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Viruses in periodontal disease: A literature review

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Abstract
Periodontitis is an inflammatory condition affecting the supporting structures of teeth and is often characterized by the loss of periodontal attachment. There are various etiological factors contributing towards the etiopathogenesis of this disease. Until recently bacterial species colonizing the tooth surfaces were considered to have the primary role in the etiology of periodontitis. This was further enhanced by the presence of other factors such as smoking, presence of underlying systemic conditions and the host response. However, recent studies have shown that although tooth surfaces are constantly colonized by various types and numbers of bacteria, their effective removal from the tooth surfaces by surgical or non-surgical periodontal therapy does not necessarily prevent the progression of the periodontal disease i.e. further periodontal attachment loss and bone destruction still persists. This brings us to the hypothesis that factors beyond the plaque bacteria have a significant role in the pathogenesis of periodontal disease. Evidence strongly suggests the presence of various viruses in the periodontal environment. In this review, we analyze the role of various viruses that cause periodontal disease and categorize the various aspects of viral role in the etiopathogeneis of periodontal disease, the bacterial-viral model of disease and the therapeutic implications. A better understanding of the viral aspect of periodontal disease progression can bring about a significant change in the future perspective of diagnosis, prevention and treatment of periodontal disease.

Keywords: Periodontitis, herpes virus, Epstein - Barr virus, cytomegalovirus, immune response

Introduction
Periodontitis is a disease affecting the supporting structures of teeth. It is a highly prevalent disease and hence its proper management requires a thorough management protocol which depends on the knowledge of precise etiology. Till the nineteenth century plaque biofilm, well organized micro colonies of bacterial cells in glycocalyx were considered the sole etiology of the disease. However, there are various aspects of periodontal disease that cannot be co-related with its bacterial etiology. Factors such as smoking, genetic variations in inflammatory response patterns have shown to impact the clinical course of periodontal disease.

Advanced diagnostics brought about a turning point in the field of periodontal etiopathogenesis in the 21st century when certain viral strains were identified associated with periodontal disease. Herpes simplex(HSV), Epstein-Barr virus(E (CMV),Human Papilloma virus(HPV),Human Immuno deficiency virus(HIV),Hepatitis B,C and Human Enterovirus (HEV) are some of the viruses to name. Out of these CMV and EBV are the most commonly discussed viruses in relation to periodontal disease and more than 1 million genome copies have been isolated from a single site of infection [1]. These viruses infect and impair polymorphonuclear leukocytes (PMNs), macrophages and lymphocytes. Herpes virus infected cells can reduce the host defense and give rise to overgrowth of pathogenic bacteria and invade the cells more efficiently. Contreras and Slots demonstrated the presence of EBV-1, HCMV and other Herpesviruses in juvenile and chronic periodontitis lesions. The most recent studies show high levels of the herpes virus in periodontal pockets showing their positive association with severity of periodontal disease. The type of periodontal disease dictates the prevalence and number of Herpesviruses in periodontal pockets.

Frequent presence of other viral species like EBV, HCMV and HSV in gingival crevicular fluid samples of chronic periodontitis patients suggest a strong relationship between the

presence of these viruses and probing depth measurement, clinical attachment loss, and severity of the disease. Evidence from studies also indicate the subgingival presence of EBV-1 and HCMV which shows strong association with aggressive periodontitis.

The host immune response attempts to control both pathogenic viruses and bacteria in periodontal sites. However, some immune mechanisms that are active against viruses may diminish antibacterial immune responses and vice versa. Major advances in the diagnosis, prevention and treatment of periodontitis mainly depends on a having a better understanding of the pathogenic infections and the host related responses.

It is important to broaden our understanding that viruses and bacteria in combination produce a greater pathogenic effect than the sum of the individual pathogens and this combined infection can change our general outlook on the pathogenesis of the destructive nature of periodontal disease and may help us in improving our treatment options for the same.

