*Advances in Health Sciences Research, volume 32*
**Proceedings of the 1st Aceh International Dental Meeting (AIDEM 2019), Oral Health**
**International Conference On Art, Nature And Material Science Development 2019**

# The Role of *Fusobacterium Nucleatum* on Chronic Periodontitis (Literature Review)

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**ABSTRACT**
Chronic periodontitis is the most often disease in the oral cavity which attacks the supporting tissues of the teeth. This disease develops slowly, resulting in teeth experiencing loss of attachment and alveolar bone loss. The main cause of chronic periodontitis is bacterial plaque which is a soft deposit in the form of a thin layer of biofilm containing a collection of pathogenic microorganisms, one of it is *Fusobacterium nucleatum*. *Fusobacterium nucleatum* is an obligate anaerobic Gram negative bacterium and found in a healthy or diseased oral cavity. *Fusobacterium nucleatum* can be isolated from the oral cavity and other infections in the human body such as skin ulcers, peritonsillar abscesses, septic arthritis and endocarditis. *Fusobacterium nucleatum* plays an important role in the formation of plaque because it functions as a "*bridge bacterium*", which is a link for bacteria found in the early phases of plaque colonization with bacteria found in the final plaque colonization. *Fusobacterium nucleatum* is one of the bacteria most isolated from periodontal pocket of patients with chronic periodontitis. Lipopolysaccharides found on the outer membrane of *Fusobacterium nucleatum* and metabolic result from this bacteria can cause periodontal tissue damage in the cases of chronic periodontitis.

***Keywords:*** *Fusobacterium nucleatum, chronic periodontitis, lipopolysaccharides*

## 1. INTRODUCTION

Chronic periodontitis is the most common infectious disease in the oral cavity. The disease process is slow, and will cause periodontal pocket formation, attachment, bone and tooth losses if it not treated. The prevalence and severity of the disease increase along with age.[1]

The main cause of chronic periodontitis is the bacterial plaque composed of various bacterial species forming a community. Bacteria in periodontal pockets use a gingival crevicular fluid as a source of carbon and nitrogen nutrients which are very useful for their growth. Bacteria are proliferating and communicating with each other using chemical signals.[2]

Communication between bacterial species in biofilms is the key to understanding how specific bacteria emerging and damaging the balance of the host. A good collaboration process is conducted by *Fusobacterium nucleatum* (*F. nucleatum*) which can be a bridge between the initial colonization, for example the *Streptococcus* species and the final colonization, especially the anaerobic obligate bacteria when the dental plaque formed.[2] *F. nucleatum* is an obligate anaerobe, but can grow under atmospheric conditions with > 6% oxygen by volume.[3]

The presence of *F. nucleatum* in biofilms causes a number of anaerobic bacteria such as *Prevotella nigrescens* and *Porphyromonas gingivalis* (*P. gingivalis*) to survive in large numbers. The ability of *F. nucleatum* to conduct the coaggregation with facultative and anaerobic bacteria causes anaerobic bacteria to survive.[4] *F. nucleatum* has characteristics of a periodontal pathogen, because its number is significantly increased in deepened periodontal pockets, it can adhere to and invade gingival epithelia and stimulate matrix metalloproteinase secretion by host cells.[5]

### *1.1. Oral microbiota*

The general environment of the mouth there exists the number of different microenvironments or niches, each of which support their own peculiar microflora (Table 1).[6]

**Table 1.** Relative proportions of oral microorganisms in health

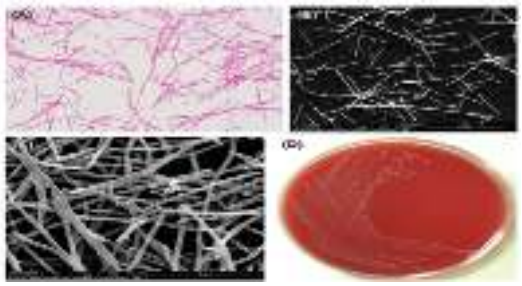
| Microorganism | Tongue | saliva | Approximal plaque | Subgingival plaque |
|---|---|---|---|---|
| *Strep. mutans* | 0 | 2 | 2 | 0 |
| *Strep. sanguis* | 2 | 2 | 3 | 2 |
| *Strep. oralis* | 3 | 3 | 3 | 2 |
| *Strep. salivarius* | 3 | 3 | 1 | 1 |
| *Actinomyces* Spp | 0 | 2 | 4 | 3 |
| *Lactobacillus* Spp | 0 | 1 | 1 | 0 |
| *Veilonella* Spp | 3 | 3 | 2 | 2 |
| *Bacteroides* Spp | 0 | 1 | 1 | 2 |
| *Fusobacterium* Spp | 1 | 1 | 1 | 2 |
| *Spirochaetes* | 0 | 0 | 0 | 1 |
| *Candida* Spp | 3 | 1 | 0 | 0 |

