Review Article

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VIRUSES IN PERIODONTAL DISEASE: A REVIEW

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ABSTRACT:

Periodontal diseases are multifactorial, and many etiological agents are suggested to play a role in their etiopathogenesis of periodontitis. Numerous risk factors are also suggested to influence the progression of periodontal disease. Until recently, specific bacteria were considered the major pathogens for periodontal disease. However, the occurrence of periodontal disease in some patient groups is still poorly understood, and the role of other initiating agents is being investigated. Evidence strongly suggests the presence of many viral strains in the periodontal environment, and possible mechanisms have also been suggested. Periodontal disease as a risk factor for other systemic diseases can also be better explained based on this viral etiology. The purpose of this review is to evaluate the evidence supporting the hypothesis that viral infection plays a role in the development of periodontitis, it's clinical implications and future directions are also discussed.

Key-words: Cytomegalovirus, Epstein–Barr virus, Herpes simplex virus, Human immunodeficiency virus, Periodontitis

INTRODUCTION

Periodontitis is a chronic multifactorial disease that progresses by destruction of supporting structures of teeth like cementum, alveolar bone, periodontal ligament.[1] The pathogenesis of periodontitis is considered to have complex interactions between microbial factors, host factors, and various of environmental factors.[2] Current periodontal therapy is successful in management of initial and moderate types of periodontitis, but may show limited efficacy in resolving late-stage disease. A greater understanding of the etiopathogensis of periodontal disease is a pre requisite for the development of efficient preventive and therapeutic strategies.Differences in case definitions and diagnostic methods can hinder the interpretation of epidemiological findings in periodontal research. Microbiological culture and culture-independent molecular studies have identified more than 1,200 bacterial species [3] in the oral cavity,of which at least 400 bacterial species inhabit subgingival sites [4]. But despite the huge array of different bacteria in periodontitis, fewer than 20 bacterial species are considered to be major periodontal pathogens.[5]The shift in the periodontal microbiota with disease development occurs as a result of a multifaceted interaction of microbial-specific traits, host immune responses and ecosystem-based factors.

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The uncertainty about the infectious and clinical events of periodontal breakdown has given rise to a number of hypotheses about the etiology of periodontitis. Some researchers proposed that specific infectious agents acts as a key to periodontal breakdown while others emphasized the importance of host immune factors or genetic characteristics in the development of periodontitis. It is assumed that periodontitis occurs in genetically or environmentally predisposed individuals, who are infected with virulent infectious agents and reveal persistent gingival inflammation and distinct immune responses .Studies on a viral cause for periodontitis mark a turning point in periodontal research, which until recently was centered almost exclusively on a bacterial etiology.

Different classifications of periodontal diseases have been proposed over the years which has improved a better understanding of the etiology and pathology of the diseases of the periodontium .The most recent classification of periodontal diseases was proposed by the 1999 International Workshop for the Classification of the Periodontal Diseases organized by the American Academy of Periodontology.[6] According to the classification proposed by AAP in 1999 viral diseases of the periodontium were placed under non-plaque induced gingival lesions, and they include herpetic gingivostomatitis, varicella zoster etc .Epstein–Barr virus and cytomegalovirus are the most commonly researched viruses in periodontology, and more than one million herpesvirus genome-copies can be identified in a single periodontitis site .[7]

But still the progress is very poor in the area even with the advanced technologies in the century because conventionally viruses are much a challenge task for detection and treatment as compared to bacteria. The main bottleneck in this area is to identify the initial stage of the disease and distinguish it properly from initial and late stage. Although the role of bacterial plaque in general seems to be evident, on the contrary the role of virus still remains unexplored and unclear. The main aim behind this review is to propose the precise role of viruses that may be potentially involved in periodontal disease, and to evaluate the evidences which support the hypotheses that viral infection plays a role in the development of periodontal disease.

PATHOGENESIS OF VIRUS-ASSOCIATED PERIODONTAL DISEASE

Viruses gain entry into the host through different routes which include: (a) Inoculation via the skin and mucosa as in case of needle stick injury, or accidental abrasions (b) inhalation through the respiratory tract as in aerosol or droplet (c) ingestion via the gastrointestinal tract as in the oro –fecal route and (d) the genitourinary tract as in sexual activity. Once, the virus gains entry to the host cell through direct local spread on epithelial and subepithelial surfaces, lymphatic spread, vascular spread, and central nervous system and peripheral nerve

spread, the viruses will interact with the host cell in two main ways namely permissive and non permissive mode.

