitis due to inherent changes or external factors [10].

Additionally, an inherent deficiency in the f-Met-Leu-Phe membrane receptor, co-receptor GP110 (glycoprotein 110), malfunctioning receptor sites or their reduced number on the neutrophil surface could all lead to disturbance of chemotaxis which in turn could lead to a periodontal attachment loss, especially those affected by localized form of aggressive periodontitis [11]. No pronounced difference in expression of adhesion intergrins (CD 18/CD11a and CD 18/CD11b) was observed when crevicular fluid neutrophils were examined in localized aggressive and chronic periodontitis patients.

Interestingly, comparison of control group versus aggressive periodontitis group revealed comparable expression of intercellular adhesion to endothelial cells [11].

According to Zietek and Konopka [12, 13], defective neutrophil phagocytosis resulting in a defect of intracellular killing of *Staphylococcus aureus* was revealed in some patients with LAgP and GAgP. However, a potential ability for correction of an imbalance following the periodontal treatment suggests the secondary nature of this defect [13].

Although the majority of the earlier research focused their attention on deficient chemotaxis and phagocytosis, a new concept of hyperactive or primed neutrophil has surfaced. A phenomenon of an oxidative burst, amplified adhesion of neutrophils, increased intracellular levels of beta-glucuronidase and myeloperoxidase is capable of accelerating tissue damage in AgP. Although pinpointing the main culprit responsible for the destruction of periodontal tissue is very complex, a comprehension of neutrophil function could be instrumental in the improvement of new diagnostic assays and treatment of both forms of periodontitis [11].

An experiment performed by Guentsch et al. [14] showed an increased oxygen reactive species release by PMNs when exposed to *P. gingivalis* and *A. actinomycetemcomitans* in patients diagnosed with chronic periodontitis than in those with aggressive periodontitis; Phagocytosis of *P. gingivalis* in chronic periodontitis ($62.16 \pm 19.39\%$) was greater than in aggressive form of the disease ($43.26 \pm 26.63\%$) at the 30-min time interval following exposure to the *P. gingivalis* ($p < 0.05$).

Gingival Crevicular Fluid Levels of Monocyte Chemoattractant Protein 1 and TNF-Alpha

Synthesis of MCP-1 and TNF-alpha by various cells within our bodies have been detected in various diseases expressing characteristics of chronic inflammation. Expression and production of these cytokines has also been documented in gingival tissues. The presence of MCP-1 and TNF-alpha was scrutinized by Kurtis et al. [15] in gingival crevicular fluid (GCF) obtained from patients experiencing both chronic periodontitis (CP) and aggressive periodontitis (AgP). In order to determine whether these proteins play any role in the development of periodontitis enzyme-linked immunosorbent, assays were performed on control groups (C) as well as those affected by CP and AgP.

Results attained revealed that, although total MCP-1 and TNF-alpha between CP and C and between AgP and C groups were statistically different, there was no statistical difference achieved at the concentration and total levels of MCP-1 and TNF-alpha when CP and AgP groups were compared. This finding suggests that the expression of MCP-1 could occur in AgP and CP patients and there is a positive relationship between MCP-1 and TNF-alpha levels of gingival crevicular fluid level, which could lead to an exaggeration of an inflammatory response leading to periodontitis [15].

Pro-Inflammatory Cytokines

Although it is generally understood that there is a correlation of periodontal disease with systemic maladies such as diabetes mellitus, rheumatoid arthritis exists, the exact mechanism of this intimate association has not been established [6, 7]. Explanation of this interrelation could be attained through measurement of pro-inflammatory cytokine level obtained from serum of those affected by either form of periodontitis [16].