0. Not usually found;
1. Occasionally present in small numbers;
2. Usually present in small numbers;
3. Usually present in moderate numbers;
4. Usually present in high numbers.[6]

Bacteria associated with healthy periodontal tissue and most of the abundant species in the mouth are the facultative Gram positive species such as *Streptococcus* and *Actinomyces*. Small numbers of Gram negative bacteria such as *Prevotella. intermedia*, *F. nucleatum*, *Capnocytophaga*, *Neisseria* and *Veilonella* are also found.[3] These microflora can be the opportunistic pathogens when their habitat is disturbed or their microorganisms are in the unusual areas.[4] The normal microbial composition of the body is believed to have major health benefits for the host.

1.1.1. *Fusobacterium nucleatumFusobacterium nucleatum* is an obligatory Gram negative anaerobic bacterium belonging to the genus *Fusobacteria*. They belong to the family *Bacteroidaceae*.[3] *Fusobacteria* are asaccharolytic, although it can use carbohydrates for intracellular synthesis. *Fusobacteria* break down amino acids such as aspartate, glutamate, histidine and lysine to produce energy.[7] *Fusobacteria* are non-motile, so that it can make contact between cells to create the necessary metabolic environment.[8] Characteristics of *F. nucleatum* cells are long filaments (5-25 μm in length) or pleomorphic rods with a fusiform or tapered end (Fig 1).[3] Bacterial cells can produce butyric acid as the major metabolic end result.[7] *Fusobacterium nucleatum* has three subspecies which are associated with healthy and diseased conditions. *Fusobacterium nucleatum* subsp. *polymorphum* is usually isolated from the normal gingival sulcus. Subspecies *Nucleatum* and subspecies *vincentii* are mainly found in periodontal pockets.[7]

**Figure 1**. (A). *Fusobacterium nucleatum* cells with Gram stain,
(B,C). *F. nucleatum* cells with SEM in glucose broth culture,
(D). *F. nucleatum* colonies in BHI blood agar.[3]



*Fusobacteria* can bind to almost all oral cavity bacteria and it cannot bind to other strains of *Fusobacteria*.[7,8] In the process of plaque formation, the bacterium *F. nucleatum* acts as a bridge between the bacteria found in the initial colonization and in the final colonization. Early colonization bacteria attach to the dental pellicle and conduct the coaggregation with other bacteria presented in the initial colonization phase and also with *F. nucleatum*. Late colonization bacteria such as *Selomonas flueggi*, *Porphyromonas gingivalis*, *Fusobacterium* species, *Actinobacillus*, *Capnocytophaga*, and *Treponema* conduct the coaggregation exclusively with *F. nucleatum*.[8] Bacteria can attach to specific substrates at the stage of colonization because of the presence of adhesins which are proteins on the bacterial cells surface.[9]

*F. nucleatum* plays a role in adhesion and coaggregation reactions which is the cause of multigeneric coaggregation found in periodontal pockets. [10]

### *1.2. Chronic periodontitis*

This is the most common form of advanced periodontal disease affecting the general population and is the major cause of tooth loss.

Chronic periodontitis is an infectious disease in the supporting tissues of teeth which causes damage to the periodontal ligament and alveolar bone accompanied by the increasing pocket depth, recession or both. Bone loss is a feature of advance forms of periodontal disease. (Fig. 2)[4,7]

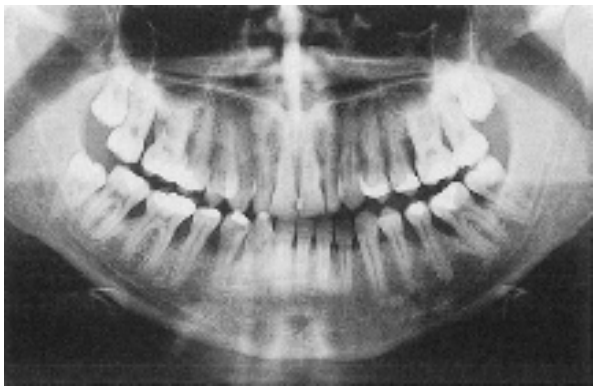


**Figure 2** Radiograph of chronic periodontitis showing extensive bone loss.[7]

The disease is caused by bacterial plaque and the process of the disease progresses slowly to moderate. Factors that cause plaque retention can worsen this disease, such as crowding, sub gingival calculus or overhanging restoration.[7] One clinically important characteristic of dental plaque is that it cannot be removed from the tooth by rinsing or spraying.[11] Unlike dental caries, many of the bacteria associated with periodontal diseases are asaccharolytic (cannot metabolize carbohydrates for energy)[7]