Viruses in periodontal disease

1. Herpes simplex viruses

Infections of HSV-1 and HSV-2 usually affect skin and mucosa.

HSV-1, principally shed in the saliva, is transmitted directly or indirectly and is mainly involved in oral-facial infections and encephalitis.HSV-2 is usually transmitted sexually and causes genital infections. Other ways of transmission include auto-inoculation by fingers to the eyes or genital tract and transmission from infected mothers to neonates [2]. Primary infection occurs in childhood from infected saliva or herpetic lesions. At the site of epithelial infection viral antigens induce a cell mediated immunity response characterized by viral replication after which the viral cells ascend the local sensory neurons and establish lifelong latency in the corresponding spinal or cerebral ganglion. (Trigeminal ganglion in case of oral infection).Reactivation can occur at any time and may be triggered by immunosuppression, stress, trauma, ultra-violet irradiation or fever. Replication of the virus is induced in some latently infected neurons. Virus is then transported down the axon to the region of original infection [2].

2. Human Cytomegalovirus

Human cytomegalovirus is the most common cause of congenital and perinatal infections. About 10% infants are infected by the age of 6 months following transmission from their mother through the placenta during delivery or by breast feeding [2]. HCMV infects many different epithelial cells, endothelial cells, smooth muscle cells, mesenchymal cells, hepatocytes, granulocytes and monocyte derived macrophages. HCMV is thus found in many body secretions such as saliva, urine, semen and breast milk. HCMV infection is responsible for cytomegalovirus inclusion disease and infectious mononucleosis [2].

3. Epstein-Barr Virus

Epstein Barr virus affects over 90% of humans and is usually transmitted by oral secretions or blood. The virus replicates in epithelial cells or B cells of the oropharynx. Resting memory B cells are the main site of persistence of EBV in the body [2]. EBV infection in adults results in infectious mononucleosis. Most of the symptoms are attributed to the proliferation and activation of T cells in response to infection. Most common symptoms of infectious mononucleosis are fever, lymphadenopathy and pharyngitis. EBV has also been associated with other diseases such as cancers and auto-immune diseases. (Thorley-Lawson and Gross, 2004) [2]

4. Human Immunodeficiency Virus (HIV)

HIV is a sexually transmitted infection. It can also be spread by contact with infected blood or from the mother to child during pregnancy, childbirth or breastfeeding. Without medication, it may take years before HIV weakens the immune system to the point of development of AIDS [2].

Following periodontal conditions are predominantly seen in HIV patients: linear gingival erythema (LGE), necrotizing gingivitis (NG), necrotizing periodontitis (NP) and chronic periodontitis.

Linear gingival erythema appears as a distinct erythematous band of marginal gingiva with either diffuse or punctuate erythema of the attached gingiva. Necrotizing gingivitis, results in the destruction of one or more interdental papillae and remains confined to the marginal gingiva.NP extends beyond the marginal gingiva involves the periodontal ligament and the alveolar bone, leading to a loss of attachment. Most studies show a higher prevalence of NG and NP in HIV infected patients than in non-HIV infected patients (Porter *et al*, 1989, Laskaris *et al*, 1992). NP may be used as a marker for immune deterioration with a 95% predictive value that CD4+ cell counts have decreased below 200 cells mul^{-1}. HIV –positive patients with chronic periodontitis suffer from greater attachment loss over time. Hence, several studies show a clear association between HIV infection and some distinct forms of periodontal infections i.e. necrotizing lesions. Extensive reports on increased prevalence and severity of chronic periodontitis in HIV- positive patients suggests that HIV infection predisposes to chronic periodontitis [2].

