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Unraveling the Etiology of Periodontitis

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Abstract

Across the globe, incidence of oral afflictions like gingivitis and periodontitis are increasing at a very fast pace. Evidence are there to support the fact that despite of being an oro-dental infection, periodontitis is associated with the systemic diseases too. Different ecological niches of oral cavity can harbor both pathogenic and non-pathogenic micro-organisms. Although the main cause of the disease is the anaerobic or the facultative anaerobic bacteria, other factors such as poor personal hygiene, diet and immune related disorders are also responsible for the progression of the disease. The vicious circle starts from deposition of the bacterial plaque/biofilm on the tooth surface then leading to gingivitis. If left untreated, it progresses to the development of periodontal pockets and ultimately tooth loss. However traditional treatment modalities like high dose of systemic antibiotics are available but antimicrobial resistance and virulence of the periodontal pathogens is the major cause of the treatment failures. This review primarily focuses on the etiology, pathogenesis and microbiology of the periodontitis. It also discusses the virulence and antimicrobial resistance factors of the periodontopathic micro-organisms. It is an attempt to develop the thorough understanding of the disease so that better therapeutic outcomes of periodonto-therapy can be attained.

Keywords: *Periodontitis; Antimicrobial Resistance; Disease virulence; Periodonto-therapy; Pathogenesis; Oral microbiota*

Introduction

Chronic gingivitis (which is also a primary stage of periodontitis) and periodontitis are the two diseases, which afflict a vast population and are often known to transcend socio-economic strata [1]. Initiation of both diseases lies in inflammation of the teeth adenexa, accompanied with painless hemorrhage. When left untreated, may leads to loss of teeth or edentulism [2]. It is believed that periodontitis is due to the accumulation of non-specific oral microbiota on the tooth and gingival surface, that can be controlled by mechanical cleaning by the dentists at regular interval [3]. But if ignored, then untreated plaques become calcified and forms dental calculus or tartar on the gingival margins. It is difficult to remove the dental calculus without surgical procedures. If left untreated for longer duration, then these periodontopathic microbes, their metabolic end-products and cell components like lipopolysaccharides (LPS) can trigger inflammatory or host response in the gingival tissue [4]. Medical conditions, that can compromise the immune system, such as autoimmune disorders, diabetes and AIDS, will also increases the chances of occurrence of periodontal disease. So, the present review describes the etiology, pathogenesis and microbiology of the periodontal infections. Also discusses the virulence factors and antimicrobial resistance factors of the periodontal pathogens, which lead to progression of the disease.

Periodontal infection

Etiology

The oral cavity has multiple ecological niches that represent very different bacterial ecosystems. There are

five major bacterial ecosystems: (1) Tongue (2) Buccal mucosa (3) Supragingival plaque (tooth-adherent bacteria that are coronal to the gingival margin) (4) Subgingival plaque (bacteria that reside apical to the gingival margins) and (5) Saliva. Most of the bacteria found in the saliva are organisms from the tongue and buccal mucosa. In an individual with moderate to heavy plaque accumulations, the saliva will also reflect the bacteria found in the dental plaque. Therefore, the saliva represents primarily a collection of bacteria shed from other ecosystems on their way to being swallowed [5].

Pathogenesis

Pathogenesis is the sequence of the events leading to the occurrence of a disease. The pathogenesis of plaque-associated gingivitis is relatively straightforward. Bacterial accumulations initiate vascular changes in terms of acute inflammatory reactions. This results in a vascular leakage of fluid and active migration of polymorphonuclear leukocytes (PMNs, or neutrophils) out of the vessels into the tissues and into the gingival sulcus.

The onset of periodontitis often owes to the setting of a collection of supragingival microbiota, which later translates itself into subgingival plaque formation [6]. The subgingival plaque therefore has three zones: 1) the tooth-adherent bacteria, 2) epithelial-associated bacteria and 3) apical bacteria.

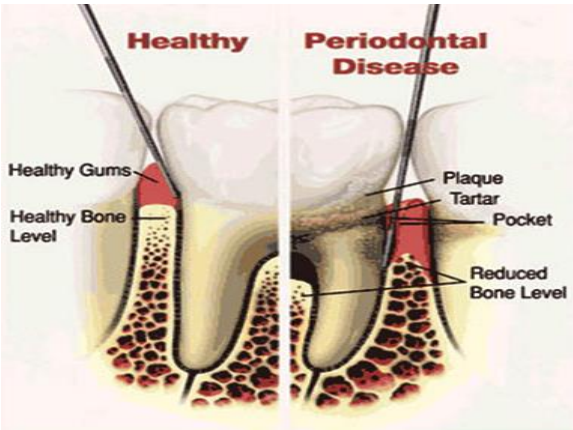

Figure 1: Schematic representation of healthy and periodontitis affected tooth.

