

## MICROBIAL ETIOLOGY OF PERIODONTAL DISEASE – MINI REVIEW

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**Summary.** *The periodontal disease is a chronic, degenerative disease which is localised on the gingiva, periodontal ligament, cementum and alveolar bone. The main etiological factor is oral biofilm with microorganisms. The search for the pathogens of periodontal diseases has been underway for more than 100 years, and continues up today. The currently recognized key Gram negative periodontopathogens include: Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Capnocytophaga species, Campylobacter rectus. All bacteria in the periodontal pocket could damage periodontal tissues, and good knowledge of these as well as an adequate treatment could be helpful in treatment of this disease. A full understanding of the microbial factors, their pathogenicity as well as host factors are of the essential importance for pathogenesis of periodontal disease. In this way, it could be possible to treat the periodontal patients adequately.*

**Key words:** *Periodontal disease, microorganisms, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis*

Periodontal disease could be defined as a disorder of supporting structures of teeth, including the gingiva, periodontal ligament and alveolar bone. Periodontal disease develops from a pre-existing gingivitis. However, not every case of gingivitis develops into a periodontal disease. The inflammation of gingiva alone is termed gingivitis, and the severe inflammation of the periodontal ligament with destruction of alveolar bone is called periodontal disease.

The current concept concerning the etiology of periodontal disease considers 3 groups of factors which determine whether active periodontal disease will occur: a susceptible host, the presence of pathogenic species, and the absence of so-called "beneficial bacteria" (1,2). It is generally accepted that the oral biofilm in association with anaerobic bacteria is the main etiological factor in periodontal disease (3,4,5).

The oral biofilm consists mainly of microbes and host proteins that adhere to teeth within minutes of a dental oral hygiene procedure. Healthy gingival sulcus has a flora dominated by equal proportions of Gram positive cocci, especially Streptococcus spp, and Actinomyces sp. Later, plaque "matures" resulting in a flora consisting from facultative anaerobic microorganisms, spirochaetes and motile rods. The proportions of strict anaerobic, Gram negative and motile organisms increase significantly in accordance with increasing severity of disease. Disease activity in periodontal disease may range from slow, chronic, progressive destruction to brief and acute episodic bursts with varying intensity and duration.

The composition of the subgingival microbial flora and the level of pathogenic species differ from subject to subject as well as from site to site. The search for the pathogens of periodontal diseases has been underway for more than 100 years, and continues up today. The currently recognized key Gram negative periodontopathogens include: Porphyromonas gingivalis (P.g), Prevotella intermedia (P.i), Bacteroides forsythus (B.f), Aggregatibacter actinomycetemcomitans (A.a), Fusobacterium nucleatum (F.n), Capnocytophaga species (C.sp), Campylobacter rectus (C.r) (6-10). Also, the following bacteria could be isolated: Eubacterium spp, Peptostreptococcus micros, Selenomonas spp, Spirochaetes. The range of putative pathogens has been extended to include not only cultivated bacteria but also non-cultivated bacteria and viruses (11-15). A correlation was found between P.g, P.i, C.r, Eikenella corrodens, Selenomonas sp, Bacteroides species, Spirochetes and adult or refractory periodontal disease (16,17).

The microorganisms could produce disease directly, by invasion on the tissues, or indirectly by bacterial enzymes and toxins.

In order to be a periodontal pathogen, a microorganism is must have the following:

- the organism must occur at higher numbers in disease-active sites than at disease-inactive sites
- elimination of the organism should arrest disease progression
- the organism should possess virulence factors relevant to the disease process

- the organism should elicit a humoral or cellular immune response
- animal pathogenicity testing should infer disease potential (18).

### ***Porphyromonas gingivalis***

This bacterium, previously known as *Bacteroides gingivalis*, is a strictly anaerobic, Gram negative rod. It is a black-pigmented microorganism which produces a black pigment. Many virulence mechanisms have been identified. P.g. has a carbohydrate capsule on its outer surface which prevents opsonization by complement and inhibits phagocytosis and killing by neutrophils. The lipopolysaccharide which is produced is not very strong, but it could inhibit chemotaxis and killing by leucocytes. This organism possesses several putative virulence factors (including proteases which degrade immunoglobulin, complement, collagen fibres, hyaluronic acid; adhesins, endotoxins, and cytotoxins) that can directly affect the periodontium or elicit host functions that result in the gingival tissue and bone damage typical for periodontal disease (19). P.g. expresses three major virulence factors-fimbriae, gingivipains and lipopolysaccharides.