•**Permissive infection**: In permissive infections, the synthesis of viral components, their assembly and release can lead to consequent death of the host cell

•**Non permissive infection**: In non permissive infections, infection can result in cell transformation often with the integration of viral DNA into the host genome. Viral replication occurs within the cell but the cell remains alive. Examples for non permissive infections include hepatitis B viruses, herpes viruses and retroviruses infection.[8]

Many bacterial infections in humans occur as super infections of viral diseases.[9] According to the studies conducted by Parra and Slots J in 1996 , they found a significantly higher prevalence of human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) in sub gingival specimens from adult periodontitis patients as compared to periodontally healthy or gingivitis patients.[10] Viruses can participate in the pathogenesis of periodontitis by altering immune defences, by activating destructive host reactions or by producing direct lytic effects on periodontal tissues.[11] For a viral infection to occur in host following steps are required which include entry, replication, dissemination and infection of target cells/organs. Latent viruses remaining in the body can become reactivated by various immune compromising events, such as smoking, stress,inflammation, trauma, and immunosuppressive diseases.[12]

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Patients with HIV can manifest a number of oral lesions and conditions which are associated with a compromised immune response. A dentist may be the first professional to make a diagnosis of these common oral lesions.[13] HIV has a strong affinity for the cells of the immune system, specifically those that carry the CD4 cells surface receptor molecule. Thus helper-T lymphocytes (T4 cells) are the cells which are most profoundly affected, but monocytes, macrophages, Langerhans cells and some neuronal and glial brain cells can also be involved. HIV gets incorporated into the DNA of the lymphocyte and can present for the life of the cell. The virus may remain latent for some period but soon becomes active and can cause cell death. A decrease in the number of T-helper cell occurs which can impair the immune function. It is this reduction in immune function that predisposes the individual to various opportunistic infections including periodontal diseases and may also facilitate herpes viruses reactivation or reinfection.[14]

Oral lesions which are strongly associated with HIV-infected patients include oral candidiasis, oral hairy leukoplakia, atypical periodontal diseases, oral Kaposi's sarcoma and non- Hodgkin's lymphoma. HIV is also associated with

the following periodontal conditions like : linear gingival erythema, necrotizing gingivitis, necrotizing periodontitis and chronic periodontitis. According to studies it is shown that,compared with HIV negative counterparts, HIV positive patients with chronic periodontitis shows a greater loss of attachment over time. Inversely, periodontal disease may initiate the onset of AIDS-related pathological changes in oral hairy leukoplakia and Kaposis sarcoma. In individuals suffering from AIDS, HIV-infected lymphocytes and monocytes are abundant in periodontal pockets, gingival tissues, and salivary glands. Direct interaction of these cells with periodontopathic bacteria and/or indirect interaction with soluble factors like butyric acid and TNF-α may induce local HIV-1 replication in the oral cavity. It is proposed that a cell in which viral transcription has been reactivated by a stimulus can spread throughout the body via the blood. In addition, TNF-α concentrations are known to be elevated in individuals with periodontal disease, which suggests that periodontal disease can act as a trigger for local and systemic breakdown of latent infection and may act as a risk factor for AIDS progression.[15]

HERPES VIRUSES

Herpes viruses is considered as the most common viruses in humans, infecting 80–90% of the global adult population.[16] Eight members of the herpes viridae family are known to cause human disease. These include EBV, HCMV, herpes simplex virus 1 and 2 (HSV-1, HSV-2), varicella zoster virus, human herpesvirus HHV- 6, HHV-7, and HHV-8. Herpes virus can alter structural cells and defense cells of periodontium which will diminish the host resistance against multiplication of periodontal pathogens and leading to further subgingival colonization.

To survive, herpes viruses need to infiltrate macrophages, lymphocytes, or other host cells for replication, while minimizing antiviral inflammatory responses of the host. Herpes virus can cause periodontal disease as a direct result of virus infection and replication, or as a result of virally induced impairment of periodontal host defences with increased aggressiveness of resident bacterial pathogens.Therefore, the hallmark of herpes infection is immune impairment. Herpesvirus associated periodontal sites also tend to harbor elevated levels of periodontopathic bacteria, like *Porphyromonas gingivalis*, *Tannerella forsythia*, *Dialister pneumosintes / Dialister invisus*, *Prevotella intermedia*, *Prevotella nigrescens*, *Treponema denticola*, *Campylobacter rectus*, and *Aggregatibacter actinomycetemcomitans*. The coexistence of periodontal HCMV, EBV, and other viruses, along with periodontopathic bacteria, and local host immune responses should be considered as a precarious balance which has the potential to lead to periodontal destruction.[17] Initially, plaque biofilm can cause gingivitis causing inflammatory cells to enter gingival tissue, with periodontal macrophages and