5. SARS-CoV-2

SARS-CoV-2 infections typically spread through respiratory droplets or by contact. Research have shown the presence of SARS-CoV-2 in saliva and feces of the affected patients. The SARS CoV-2 enters the cells through the angiotensin converting enzyme 2(ACE2) receptor and use it for cell invasion and promote human to human transmission.ACE2+ cells are predominantly present in the respiratory tract and in the salivary glands due to which they were considered the main targets of SARS coronavirus infection. SARS CoV-2 infection in humans results in mild symptoms to severe respiratory failure. On binding to epithelial cells in the respiratory tract, SARS CoV-2 starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs. The rapid replication of SARS CoV-2 in the lungs may induce a strong immune response. Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure leading to severe complications including death [3-7].

Herpesviral-Bacterial Model of Periodontitis

Abundant Herpesviruses are found to be present in periodontitis lesions and hence redefines the pathogenic paradigm of the disease. According to this latest research, development of periodontitis, has a sequential infectious process that proceeds from bacteria to Herpesviruses to bacteria. Firstly, bacteria in the dental biofilm induce gingivitis, which activates latent Herpesviruses, embedded in the DNA of macrophages, B lymphocytes and T lymphocytes, to infiltrate the periodontium. Cytomegalovirus can replicate in gingival tissue, which may help to sustain the periodontal

infection. Re-activation of the latent herpesvirus may occur spontaneously or during periods of decreased host defense, resulting from drug-induced immunosuppression, frequent infections, prolonged emotional stress, hormonal changes, physical trauma etc. Probably, not coincidentally, most herpes virus activating factors are also suspected risk factors for periodontitis [8].

As a result of active herpes virus infection, the host immunity induces a robust T- cell mediated immune response, comprised primarily of CD8+ T cells. To survive the hostile host environment, Herpesviruses in turn execute strategies to down-regulate antiviral host defenses. Herpesviruses evade immune responses by disintegrating components of the MHC (Major Histocompatibility Complex) and interfering with antigen presentation, by suppressing natural killer cells, by using a viral homolog of IL-10, by diverting potent cytokine responses and by inhibiting apoptosis. The interaction between antiviral host defenses and virally driven anti-host responses results in a major release of pro-inflammatory cytokines that have the potential to activate osteoclasts and to impair antibody-mediated host defenses against exogenous-like bacterial species, such as P. gingivalis and A. actinomycetemcomitans the ensuing increase in pathogenic bacteria provides additional mechanisms of periodontal tissue destruction [8].

Cytomegalovirus or other herpesviruses can exert acute cytopathogenic effects on fibroblasts, epithelial cells, keratinocytes, endothelial cells, inflammatory cells and bone cells. A severe herpesviral infection in extremely immuno compromised patients may destroy periodontal cells and tissue by cytotoxic mechanisms, similar to patients with necrotizing ulcerative gingivitis and noma. Herpesvirus infections can cause oral collagen degradation and can potentially interfere with periodontal tissue turnover and healing. Herpesvirus infections have also been related to diminished repair in periodontal guided tissue regeneration and to dry socket formation after tooth extraction [8].

In the herpesviral-bacterial model of periodontitis, herpesvirus related cytopathogenic effects, immune evasion, immunopathogenecity, latency, re-activation from latency and tissue tropism comprise important aspects of periodontal pathosis. It is likely that the early stages of periodontitis in immunologically compromised hosts involve an active herpesviral infection that mainly cause cytopathogenic effects, while most clinical manifestations in immunocompetent individuals are secondary to cellular or humoral immune responses. The proposed model may be useful to clarify at least some of the clinical characteristics of periodontitis. The propensity for site tropism of herpesviruses may explain why periodontal tissue destruction can differ significantly from tooth-to-tooth in the same patient. A strong anti-herpesvirus host defense will ensure a prolonged period of periodontal stability, even in the presence of virulent bacteria. Herpesvirus re-activation from a period of latency may trigger a series of periodontal tissue damage and progressive disease. However, most immunocompetent individuals experience episodes of oral herpesvirus re-activation lasting only a few hours or few days, which is probably too short a time span to initiate or aggravate clinical periodontal disease [8].

Therapeutic Implications

The herpesviruses-bacterial model of periodontitis provides a rationale for considering new approaches to disease prevention and treatment. Patients who presented with refractory periodontitis and high counts of subgingival Epstein-Barr virus counts were treated with the anti-herpesviruses drug, Valacyclovir HCL, 500mg twice a day for 10 days (Sunde *et al*) [9]. The treatment suppressed subgingival Epstein-Barr virus to undetectable levels for atleast 1 year and resulted in a dramatic clinical improvement [9]. Sunde *et al*. proposed employing virus screening in periodontal treatment to determine when antiviral intervention is appropriate.

Periodontal viruses maybe identified successfully by using diagnostic DNA microarrays that are able to detect simultaneously herpes simplex virus types 1 and 2,Epstein-Barr virus and cytomegalovirus as well as other viruses or by using multiplex real-time PCR technology to quantify the number of genome-copies of herpes simplex virus, Epstein-Barr virus, cytomegalovirus and human herpesvirus-6.Newer metagenomic pyrosequencing techniques maybe even more successful in identifying known and unknown periodontal viruses.

The viral load in saliva can be reduced by anti-herpesvirus chemotherapy. A short course of valacyclovir, 2g two times on day of treatment and 1g two times the following day, resulted in significant decrease in the occurrence of Epstein-Barr virus in saliva compared with controls. Valacyclovir, 500mg orally twice daily for 1 month, given to elite male distance runners, reduced the salivary load of Epstein-Barr virus by 82% compared with placebo. Valacyclovir therapy, 3g per day for 14 days, resulted in a reduction, of more than 100-fold, of Epstein-Barr virus genome-copies in oral wash fluid of patients with acute infectious mononucleosis [10].

Chemotherapeutics are effective against viruses in the lytic phase, but not against viruses in the latent phase, limting their potential use to disease-active infections. Acyclovir types of drugs inhibit herpesviral DNA polymerase and replication of the viral genome. The orally administered form of acyclovir, Valacyclovir, can reach serum concentrations same as intravenously administered acyclovir and is prescribed for a variety of herpesviral diseases [11]. Prolonged treatment with Valacyclovir at dosages of 500-1000mg/day is well tolerated, except in immunosuppressed individuals and the adverse events are infrequent and generally mild with headache being reported most often. [12].

More randomized controlled trials are needed before anti-herpesviral chemotherapy can be considered as standard clinical practice in the treatment of advanced periodontitis.

Future management of periodontal diseases may benefit from anti-herpesviral immunotherapeutic agents: either prophylactic vaccines, which harness the immune system of healthy subjects to prevent infection with disease causing viruses, or therapeutic vaccines, which stimulate the immune system into combating existing viruses and disease [13]. An efficient vaccine against herpesviruses may also provide clinical proof of the principle role of periodontopathic viruses. The concept of herpesviral bacterial synergism in periodontitis implies that vaccination against herpesviruses can also contribute to the control of periodontopathic bacteria.

Conclusion

The etiopathogenesis of periodontitis includes virulence factors of herpesviruses and bacteria, host immune responses against viral and bacterial infections and manipulation of host-cell processes by the infectious agents. The interplay of herpesviruses and bacteria in periodontitis maybe compared to a marionette theatre where the puppeteer is the virus and the puppets are the bacteria. Even if the puppeteer (virus)

controls the performance (disease), both the puppeteer and the puppets are necessary for the marionette theatre to function. Complete prevention and elimination of periodontal diseases might be accomplished with the simultaneous elimination of periodontopathic bacteria and viruses from the oral environment. Virological testing for the pathogen should be part of diagnostic process, atleast for non-responsive and recurrent cases, to institute specific therapy. The evolution of periodontal vaccination against target viruses in the not too distant future makes the topic of periodontopathic herpesviruses even more intriguing. More research needs to be conducted in the treatment arena to identify the most efficient local and systemic antiviral agents for periodontal therapy, and to establish clear guidelines for periodontal treatment based on viral-mediated periodontal pathogenesis.

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