The main bacterium which causes chronic periodontitis is *P. gingivalis*. This periodontal pathogenic bacterium can survive in dental plaque through selective attachment to existing bacteria, namely the *Fusobacteria* species through the process of coaggregation and coadherens.[7] *F. nucleatum* conducts coaggregation with *P. gingivalis* through galactose containing carbohydrates from *P. gingivalis* and outer membran protein (OMP) from *F. nucleatum*.[12,13]

Coaggregation is only found to occur in bacteria in the human oral cavity and measly found in bacteria which live in ecosystems other than the oral cavity, or even no coaggregation occured.[14] The attachment of bacteria/coadherens is very important in colonization because it is a virulence factor besides toxins, enzymes and capsular substances produced by microorganisms.[15]

In chronic periodontitis, most Gram negative bacteria gather around the tooth root and produce virulence factors such as lipopolysaccharides (LPS), cytotoxic metabolites and immunoreactive molecules. The host will issue an inflammatory response to microbes by producing prostaglandins and pro-inflammatory cytokines. [7]

## 2. DISCUSSION

*Fusobacterium nucleatum* is a Gram negative anaerobic bacteria found as normal flora of the oral cavity and plays a role in the occurrence of periodontal disease. *Fusobacterium nucleatum* has an outer protein membrane which functions as a receptor in the process of mitosis, nutrient transport and coaggregation between bacteria. *Fusobacterium nucleatum* is one of the bacteria most isolated from gingival sulcus in patients with periodontitis. [16]

Lipopolysaccharide (LPS) is a protein found in the outer membrane of bacteria and a characteristic of Gram negative bacteria. Lipopolysaccharides extracted from cell walls of Gram negative bacteria play an important role in the pathogenesis of periodontal disease.[17] LPS containing crevicular fluid shows endotoxic activity which is associated with the degree of inflammation clinically and histologically in periodontal tissue.[16] Research conducted by Morrison proposes an outer membrane protein component showing a strong immunobiological activity, mostly from LPS and peptidoglycan.[18]

The metabolic results of *Fusobacteria* in the form of butyrate, propionate and ammonium ions can inhibit the proliferation of fibroblasts from human gingiva.[19] These bacteria have the ability to penetrate into the gingival epithelium and are found in large quantities in plaques with periodontitis patients.[20] *F. nucleatum* produces large concentrations of butyrate and volatile Sulphur compounds that penetrate to epithelium gingiva can induce further damage.[7] Bone resorption can be induced by melecules from periodontal pathogens, e.g. LPS, lipoteichoic acid and surface associated proteins.[7]

The first defense mechanism in periodontal pockets is polymorphonuclear (PMNs) which contains 90% of leukocytes in the gingival fluid.[21] Cell attachment is one of the earliest events seen after PMN activation. Seow found that *F. nucleatum* increased PMN attachment. The stimulating effect of *F. nucleatum* results in the release of toxic oxygen radicals and lysosomal enzymes which result in damage to periodontal tissue.[22]

Research conducted by Takada et al. showed that the porin protein from *F. nucleatum* plays an important role in the pathogenesis of chronic periodontitis. It was found that porin bioactivity compared with LPS, the amount of porin in the bacterial outer membrane was more than the amount of LPS. Porin and LPS work synergistically in the process of periodontal disease.[23]

Lipopolysaccharides derived from *F. nucleatum* are attached not only to the epithelium but also to the surface of the teeth including the root teeth cementum, so it is necessary to remove the contaminants which exist in the teeth roots through scaling and root planing to create new attachments.[24]

*F. nucleatum* conducts coaggregration with *P. gingivalis* through galactose containing carbohydrates in *P. gingivalis* and the outer membrane of proteins of *F. nucleatum*.[12] Kolenbrander et al. reported that large amounts of coaggregation were found to occur between *F. nucleatum* and *P. gingivalis*. Therefore, *F. nucleatum* plays an important role in the survival of *P. gingivalis* in periodontal pockets and coaggregation is a prerequisite for successful colonization by *P. gingivalis*.[25] *Porphyromonas gingivalis* is mainly

found in patients with periodontal disease, in contrast to *F. nucleatum* which can be found on the healthy side and the side which has periodontal disease.

*Fusobacterium nucleatum* has the capacity to form intracellular polymers from glucose, galactose and fructose in the excess amino acid conditions and ferment sugars when amino acid conditions are reduced. This might explain how *F. nucleatum* can survive in the oral environment and periodontal disease.[26]

## 3. CONCLUSION

Lipopolysaccharide and metabolic result of *Fusobacteria nucleatum* play a pathogenic role in periodontal disease.

Bacteria can be pathogenic individually, but performing combination with other bacteria can produce synergy or more severe damage to periodontal tissue as shown by *P. gingivalis* and *F. nucleatum* in causing chronic periodontitis.

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