Comparison of inflammatory mediator level (TNF-alpha, IL-17, IL-23, IFN-gamma) in patients diagnosed with GAgP and GCP was the main objective of Duarte et al. [17]. These authors have investigated that the level of TNF factor alpha and IL-17 were significantly higher (TNF-alpha - $p = 0.0006$ and IL-17 - $p = 0.02$) in patients affected by GAgP compared to those with GCP and healthy individuals. Similarly Olfat et al. [18] reported a significantly higher level of IL-17 in patients with aggressive type of periodontitis than in those with chronic group ($p < 0.001$), suggesting its potential role in aetiopathogenesis, whereas the level of the IL-11 concentration was greater in patients with chronic periodontitis than in aggressive type of periodontitis ($p < 0.001$). The disproportion of the IL-11/IL17 ratio suggests a discrepancy among anti-inflammatory and the pro-inflammatory factors [18].

Factors such as collagenase, prostaglandins, bone resorption factors (TNF-alpha) as well as mediators IL-1beta, IL-6 CRP (IL-17) are the main cause of inflammatory state and periodontium destruction. Giannopoulou et al. [19] has also reported that IL-1 level obtained from gingival crevicular fluid (GCF) was higher in GAgP patients compared to GCP and healthy subjects.

According to Rescala et al. [20] and Suzuki et al. [21] the analysis of an elastase level and biomarkers IL-1 beta 2, 4, 8 and IFN-gamma acquired from a GCF did not show to be statistically significant in patients affected by GAgP and GCP.

According to various research data, it could be hypothesized that pro-inflammatory cytokine level depends exclusively on the intensity and advancement of an inflammatory process in periodontal tissues and not on the disease type. However, a comparison of a healthy subgroup revealed a markedly increased cytokine level in those affected by either form of periodontitis [20, 21].

Clearly there is a correlation between the pro-inflammatory factors and an increased risk of systemic diseases; therefore, a proper diagnosis and treatment method ought to be implemented, especially in those affected by GAgP, due to its accelerated rate of destruction. [20, 21].

Immunoexpression of Angiogenesis, Nitric Oxide Synthase

Formation of new capillary vessels, known as angiogenesis, plays an instrumental role in wound healing, inflammatory processes and tumor formation. Numerous growth factors have

been analyzed to precisely estimate growth intensity [22–24].

Artese et al. [22] estimated levels of VEGF factor, NOS-1 and 3 and antibody Ki-67 allowing for detection of cellular proliferation, typically found in inflammatory and reparative processes as well as synthesis of nitric oxide responsible for intercellular communication. According to Artese et al. [22] patients affected by GAgP compared with those affected by GCP ($P < 0.05$) exhibited significantly increased level of all parameters (VEGF, NOS 1 and 3 and Ki-67).

Although newly formed vessels supply oxygen and necessary nutrients to the inflammatory site, they also provide substrates for the production of cytokines and other factors which intensify inflammatory process. Results obtained by Artese et al. [22] confirm the amplified intensity of inflammatory process in patients with GAgP compared to those affected by GCP.

Periodontopathic and Superinfecting Bacteria in Chronic and Aggressive Periodontitis

Diverse composition of subgingival microorganisms can be found in various ethnic groups throughout the course of periodontal disease [25–27].

Through the utilization of cell culture, biochemical tests and PCR, Botero et al. [28] has described different types of subgingival bacteria and clinical parameters (plaque index, bleeding on probing, clinical attachment level and probing depth) in chronic and aggressive periodontitis in Colombian population. Habashneh and Karasneh [29] performed similar research in the Jordanian population and established no significant difference in the subgingival microflora.

Clinical parameters of patients affected by either CP or AgP were significantly increased when compared with disease-free individuals ($p < 0.001$). No difference was observed between groups affected by periodontitis. Species such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Eikenella corrodens* showed a higher prevalence in AgP compared to CP and disease-free individuals [28]. In addition, patients diagnosed with AgP showed higher incidence of gram negative rods ($p < 0.01$). These observations suggest that composition of subgingival bacterial flora should be carefully screened prior to mechanical and antimicrobial therapy [28]. Dogan et al. [30] and Darby et al. [31] suggested significant differences in

bacterial flora amongst patients diagnosed with CP and AgP, whereas Ximenez-Fyvie et al. [32] reported only slight variation amongst microbiological flora.