T-lymphocytes which harbors latent HCMV and periodontal B-lymphocytes harbouring latent EBV. Immunoglobulin A antibodies against HCMV, EBV, and HSV in gingival crevicular fluid is believed to originate mainly from local plasma cell synthesis rather than from passive transudation from serum, which further indicates presence of a gingival herpesvirus.[18] Herpes viral activation will initiate increased inflammatory mediator responses in macrophages and also in connective tissue cells within the periodontal lesion. After reaching a critical virus load, activated macrophages and lymphocytes may trigger a cytokine/chemokine'storm of interleukin (IL)-1β, TNF-α, IL-6, prostaglandins, interferons, and other inflammatory mediators, some of which have the potential to stimulate bone resorption.[19] In a vicious circle, the triggering of cytokine responses may stimulate latent herpes viruses, and that may lead to further aggravation of periodontal disease. It is proposed that herpes viruses rely on coinfection with periodontal bacteria to produce periodontitis and, inversely, periodontopathic bacteria may depend on viral presence for the initiation and progression of some types of periodontitis.[20]

EPSTEIN–BARR VIRUS AND PERIODONTITIS

EBV affects over 90% of humans, and is generally transmitted by oral secretions or blood. The virus replicates in epithelial cells or B cells of oropharynx. Memory B cells are the main site where EBV viruses are remains latent.[21] In periodontitis, the presence of EBV is related to an elevated presence of periodontopathic bacteria like *Porphyromonas gingivalis*, *Tannerella forsythia*, *Campylobacter* spp. etc.Bacteria induced gingivitis will lead to EBV-infected B lymphocytes to enter the periodontium. These cells are seen more prominent in progressive periodontal lesions. Oral hairy leukoplakia is one of the main lesion associated to EBV. Clinically oral hairy leukoplakia appears as a raised, white, corrugated lesion that most often develops on the ventral–lateral aspect of the tongue.

HUMAN CYTOMEGALOVIRUS AND PERIODONTITIS

Human cytomegalovirus is considered as one of the common cause of congenital and perinatal infections. HCMV infects epithelial cells, endothelial cells, smooth muscle cells, mesenchymal cells, hepatocytes, granulocytes, and monocyte-derived macrophages. Thus human cytomegalovirus is found in many body secretions including saliva, urine, semen, and breast milk. HCMV infection, although generally subclinical, is responsible for cytomegalovirus inclusion disease and infectious mononucleosis.[22] The cytomegalovirus latent genome is carried into the periodontium by infected macrophages and T cells, and cytomegalovirus activation may subsequently give rise to infection of additional cell types. The down regulation of these cells because of the periodontal defense mechanisms may lead to bacterial superinfection resulting in

enhanced virulence of resident bacteria including *Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens,Campylobacter rectus, Treponema denticola and Aggregatibacter actinomycetemcomitans*

An active cytomegalovirus infection in macrophages and T cells induces release of IL-1β and tumor necrosis factor (TNF) α. These proinflammatory mediators recruit antiviral inflammatory cells to the infection site but also induces osteoclast formation and production of matrix metalloproteinases (MMPs) which can lead to bone destruction. An active cytomegalovirus periodontal infection is associated to disease-active periodontitis, and the virus may also play an important role in other types of periodontal diseases such as aggressive periodontitis and refractory periodontitis.[23]

HUMAN PAPILLOMAVIRUS AND PERIODONTITIS

HPV belongs to Papilloma viridae family and is a double stranded, non enveloped DNA virus. HPV exihibit tropism for epithelial tissue thereby it can affect both skin and mucosa. HPV causes characteristic cytopathic effects called koilocytosis and proliferation of epithelial cells. Since proliferation and migration of the junctional epithelium is considered as a major hallmark of periodontal breakdown, these known biological effects of HPV might provide a link between role of viral infection and periodontal disease .[24]

VIRAL DIAGNOSTIC METHODS

The fact that viruses cannot multiply outside a living host cell complicates their detection,enumeration,and identification, and viral diagnosis is a major challenging task in periodontal cases. However, the field of virology has advanced greatly over the past two decades because of the introduction of sophisticated molecular tools, such as monoclonal antibodies, polymerase chain reaction based amplification, DNA sequencing, DNA and protein micro array chip assays, rapid diagnostic tests. These technologies identify the viral bodies, proteins and nucleic acids in body fluids and tissue samples. The presence of viral species has been demonstrated through DNA probes, flow cytometry, immunofluorescence staining, and culture.[25] Rapid diagnosis can be achieved by molecular techniques like PCR, reverse transcription-PCR. Other successful diagnostic approach is use of DNA microarrays , which uses multiplex real-time PCR techniques to quantify the numberof genome-copies simultaneously.

CONCLUSION:

Better understanding of etiology of periodontitis is critical for developing detection systems and therapies that will enable periodontists to ensure disease control. Maintaining gingival health by professional periodontal therapy and oral hygiene measures reduce the risk of transmissible viral disease. Rapid advances in medical virology may also help to uncover the pathogenesis and treatments of viral diseases of mouth. Prevention and therapy based upon antiviral approaches might avert the

initiation and progression of periodontal disease caused by viruses.

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