These microbial deposits very rarely lead to overt conditions, but they trigger the host response in terms of inflammation. Cyclo-oxygenase-II (COX-II), Tissue necrosis factor (TNF-α) and Interleukin-6 (IL-6) are majorly responsible for the host response related inflammation [7]. Initial stage of such inflammation is always manifested in form of swelling of gingiva, bleeding and bad breath. Next to this, action of matrix-metalloproteinases' (MMP-8) leads to the dissolution of gingival fibers (collagen), resulting in the development of periodontal pockets [8]. This pocket can be of 4 to 12 mm in depth (Figure 1) and can serve as the habitat of more than 10^9 bacterial cells [9]. In later stages suppression of bone morphogenetic proteins on the tooth surface leads to alveolar bone loss [10].

Microbiology

The pathogens responsible for the initiation and progression of periodontitis has engaged the attention of researchers for more than four decades [11]. The latest research involving sequencing of 16S rRNA lead to the identification of approx. thousand bacterial species, phylophytes and so many unculturable micro-organisms [12].

Most of the germs, causing periodontitis are anaerobic collagenase secreting gram-negative bacteria and are known as 'red complex' bacteria [12]. Table 1 enlists the major pathogens responsible for periodontal infections. Apart from these pathogens, the newly discovered bacteria's such as *Pseudoramibacter alactolyticus*, TM7 species, *Filifactor alocis*, *Selenomonas noxia*, *Deferribacter* species, *Bacteriodetes* species OT 272, *Solobacterium moorei*, *Desulfobulbus* species OT 041, *Megasphaera* species, *Shuttleworthia satelles*, *Mogibacterium timidum*, *Catonella* species, *Brevundimonas diminuta*, *Granulicatella adiacens*, *Synergistes* species cluster II and *Sphaerocytophaga* species are yet to be explored for their periodontopathic potential [13]. Although Actinomyces species and Alpha-hemolytic *streptococci* does not possess periodontitis causing capacity, but they abundantly found in healthy periodontal microbiota [14].

The existence of complex oral hygiene levels in individuals due to different socio-economic background, acts as a major hurdle in periodontal microbiology studies [15]. But with the advancements in diagnostic tools such as ELISA, DNA hybridization, End point PCR, Real time PCR, immunofluorescence and availability of various sequencing techniques [16]; the real culprits of periodontitis may be identified.

Virulent nature of periodontal pathogens

The severity of periodontal infection is augmented by the mutual interaction between the anaerobic and aerobic bacteria. Polymicrobial nature of the disease helps in bolstering the synergistic survival mechanisms of anaerobic and aerobic organisms as these organisms have complementary.

Aerobic bacteria create the optimum physical conditions for the survival and replication of the

anaerobic bacteria by reducing the oxidation-reduction potential of the host tissue. It is believed that more chronic the infections, greater is the lack of oxygen in the periodontal tissue and higher is the density of anaerobes. Bacteria also support each other by providing nutrients. For example, succinate is produced by Klebsiella, which supports the growth of *Porphyromonas asaccharolytica* and vitamin K1 is the growth supplement *for Prevotella melaninogenica*, produced by oral diphtheroids. Apart from this, few other virulent factors are produced by the anaerobic bacteria, which can provide the resistance from the beta-lactam antibiotics, such as-

a. Presence of a capsule for phagocytosis inhibition
b. Release of beta-lactamase enzyme
c. Production of metabolic end-products like succinic acid that can stops the polymorphonuclear cells migration, enzymes such as superoxide dismutase, catalase immunoglobulin proteases, coagulation-promoting and spreading factors.

Other factors that contribute to the virulence of anaerobic bacteria includes mucosal surface damage and presence of blood in an infected area [17].

Table 1: Microorganisms associated with periodontal infections.

Aerobic and Facultative Anaerobic Bacteria	**Anaerobic Bacteria**
Gram-positive cocci *Streptococcus* species: Beta-hemolytic streptococci, *Streptococcus milleri* group (viridans), *Streptococcus mutans* group **Gram-positive bacilli** *Rothia dentocariosa*, *Lactobacillus* species* **Gram-negative cocco-bacilli** *Actinobacillus* species., *Actinobacillus* actinomycetemcomitans, Campylobacter species, *Campylobacter rectus*, *Capnocytophaga* species., *Eikenella* species. **Gram-negative rods** *Pseudomonas* species.‡, *Enterobacteriaceae*‡ *Microorganisms associated with dental carries. ‡Rare periodontal pathogens.	**Gram-positive cocci** *Peptostreptococcus* species: *Peptostreptococcus micros* **Gram-negative bacilli** *Veillonella* species. **Gram-positive bacilli** *Actinomyces* species, *Eubacterium* species., *Propionibacterium* species., *Lactobacillus* **Spirochetes** *Treponema denticola*, *Treponema sokranskii* **Gram-negative bacilli** *Prevotella* species: *Prevotella intermedia* *Prevotella nigrescens*, *Porphyromonas* species: *Porphyromonas gingivalis*, *Bacteroides* species: *Bacteroides forsythus*, *Fusobacterium* species, *Fusobacterium nucleatum*, *Selenomonas sputigena*