Chronic and Aggressive Periodontitis and Their Molecular Differences

Although previous research projects attempted to evaluate histological and immunological differences amongst the two forms of periodontitis, no major breakthrough has been attained in terms of pathophysiological groundwork. Kerschull et al. [33] investigated characteristic gene expression of two principal forms of periodontitis through utilization of a microarray assays. Gene expression profiles obtained from gingival tissues of healthy individuals and from systematically healthy non-smokers, revealed that the transcriptional profiles did not show a substantial difference in patients with AgP and CP.

Overexpression of genes responsible for the production of proteins required for immune function, apoptosis and signal transduction was seen in those affected by AgP, whereas over expression of genes associated with epithelial cohesiveness and metabolism was discovered in those patients affected by CP [33]. Utilization of molecular profiling calls for further development of intrinsic assays due to unsubstantial differences found between two forms of periodontitis [33]. A research team of Brett et al. [34] has carried out genotyping of ten functional polymorphisms in seven candidate genes. The results indicate statistically significant differences ($p \leq 0.05$) in chronic and aggressive form of periodontitis (IL-1A –889) and general form of periodontitis as well as controls (VDR – 1056, TLR-4 399 & IL-6 – 174). Their observations suggest specific genetic similarities in chronic and aggressive type of periodontitis.

In 2002 Gonazles et al. [35] investigated IL-10 gene promoter polymorphism and its potential association with chronic and aggressive periodontitis. No statistical difference was achieved in the allele frequencies between controls and AP patients or CP patients.

Schulz et al. [36] has investigated genetic markers of tumor necrosis factor alpha in both chronic and aggressive form of periodontitis through an analysis of single nucleotide polymorphisms (SNPs) c.-308G4A, c.-238G4A and haplotype by a PCR with sequence-specific primers (PCR-SSP). Although the results showed a higher frequency rate of *P. intermedia* in patients with the

_308GG/_238GG haplotype combination, there is no clear evidence that TNF alpha is an independent risk factor for either aggressive or chronic periodontitis.

It is critical to emphasize that no clear-cut clinical distinction has been found and the size of the study group has not been large enough [37, 38].

Another factor associated with an increased risk for periodontitis is a Human Leukocyte Antigen (HLA 1 and HLA 2). Stein et al. [39] has investigated the homozygosities and heterozygosities in those affected by chronic and aggressive periodontitis. Although there is a certain level of correlation between HLA markers and a periodontal disease, no significance has been established. While HLA-A2 and HLA-B5 seem to act as protective feature against periodontitis, however, patients with aggressive type of periodontitis showed an association with HLA-A9 and HLA-B15. It has been established that HLA class II antigens recognize and bind to antigenic peptides manufactured by bacteria and present them to T cells, while HLA class I antigen present self and viral antigens to cytotoxic T cells [40].

Since no correlation between aggressive periodontitis and HLA-2 has been determined, it could be suggested that individuals with HLA-A9 or

HLA-B15 show the inadequacy of attachment and presentation of viral proteins to cytotoxic T-cells, ultimately leading to aggressive periodontitis [39].

Overview

Elucidation of the conundrum of periodontal disease types through development of new technologies in the fields of biochemistry, microbiology and genetics have been tedious and provided clinicians with minimal amount of success. One ought to ask oneself why is the classification of periodontal diseases so challenging. The answer is that these two types of diseases share many similarities and we are simply unable to truly comprehend the reason behind it. Therefore, traditional diagnostic tools such as probing depth, clinical attachment loss and clinical signs of inflammation are still the gold standard. Although future prospects of molecular biology may assist clinicians with the development of a innovative "intrinsic" classification, we still have to develop a better understanding of the etiological factors, pathogenesis, genetics and the way microorganisms are linked with various types of periodontal disease [9, 33].

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