P.g. is one of the major periodontopathogen (20-23) with the ability to adhere (24-27), and to invade (28-31) oral epithelia in vitro. Differences exist in the adhesion capacity of P.g. among laboratory and clinical strains (26-30). This has been attributed to the differences in the surface characteristics between strains (32), especially the presence of fimbriae (32-34).

The lipopolysaccharide of P.g. is unique, based on the chemical structure of its core polysaccharide and lipid A regions and in its biological activity (35).

Its importance as a periodontal pathogen is also highlighted by the research efforts aimed at developing a vaccine aimed at immunization against this bacterial species and thus preventing a chronic periodontal disease (36-38).

### ***Aggregatibacter actinomycetemcomitans***

A.a., previously *Actinobacillus actinomycetemcomitans*, is a Gram negative facultative non motile coccoid bacillus. Its presence in the periodontal pocket is associated with preadolescent (39), localized juvenile (3,20) and advanced adult aggressive periodontal disease (40,41). Several virulence factors are reported: the leukotoxin is the most important, cytolethal distending toxin, immunosuppression factors, inhibition of PMNS functions etc.

Leukotoxin, is an RTX (Repeats in Toxin) toxin (42) and shares sequence similarity with the  $\alpha$ -hemolysin from *Escherichia coli*, the cytolysin from *Pasteurella haemolytica* and the leukotoxin from *Actinobacillus pleuropneumoniae* (43). Leukotoxin from A.a. could kill human and non-human primate polymorphonuclear leukocytes and peripheral blood monocytes (44,45). So,

the innate immune response could be attacked directly. A.a. endotoxin has the potential to modulate host responses and contribute to tissue destruction. The ability of the A.a. lipopolysaccharide to stimulate macrophages to release interleukin IL-1, IL-1 $\beta$ , and tumor necrosis factor (TNF) is of big importance. These cytokines, among other their activities, are capable of stimulating bone resorption (46).

P.g. and A.a. are suggested to represent exogenous microorganisms (47,48) based on their low levels in periodontally healthy subjects (49). It has been suggested that periodontal infections associated with these pathogens represent "true infection" (47).

### ***Prevotella intermedia***

*Prevotella intermedia*, former *Bacteroides intermedius*, is a black pigmented Gram negative bacterium. This species resists phagocytosis, probably by virtue of its capsule. P.i. is an important periodontal pathogen, in association with P.g. and A.a. (4,17,18,41).

### ***Fusobacterium nucleatum***

F.n. is an important periodontal pathogen, particularly in the beginning of the rapidly progressive periodontal disease. It creates very strong lipopolysaccharide as well as butyric acid as a metabolic end product (4,17,18).

### ***Bacteroides forsythus***

*Tannerella forsythensis* (T.f) - formerly *Bacteroides forsythus* - is a non-pigmented saccharolytic anaerobic gram-negative rod. T.f. possesses several virulence factors including the production of a trypsin-like protease and lipopolysaccharide (50,51) but recently, its ability to penetrate into host cells or induce apoptosis (52,53).

### ***Capnocytophaga species***

*Capnocytophaga* are micro-aerophilic Gram negative rods. There are three species – *C. ochracea* (formerly *Bacteroides ochracea*), *C. sputigena* and *C. gingivalis*. *C. ochracea* is implicated in the beginning of a juvenile periodontal disease, and adult periodontal disease. This bacterium produces lipopolysaccharide with activity on alveolar bone, extracellular proteases which could damage immunoglobulins.

### ***Peptostreptococcus micros***

*Peptostreptococcus micros* (P.m) is an anaerobic, Gram positive bacterium which is associated with periodontal disease as well as several other polymicrobial infections in other systemic diseases (7,17,54,55). The prevalence of P.m. in advanced adult periodontitis

was reported as 58% to 63%, with P.m representing 12% to 15% of the cultured viable counts<sup>54</sup>. In periodontal patients, the prevalence of P.m was higher in those with active disease, which supports an etiological role of P.m in progressive attachment loss (54). This finding was supported in another study where P.m, *Wolinella recta*, and *F.n* were the only species detected in one or more samples from patients with active disease sites (56). P.m was also positively associated (18% of the time) with recurrent or refractory periodontal disease and implant failure (55,57,58). All of these present a strong association of P.m in periodontal disease and periimplantitis.