Antimicrobial resistance factors

Major cause of treatment failure in dental infections is the production of beta-lactamase enzymes by the gram-negative periodontopathic bacteria such as *Prevotella intermedia*, *Porphyromonas gingivalis* and *Bacteroides forsythus*. From infection point of view, Beta lactamase producing bacilli (BLPB) are pioneer in nature as they itself have the capacity to produce pathogenic effect, they survive in penicillin therapy and shield the other penicillin susceptible co-pathogens from the effect of penicillin by releasing the free beta-lactamase enzyme. High levels of this enzyme in saliva indicates the presence of many BLPBs [18]. The best possible way to control the emergence of penicillin resistant bacteria is the use of such antimicrobials which are active against the beta-lactamase enzyme [19]. Also, substantial evidence throughout the world suggests that if bacterial plaque accumulates on the teeth for prolonged periods, periodontitis will develop only if the host is susceptible. The susceptibility of the host is a significant factor in the disease process. In periodontal disease the host

biology interprets the bacterial challenge to produce the pathological and clinical signs of disease.

Conclusion

The forgoing discussion highlights the severity of disease, and develops the understanding for etiology, microbiology and pathogenesis of the periodontitis. It also enlists the various antimicrobial resistance and virulence factor of the periodontopathic micro-organisms which are majorly contributing to the treatment failures. Hence it can be concluded that the thorough understanding of the disease is very important for the better therapeutic outcomes and patient compliance.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Kassebaum N, Bernabé E, Dahiya M, et al. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dental Res 2014; 93:1045-1053.
2. Slots J. Periodontitis: facts, fallacies and the future. Periodontology 2000. 2017; 75:7–23.
3. Sousa V, Mardas N, Farias B, et al. A systematic review of implant outcomes in treated periodontitis patients. Clin Oral Implants Res 2016; 27: 787–844.
4. Graziani F, Karapetsa D, Alonso B, et al. Nonsurgical and surgical treatment of periodontitis: how many options for one disease? Periodontology 2000. 2017; 75:152-188.
5. Socransky SS, Haffajee AD. The Bacterial Etiology of Destructive Periodontal Disease: Current Concepts. J Periodontology [Internet] 1992; 63: 322-331
6. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation. Nature Reviews Immunol 2015; 15: 30.
7. Jain P, Aamir Mirza M, Talegaonkar S, Nandy S, Dudeja M, Sharma N, et al. Design and in vitro / in vivo evaluations of a multiple-drug-containing gingiva disc for periodontotherapy. RSC Advances. 2020;10(14):8530–8.
8. Jain P, Mirza MA, Iqbal Z. A 4-D approach for amelioration of periodontitis. Medical Hypotheses 2019; 133: 109392.
9. Genco R, Zambon J, Christersson L. The origin of periodontal infections. Advances Dental Res 1988; 2: 245-259.
10. Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis. Periodontology 2000. 2015; 69: 7-17.
11. Berezow AB, Darveau RP. Microbial shift and periodontitis. Periodontol 2000. 2011; 55: 36-47.
12. Contreras A, Moreno SM, Jaramillo A, et al. Periodontal microbiology in Latin America. Periodontology 2000. 2015;67: 58-86.
13. Kuboniwa M, Inaba H, Amano A. Genotyping to distinguish microbial pathogenicity in periodontitis. Periodontology 2000 2010; 54: 136-159.
14. Colombo APV, Boches SK, Cotton SL, et al. Comparisons of subgingival microbial profiles of refractory periodontitis, severe periodontitis, and periodontal health using the human oral microbe identification microarray. J Periodontol 2009; 80: 1421-1432.
15. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000. 2013; 62: 59–94.
16. Palmer RJ. Composition and development of oral bacterial communities. Periodontol 2000. 2014; 64: 20-39.
17. Ji S, Choi Y, Choi Y. Bacterial invasion and persistence: critical events in the pathogenesis of periodontitis? J Periodontal Res 2015; 50: 570-585.
18. Palmer NO. Antimicrobial resistance and antibiotic prescribing in dental practice. Dental update 2016; 43: 954-960.
19. Marra F, George D, Chong M, et al. Antibiotic prescribing by dentists has increased: why? The J American Dental Association 2016; 147: 320-327.

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