Review Article

Role of Viruses in Periodontal Diseases

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ABSTRACT

Periodontitis is a disease attributable to multiple infectious agents and interconnected cellular and humoral host immune response. However, it has been difficult to unravel the precise role of various putative pathogens and host responses in the pathogenesis of periodontitis. It is generally believed that both gingivitis and periodontitis are caused by bacteria colonizing on the tooth surfaces and that the major mechanisms of periodontal destruction are initiated by bacteria. Although constantly colonized by varying numbers and species of bacteria even established periodontal lesions do not invariably progress. Some viruses like Herpesviruses can infect or alter structural cells and host defense cells of the periodontium and thereby reduce the ability of periodontal tissues to resist bacterial insults. Tissue damage induced by cytotoxic immune reactions may also facilitate the binding of bacteria to exposed basement membranes. Viruses are also capable of infecting and impairing polymorphonuclear leukocytes (PMNs), macrophages, and lymphocytes. Finally, viruses may attenuate or even evade immune responses by stimulating the release of cytokines from cells that in turn inhibit expression of MHC molecules. Viruses can act synergistically to enhance the replication or infectivity of one another. Hence it is suggested that the coexistence of periodontal HCMV, EBV and possibly other viruses, periodontopathic bacteria, and local host immune responses should be viewed as a precarious balance that has the potential to lead to periodontal destruction.

Key Words: Acute Necrotizing Nlcerative Gingivitis, Ebsteinbarr virus, Herpesvirus, Periodontitis,

INTRODUCTION

Periodontitis is a disease attributable to multiple infectious agents and interconnected cellular and humoral host immune response. However, it has been difficult to unravel the precise role of various putative pathogens and host responses in the pathogenesis of periodontitis.[1, 2]

Henle-Koch postulates of disease aetiology were proposed, which can address monocausal infectious diseases and are not readily applicable to multicausal infectious diseases such as periodontitis, which may result from a synergistic interaction among different pathogenic agents that individually may not lead to disease.[3] It is not understood why, in hosts with comparable levels of risk factors, some periodontal infections result in loss of periodontal attachment and alveolar bone while other infections are limited to inflammation of the gingiva with little or no discernible clinical consequences. Also many patients do not show a remarkable level of classical risk factors.

Detection and quantification of periodontopathic bacterial species are useful for identifying subjects at elevated risk of periodontitis; it is unlikely that a single agent or even a small group of pathogens are the sole cause or modulator of this

heterogeneous disease. It is generally believed that both gingivitis and periodontitis are caused by bacteria colonizing on the tooth surfaces and that the major mechanisms of periodontal destruction are initiated by bacteria. Although constantly colonized by varying numbers and species of bacteria even established periodontal lesions do not invariably progress i.e., show further loss of supporting periodontal tissues. Episodic disease activity at specific sites has been documented.[3] These uncertainties have galvanized to find additional etiological factors for periodontitis. In mid 1990's herpes viruses have emerged as putative pathogens in various types of periodontal disease.[4] In particular, human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV) seem to play important roles in the etiopathogenesis of several types of periodontitis.[3]

Patients with acute viral infections are at increased risk for certain bacterial infections. The most compelling evidence of this in humans comes from the study of influenza outbreaks. Super infections by bacteria such as Streptococcus pneumonia and Staphylococcus aureus are the major cause of morbidity and mortality during influenza epidemics.[5] Adolescents with viral respiratory infections are also predisposed to otitis media, sinusitis, acute bronchitis, and pneumonia.[6] This predisposition may be related to the immunopathology of viral infections.[7,8] Some viruses like Herpesviruses can infect or alter structural cells and host defense cells of the periodontium and thereby reduce the ability of periodontal tissues to resist bacterial insults. Tissue damage induced by cytotoxic immune reactions may also facilitate the binding of bacteria to exposed basement membranes. Viruses are also capable of infecting and impairing polymorphonuclear leukocytes (PMNs), macrophages, and lymphocytes. Finally, viruses may attenuate or even evade immune responses by stimulating the release of cytokines from cells that in turn inhibit expression of MHC molecules.[9]

Viruses can act synergistically to enhance the replication or infectivity of one another. For example, certain strains of the Epstein-Barr virus (EBV) can augment replication of the human immunodeficiency virus (HIV) within CD-4 cells in vitro.[10] In the presence of herpes simplex virus (HSV)-1, the HIV can also invade keratinocytes, which are normally resistant to invasion since they lack the CD-4 molecule.[11] Hence it is suggested

that the coexistence of periodontal HCMV, EBV and possibly other viruses, periodontopathic bacteria, and local host immune responses should be viewed as a precarious balance that has the potential to lead to periodontal destruction.[4]

STRUCTURE OF VIRUS

Virus consists of a nucleic acid core containing viral genome, surrounded by a protein shell called capsid. The capsid protects the delicate nucleic acid contained within it. The entire structure, which includes nucleic acid and capsid, is referred to as nucleocapsid. The viruses may be naked or enveloped, envelope is a lipoprotein sheath derived from the host cell membrane. The complete virus particle, called a viron, generally has diameter of only 30-150 nm.[12]

Viral nucleic acid - Contain either DNA or RNA and DNA or RNA may be single strand or double strand.

Viral proteins - The major bulk of virus is protein, which offers a protective sheath for the nucleic acid and surface proteins may have a special affinity for receptors on the surface of susceptible cells and hear antigenic determinants.

Viral lipids - Viral lipids and carbohydrates are found only on their envelopes and are mostly derived from the host cells and About 50-60% of the lipids are phospholipids and remainder is cholesterol.[12]

VIRUS SYMMETRY

The nucleocapsids of viruses are arranged in a highly symmetrical fashion. Three kinds of symmetry are recognized. Icosahedral symmetry - The nucleocapsid is arranged as a 20 sided cubic structure. This kind of symmetry is seen in herpes viruses.
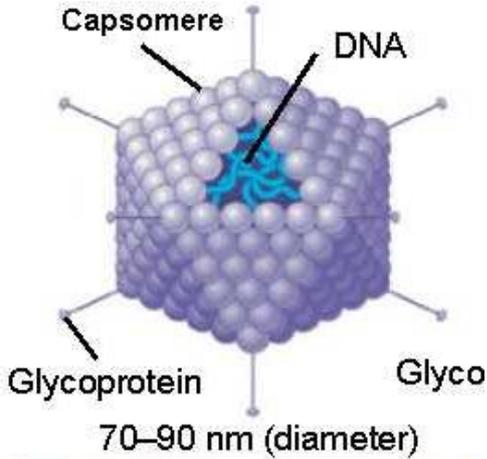

FIGURE 1 - ICOSAHEDRAL SYMMETRY[21]

Helical symmetry — The nucleocapsid is arranged in a spiral fashion. Mostly seen in RNA viruses.
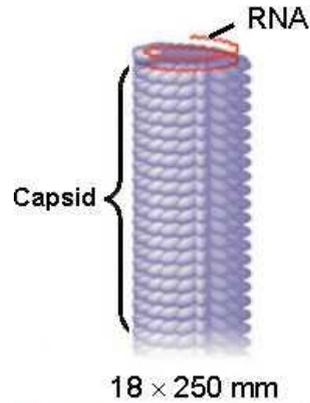

18 × 250 mm

FIGURE 2 – HELICAL SYMMETRY[21]

Complex symmetry — due to the complex structure of certain viruses, the nucleocapsid has a complex symmetry. Seen in retroviruses and poxviruses.
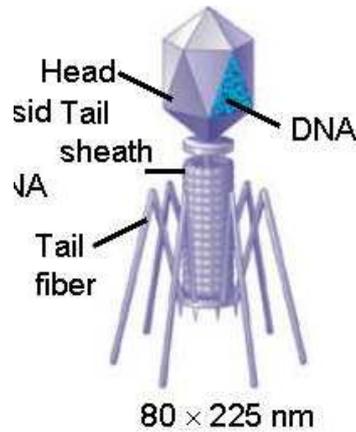

80 × 225 nm

FIGURE 3 – COMPLEX SYMMETRY[21]

CLASSIFICATION OF VIRUS [12]

TABLE 1

NUCLEIC ACID	VIRAL FAMILY	NUCLEO-CAPSULE SYMMETRY	ENVELOPE	VIRION SIZE (nm)
	PARVOVIRIDAE	ICOSAHEDRIC	_	18-20
	PAPOVIRIDAE	ICOSAHEDRIC	_	45-55
	ADENOVIRIDAE	ICOSAHEDRIC	_	70-80
DNA	HERPESVIRIDAE	ICOSAHEDRIC	+	150-180
	POXVIRIDAE	COMPLEX	+	250-300
	HEPADNAVIRIDAE	COMPLEX	+	42

NUCLEIC ACID	VIRAL FAMILY	NUCLEO-CAPSULE SYMMETRY	ENVELOPE	VIRION SIZE (nm)
	PICORNAVIRIDAE	ICOSAHEDRIC	_	20-30
	REOVIRIDAE	ICOSAHEDRIC	_	50-80

UNDERLYING MECHANISMS OF POLYMICROBIAL DISEASE PATHOGENESIS

1. Predisposing factors in the host

Stress, physiologic abnormalities and metabolic disease favor the colonization of multiple organisms (examples include Bovine respiratory disease complex, respiratory infections, oral infections, and periodontal diseases).

2. Alterations in mucosa induced by microbial infection favor the colonization of other microorganisms

Viral or bacterial infections may contribute to increased adherence and replication of other microorganisms, as in respiratory diseases.

3. Synergistic triggering of proinflammatory cytokines by microorganisms

Increases the severity of disease, reactivates latent infections or favors the colonization of other microorganisms. Synergistic induction and release of proinflammatory cytokines can lead to extensive clinical and pathologic polymicrobial disease in situations where individual organisms cannot induce high and sustained cytokine levels alone (examples include HIV and respiratory infections where LPS induces release of TNF-α, IL-1, or virus from virus-infected cells).

4. Sharing of determinants among organisms

It allows non-pathogenic or weakly pathogenic microorganisms to cause disease. In 1982, UB's Smith proposed the concept of pathogenic synergy in which determinant-deficient organisms share virulence determinants to allow activities that no single microorganism can conduct by itself (examples include bovine respiratory disease, periodontal diseases and abdominal abscesses).

5. Suppression of the immune response by one organism allowing colonization by others

Infection by some viruses and bacteria results in extensive immunosuppression leading to polymicrobial infections involving other viruses, bacteria, fungi, protozoans, and parasites examples include diseases caused by those microorganisms.[20]

HERPESVIRUS IN PERIODONTAL ABSCESS

The periodontal abscess is a localized purulent infection of tissues adjacent to a periodontal pocket. Periodontal abscesses occur mostly in conjunction with preexisting periodontitis, but can also develop at sites exhibiting little or no attachment loss. The major symptom of a periodontal abscess is spontaneous or evoked pain. Gingival or mucosal swelling is usually present and affected tissue appears red or reddish blue. Suppuration may appear. Affected teeth typically experience rapid periodontal tissue destruction with deep pocket formation, teeth may become hyper mobile and sometimes extrude from the alveolar socket.

Microbiologically, periodontal abscess include the multiplication and tissue invasion of one or more subgingival bacterial species. In periodontal abscess of specific microbiota there is high occurrence of P. gingivalis, P. intermedia and F. nucleatum as well as A. actinomycetemcomitans and C. rectus.

Recent investigations have identified genomes of HCMV and EBV-1 in aggressive types of periodontal disease. HCMV and EBV infection have the potential to increase the virulence of resident bacterial pathogens. Herpesviral infections may enhance bacterial adherence to and bacterial invasiveness into epithelial cells, thereby facilitating the penetration of pathogenic bacteria into connective tissue.

It is hypothesized that some types of periodontal abscesses develop as a result of a series of interactions among herpsevirus, bacteria and host immune reactions. Herpesviruses exert higher pathogenicity during productive replication than in latent state of infection. Reactivation of latent viruses can occur spontaneously or after tissue trauma, emotional stress, fever, drugs and immunosuppression. Present evidence supports the notion that herpesviruses are not merely passive bystanders to inflammation and periodontal breakdown.[13]

HERPESVIRUS AND AGGRESSIVE PERIODONTITIS

The course of periodontitis can vary considerably between young and older individuals. The disease course in adolescents and young adults is typically aggressive and relatively brief. In older individuals, the course is more often slow and frequently associated with pronounced gingival inflammation and heavy

accumulation of dental plaque and calculus. The pathogenic events that initiate aggressive periodontitis have been difficult to delineate because of the complexity of the pathogenic microbiota and the multiple pathophysiologic effects of several pro- and anti-inflammatory mediators.

Human cytomegalovirus (HCMV) and Epstein—Barr virus (EBV) occurs frequently in aggressive periodontitis sites.[14] Herpesvirus 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 heightened virulence of resident pathogenic bacteria. HCMV, EBV-1 and HSV-1 periodontal infections contribute to the etiopathogenesis of aggressive periodontitis. The three herpesviruses were each detected in approximately 75% of aggressive periodontitis lesions but were virtually absent in healthy periodontal sites.

Ting et al. reported that the high rate of active HCMV infection in early localized aggressive periodontitis can have several causes. They suggested that puberty is an important period for HCMV and EBV primary infection or reinfection. Puberty-related perturbation of the immune system may also contribute to HCMV activation. Reports indicate that aggressive periodontitis patients have many neutrophil deficiency defects HCMV infection can also upregulate the release of proinflammatory cytokines from fibroblasts and interleukin (IL)-1β and tumor necrosis factor (TNF)-α gene expression of monocytes and macrophages. These proinflamrnatory cytokines have been found to be associated with the initiation and progression of destructive periodontal disease.

Ting et al. reported a close relationship between HCMV active infection and advancing disease. HSV-2 was rarely detected in the aggressive periodontitis lesions and was not statistically associated with the disease.

Significant associations were found between HCMV and HSV-1 and P. gingivalis, P. intermedia, T. forsythia and C. rectus, and between EBV-1 and P. gingivalis, T. forsythia and C. rectus.[15]

HCMV has been linked to an elevated occurrence of A. actinomycetemcomitans in localized aggressive periodontitis in the USA and Jamaica.

HERPESVIRUS IN ACUTE NECROTIZING ULCERATIVE GINGIVITIS

Acute necrotizing ulcerative gingivitis (ANUG) affects immunocompromised, malnourished and psychosocially stressed young individuals, and the disease may occasionally spread considerably beyond the periodontium and give rise to the life-threatening infection termed noma/cancrum oris. It is estimated that 770,000 people are currently afflicted by noma sequelae. A significantly higher occurrence of DNA of HCMV and other herpesviruses was detected in ANUG lesions of malnourished children than in non-ANUG, normal, and malnourished children.

In Europe and the U.S.A., ANUG affects mainly adolescents, young adults, and HIV-infected individuals and virtually never young children. The occurrence of ANUG in children in Africa may be due to an acquisition of herpesviruses in early childhood, malnutrition that may promote herpesvirus Occurrence of human cytomegalovirus (HCMV) and Epstein-Barr type 1 (EBV-1) in ANUG sites and normal periodontal sites of Nigerian children with and without malnutrition that may promote herpesvirus activation, and the presence of particularly virulent periodontal bacteria. Occurrence of human cytomegalovirus (HCMV) and Epstein-Barr type 1 (EBV-1) in ANUG sites and normal periodontal sites of Nigerian children with and without malnutrition.[16]

HERPESVIRUS AND CHRONIC PERIODONTITIS

A causal relationship exists between herpesviruses and pathogenic bacteria in periodontal disease, similarly to reported medical infections, it is more likely that viral infections promote subgingival pathogenic bacterial infection than vice versa. A longitudinal microbiological study might delineate the sequential establishment of subgingival herpesviruses and periodontopathic bacteria. EBV, HCMV, and mixed herpesviral infections might promote subgingival colonization of pathogenic organisms by a multiplicity of mechanisms. A gingival herpesviral infection may impair the local host defense by infecting and altering the function of polymorphonuclear leukocytes, lymphocytes and macrophages. A virally induced neutrophil dysfunction may serve to potentiate the overgrowth and virulence of P.gingivalis and other microbes of the subgingival microbiota. In addition, herpesvirus infections can lyse or affect oral epithelial cells.

EBV-1, HCMV, and mixed viral co-infections are positively associated with increasing age. The highest detection rate of subgingival herpesviruses in adult periodontitis patients may be due to local viral reactivation phenomena. Recurrent herpesvirus reactivation in elderly individuals occurs as a consequence of age related inimunosuppression. An age related herpesvirus presence in the periodontium may partly explain the increased severity of periodontitis in elderly subjects.[17]

HERPESVIRUS IN HIV INDUCED PERIODONTITIS

HIV- associated periodontal disease that originally was described by Winkler & Murray (1987) increases in severity with increasing immunosuppression. Linear gingival erythema appears in the early phases of HIV-periodontal disease (Langford 1994). Periodontitis in HIV patients may resemble that of rapidly progressing periodontitis in non HIV-infected individuals, or be associated with necrotic gingiva.

Three types of necrotizing periodontal disease occur in HIV patients: necrotizing gingivitis, necrotizing periodontitis and necrotizing stomatitis. The reason for the unique clinical appearance of HIV periodontal disease is not known.

HIV- induced immunosuppression is known to facilitate herpesvirus reactivation or re-infection. Herpesvirus-associated diseases are common in the mouth of HIV patients and often indicators of severe immunosuppression. HIV-periodontitis lesions demonstrated significantly more herpesvirus co infections than periodontitis lesions in non HIV patients. Herpesvirus co infections can give rise to particularly severe Immunosuppression that might trigger proliferation of periodontopathic bacteria and other pathological events associated with destructive periodontal disease. HCMV that was detected in 81% of HIV-periodontitis lesions may also contribute to periodontal disease pathogenesis.

HIV-periodontitis may accentuate local immune suppression, impair protective periodontal immunity, induce proinflammatory cytokine production, alter the structural integrity of the periodontium, and lead to overgrowth of periodontopathic bacteria. It was proposed that HIV-periodontitis is the result of HIV-herpesvirus-bacterial mixed infection. HIV-induced activation of herpesviruses may account for some of the rapid periodontal breakdown in HIV periodontitis. Severely immunosuppressed patients may experience herpesvirus mediated gingival necrosis.

Even though several herpesvirus species have been detected in gingiva and gingival crevicular fluid, the periodontal occurrence of HHV-6, HHV-7 and HHV-8 remains to be determined. A cross-sectional study aimed to determine the periodontal presence of these three herpesviruses in HIV-seropositive and HIV-negative periodontitis patients.

However, the major putative periodontopathic herpesviruses HCMV and EBV are also frequently found in HIV periodontitis, and these herpesviruses may independently or in concert with HHV-6, -7 and -8 play critical roles in the development of HIV periodontitis.[18]

EPSTEIN—BARR VIRUS IN ORAL DISEASES

Epstein—Barr virus (EBV), a B-Iymphotropic gamma-herpesvirus causes infectious mononucleosis and oral hairy leukoplakia and is associated with various types of lymphoid and epithelial malignancies. Saliva is the main vehicle for EBV transmission from individual to individual. Recent studies have also implicated EBV in the pathogenesis of advanced types of periodontal disease. EBV DNA is detected in 60-80% of aggressive periodontitis lesions and in 15-20% of gingivitis lesions or normal periodontal sites. The periodontal presence of EBV is associated with an elevated occurrence of periodontopathic anaerobic bacteria. Despite the inflammatory and growth-transforming inducing capabilities of EBV, most infected individuals control the virus efficiently and remain free of EBV-associated diseases.

The life cycle of EBV involves two compartments the peripheral blood and the oral cavity. EBV resides in B lymphocytes. Latently infected memory B lymphocytes circulate in the peripheral blood and are believed to constitute the main reservoir for EBV persistence. Permissively EBV-infected B lymphocytes in periodontal and perhaps also tonsillar, tissues play a major role in the egress of virions into saliva. The ability of EBV latent infections to transform B lymphocytes and epithelial cells can give rise to tumors in lymphoid tissue and in naso- and oropharyngeal epithelial tissue. The occurrence of EBV in periodontitis lesions from various parts of the world, all published studies describe a significantly higher occurrence of EBV DNA in aggressive periodontitis than in gingivitis or non progressing periodontitis.[19]

EBV-HCMV periodontal co-infection to be associated with particularly severe types of periodontal disease, perhaps because of the potential of an active herpesvirus infection to transactivate other co-resident herpesvirus species. Simultaneous EBV—HCMC replication may significantly expand the CD8-positive cytotoxic/suppressor T- lymphocytes subset and decrease the number of functional CD4 T lymphocytes, resulting in a wide-ranging suppression of antibacterial host defenses within the periodontium.

In periodontitis, the presence of EBV DNA is related to an elevated occurrence of Porphyromonas gingivalis, Tannerella forsythia, Campylobacter species and other periodontopathic bacteria. Herpesvirus-related periodontal disease may progress in a series of steps. Initially, bacterially induced gingivitis permits EBV-infected B lymphocytes to enter the periodontium.

Studies are needed to elucidate key elements of EBV periodontal infection, including periodontal tropism, persistence, and periodontopathic determinants of the virus, all of which are poorly understood.

DISCUSSION

It is not understood why periodontitis tends to progress in a localized pattern in many patients, the propensity to bilateral symmetry of tissue breakdown and the intermittent exacerbation of the disease in individual teeth. It is particularly troubling that no detailed explanation exists as to the pathogenic events that trigger the conversion of a gingivitis lesion to periodontitis or a stable periodontitis site to a disease active lesion. No unequivocal association has been established with cytokine polymorphisms or HLA haplotypes and periodontitis, although HLA-DR4 carriers may be at elevated risk for the disease. Herpesvirus periodontal infections may cause direct damage to periodontal tissues or impair the resistance of the periodontium, thereby permitting subgingival overgrowth of pathogenic bacteria. The question of coincidence or a

causal nexus between herpesviruses and periodontitis can be appraised on the basis of Hill's criteria of causality. The measures for strength of association, consistency, temporal sequence, biologic plausibility, and analogy seem to be met.

The effective treatment of gingival inflammation can reduce gingiva and salivary herpesvirus loads, and may help diminish the risk of transmitting herpesviruses to other individuals. On the other hand, antiviral chemotherapeutics have a limited, short-term effect on oropharyngeal herpesvirus shedding and are probably ineffective in treating periodontitis. The limited usefulness in the routine diagnosis of uncomplicated periodontal disease, tests to monitor the state and level of viral replication may serve a valuable diagnostic purpose in severe periodontal infections in immunocompromised patients.

In summary, destructive periodontal disease is a heterogeneous group of pathoses characterized by a predominance of specific infectious agents in the face of inadequate local host defenses. Predisposing factors of periodontal tissue destruction are becoming better understood, but the magnitude of the effects of the most commonly reported risk factors has not been adequately quantified in population based studies. Resolving the many questions about the etiopathogenesis of periodontal diseases may require a readiness to give up bacteria as a single cause of periodontitis development. Synergistic interactions between periodontal herpesviruses and bacteria may enhance the risk of tissue breakdown.

CONCLUSION

Even though bacteria are recognized to be indispensable for the development of Periodontitis and although current hypotheses on the etiopathogenesis of periodontitis correctly emphasize the importance of assessing bacterial and host factors collectively, bacterial-host interaction alone seems insufficient in explaining important clinical characteristics of the disease. Herpesvirus periodontal infections may cause direct damage to periodontal tissues, or impair the resistance of the periodontium, thereby permitting sub gingival overgrowth of pathogenic bacteria. Henle-Koch postulates of disease etiology address mono causal infectious diseases and are not readily applicable to multi causal infectious diseases such as periodontitis, which may result from a synergistic interaction among different pathogenic agents that individually may not lead to disease.

Research on the importance of herpes viruses in periodontal disease is in its infancy. Studies are needed to identify oral sites of herpesviral latency and characterization of viral gene expression during latency, to establish oral targets of active herpes viral infection and effect of herpe sviruses on infected cells of the periodontium, to determine whether herpes viral replication, host immune response or direct effect of herpes viruses on immune cells act as determinants of periodontal disease, and to define components of the immune system that play a critical role in maintaining herpes viral latency in the periodontium. We do not understand why, in hosts with comparable immune status, some periodontal herpes virus infections reactivate relatively frequently and may cause disease progression while others are limited to latent or asymptomatic virus infections with no discernible clinical consequences. Important research aims are also the delineation of mechanisms by which periodontal herpes viruses might increase the virulence of periodontopathic bacteria and the establishment of means to disrupt pathogenically important interconnects between periodontal herpesviruses and periodontopathic bacteria. Despite circumstantial evidence of a role of herpesviruses in destructive periodontal disease, a cause-and-effect relationship remains to be established. The possible involvement of human herpesviruses in the etiology of periodontal diseases merits further investigation.

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