### ***Spirochaetes***

Spirochaetes are motile spiral-shaped microorganisms with flagella. They are not associated with localized juvenile periodontal disease, but two important species – *Treponema denticola* (T.d) and *Treponema vincentii*. They could be implicated in periodontal disease. Both of them produce a lipopolysaccharide, and unusual metabolic end products, like indole, hydrogen sulphide, ammonia, which are potentially toxic to host cells.

Spirochetes were observed in a higher proportion of patients with periodontal disease than in periodontally healthy patients (59,60).

T.d is frequently isolated from severely diseased sites in patients with a periodontal disease (61). Many studies have attempted to elucidate the role of T.d in periodontitis (62-65). T.d has been shown to attach to human gingival fibroblasts, basement membrane proteins, as well as other substrates by specific attachment mechanisms, the binding of the spirochete to human gingival fibroblasts resulted in cytotoxicity and cell death due to enzymes and other proteins (66,67).

Takeuchi et al 2001 found that *Treponema socranskyi* (T.s), T.d and P.g. were frequently detected in patients with a periodontal disease by PCR technique in plaque and saliva samples (68). They also found that the presence of T.s was associated with periodontitis, as well as that *T.socranskii* was more frequently detected in plaque samples from aggressive or chronic periodontitis patients than from healthy subjects. T.s were detected more frequently at sites where a severe periodontal tissue destruction was observed.

### ***Human viruses***

Human viruses have also been implicated in periodontitis. Recent findings have begun to provide a basis for a causal link between herpes viruses and aggressive periodontitis. One theory is that herpes viruses cooperate with specific bacteria in the etiopathogenesis of the disease. Namely, periodontal herpes viruses comprise an important source for triggering periodontal tissue destruction (69,70). In cross sectional studies, viruses in Herpes family have been isolated from the lesions of periodontitis patients (71). Their genomes have been found in chronic periodontal disease (72), aggressive periodontal disease (71) and periodontal disease associated with systemic diseases (71).

Herpes virus productive infection may initiate or accelerate periodontal tissue destruction due to a virally mediated release of cytokines and chemokines from inflammatory and non-inflammatory host cells, or a virally induced impairment of the periodontal defense resulting in a heigh-tened virulence of resident pathogenic bacteria (71). Human cytomegalovirus and Epstein-Barr virus occur frequently in aggressive periodontitis sites (74-77). Also, the periodontal presence of Human cytomegalovirus has been linked to a high occurrence of subgingival P. g (78), *Dialister pneumosintes* (79) and other periodontal pathogens (80,81).

In addition to these bacteria and viruses, a few new cultivated species are associated with a periodontal disease. These include *Eubacterium saphenum* and *Mogibacterium timidum* (82); *Prevotella corporis*, *Prevotella distens* and *Peptostreptococcus magnus* (83), *Eubacterium nodatum* (84,85) and *Slackia exigua* (84), *Streptococcus faecalis*, *Escherichia coli* and *Bartonella sp.* (86).

Bacteria presented in the periodontal pockets could be detected by microbiological culture techniques, detection of the certain microbial enzymes, immunological methods, DNA/RNA probes (87,88). Bacteria recognized in periodontal pockets could be successfully treated by antibiotics. This is one of the main aims in the treatment of periodontal disease.

### **Conclusion**

A full understanding of the microbial factors, their pathogenicity as well as host factors are of the essential importance for pathogenesis of periodontal disease. In this way it could be possible to treat the periodontal patients adequately.

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## MIKROBIOLOŠKA ETIOLOGIJA PARODONTOPATIJE

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Kratak sadržaj: *Parodontopatija predstavlja hroničnu, destruktivnu bolest, koja zahvata čitav potporni aparat zuba (gingiva, cement, alveolarna kost i periodoncijum). Glavni etiološki faktor u nastanku ovog oboljenja je oralni biofilm sa mikroorganizmima. Poslednjih 100 godina istraživači ispituju sastav mikrobiološke flore parodontalnog džepa. Do danas ključni Gram negativni periodontopatogeni su: Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Capnocytophaga species, Campylobacter rectus. Sve prisutne bakterije u parodontalnom džepu mogu oštetiti parodontalna tkiva, i dobro poznavanje mikroorganizama omogućava i adekvatan tretman parodontopatije. Potpuno poznavanje mikrororganizama, njihove patogenosti, kao i poznavanje odgovora domaćina su osnovni za razumevanje patogeneze parodontopatije. ovo bi omogućilo i lečenje pacijenata sa parodontopatijom na odgovarajući način.*

Ključne reči: *parodontopatija, mikroorganizmi, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis*