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Viruses: Are They The Bystanders for Periodontal Diseases

KEYWORDS: Virus, Periodontal disease, Periodontopathogenic bacteria

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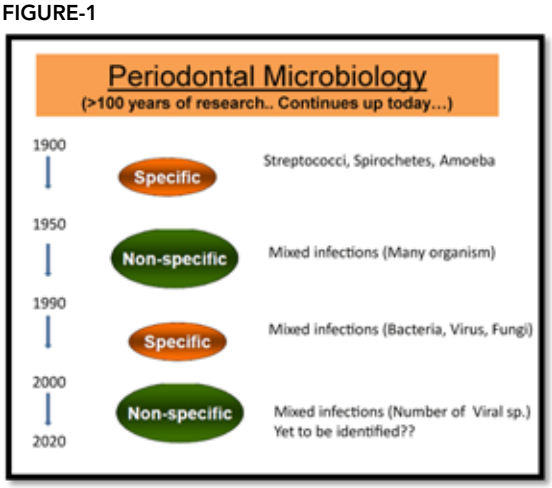
ABSTRACT *Periodontal disease is a multifactorial disease that triggers inflammation, loss of connective tissue attachment and alveolar bone around the teeth. Although it is of bacterial origin, studies have suggested the association of periodontal disease and viruses. Viral DNA has been detected in gingival tissues, gingival crevicular fluid (GCF) and subgingival plaque from periodontaly diseased sites. Virus infection impairs periodontal defense and permits overgrowth of periodontopathogenic bacteria. Therefore the following article reviews the role of viruses in periodontal disease.*

Periodontal disease affects millions of people worldwide. It is a multifactorial disease and many etiological agents and risk factors are suggested to play a role in its etiopathogenesis. The main etiological factor is bacterial plaque. Non-bacterial microorganisms that are found in plaque include viruses, mycoplasma, yeasts and protozoa. The development of periodontal disease depends upon the cooperative interaction among specific pathogenic bacteria, viruses and tissue destructive inflammatory mediators (Kolliyavar B, Shetty S, Patil A and Thakur SL, 2013).

The uncertainty about the infections and clinical events of periodontal breakdown has given rise to a number of hypotheses about the etiology of periodontitis. As the research work progressed, it was found that periodontal diseases are complex infectious diseases that can be attributed to multiple viral agents which in turn induce host immune responses. Studies on a viral cause for periodontitis marked a turning point in periodontal research, which until recently was centered almost exclusively on a bacterial etiology.

FIGURE-1



Viruses are obligate intracellular organisms, which are pathogenically and metabolically inert outside the host cell.

Classification of viruses is based on type of nucleic acid genome (DNA or RNA) present.

TABLE-1

DNA VIRUSES	GENUS	PATHOLOGY	ORAL MANIFESTATION
Herpesviruses	Herpes simplex viruses (HSV)	Primary herpetic gingivostomatitis	Vesiculous ulceration
		Herpes labialis	
		Recurrent herpetic gingivostomatitis	
		Chronic herpetic gingivostomatitis	
	Varicella-Zoster virus (VZV)	Varicella (chickenpox)	Vesiculous ulceration
		Herpes zoster (shingles)	
	Epstein-Barr virus (EBV)	Infectious mononucleosis	Ulcerations and palatal petechiae
		Hairy leukoplakia	White lesion
		Lymphomas	
	Cytomegalovirus (CMV)	Infectious mononucleosis	Vesiculous ulceration
	Human herpes virus 6 (HHV-6)	Unknown	Unknown
	Human herpes virus 7 (HHV-7)	Unknown	Unknown
	Human herpes virus 8 (HHV-8)	Kaposi's sarcoma	
Papovaviridae	Papilloma viruses	Focal epithelial hyperplasia	Epithelial nodules
		Oral squamous cell papillomas	Papillomatous vegetation
		Verrucae vulgaris	Epithelial nodules
		Condyloma acuminata	Epithelial nodules

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TABLE-2

RNA VIRUSES	GENUS	PATHOLOGY	ORAL MANIFESTATION
Retroviridae	HIV	AIDS	Candidiasis
		Fungal infections	Recurrent herpetic gingivitis
		Viral infections	Kaposi's sarcoma
		Tumors	Non-Hodgkin's lymphoma
		Auto-immune disease	Petechiae
		Bacterial infection	Necrotizing gingivitis
Picornaviridae	Enterovirus species Coxsackivirus	Herpangina	Ulcerative stomatitis
		Hand-foot-mouth disease	Stomatitis

Among the herpes viruses present, HHV-6 and HHV-8 were detected in biopsies from periodontal lesions. Recent microbiological researches have revealed the possible role of herpes virus and an association has been demonstrated between HIV infection and some distinct forms of periodontal infections (i.e. necrotizing lesions). The involvement of herpes viruses in the etiology of periodontal disease is suggested by their presence in gingival tissue, gingival crevicular fluid (GCF) and subgingival plaque, in periodontal disease (Cappuyns I, Gugerli P and Mombelli A, 2005).

The classification given by American Academy of Periodontology (AAP) in 1999 has included gingival diseases of viral origin as an etiological factor for non-plaque induced gingival lesions.

Human Immunodeficiency Virus (HIV)

Patients with HIV can present with a number of oral lesions and conditions that are associated with a compromised immune response. The dentist may be the first professional to make a diagnosis of these common oral lesions (Slots J, 2010).

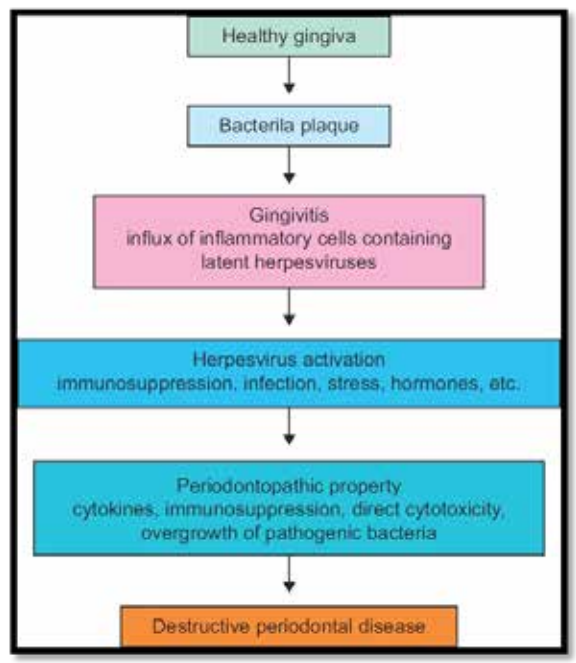
HIV has a strong affinity for the cells of the immune system, most specifically those that carry the CD4 cells surface receptor molecule. Thus helper-T lymphocytes (T4 cells) are most profoundly affected, but monocytes, macrophages, Langerhans cells and some neuronal and glial brain cells may also be involved.

A strong co-relation has been identified between HIV infection and oral candidiasis, oral hairy leukoplakia, atypical periodontal diseases, oral Kaposi's sarcoma and oral non-Hodgkin's lymphoma. In addition HIV is also associated with the following periodontal conditions: linear gingival erythema, necrotizing gingivitis, necrotizing periodontitis and chronic periodontitis. A study by Yeung et al (1993), Ryder (2002) has shown that when compared with HIV negative counterparts, HIV positive patients with chronic periodontitis suffer from a greater loss of attachment over time.

Herpes Viruses

Herpes virus can alter structural cells and host defense cells of periodontium which will reduce the host resistance against multiplication of periodontal pathogens and subgingival colonization. Herpes viruses may cause a direct cytopathic effect on fibroblasts, keratinocytes, endothelial cells, inflammatory cells and possibly bone cells. In addition, herpes virus infection hampers tissue turnover and repair following regenerative periodontal therapy, may increase the pathogenicity of periodontal microbiota and may induce abnormalities in the adherence, chemotaxis, phagocytic and bactericidal activities of polymorphonuclear leukocytes. In adult periodontitis, the presence of subgingival HCMV or EBV-1 DNA is related to an elevated occurrence of the periodontal pathogens P. gingivalis, T. forsythia, D. pneumosintes, P. intermedia, P. nigrescens, C. rectus and T. denticola (Slots J, 2009).

FIGURE-2



Human Cytomegalovirus (HCMV)

The sero-prevalence of CMV infection in the world varies widely in up to 95% of population depending on the geographic area (developed /developing countries). During childhood, many people acquire primary infection with HCMV. In case of reactivation of these viruses, chronic infection may occur. Re-activation of HCMV in periodontal lesions is considered to be associated with periodontal disease progression, especially in localized juvenile periodontitis. This might explain several hallmarks of periodontal disease such as

Episodic progressive nature of periodontal disease (due to transient local immunosuppression depending on active or latent viral infections)

Localized pattern of tissue destruction (due to viral tissue tropism)

Some individuals carry periodontopathogenic bacteria and still maintain periodontal health (due to absence of viral infection)

Cytomegalovirus and Porphyromonas gingivalis detected in sites with localised aggressive periodontitis in Afro-Caribbean adolescents, acted synergistically to influence the risk for both the occurrence and extent of disease. Hormonal changes at the onset of puberty may re-activate a periodontal CMV infection, resulting in suppression of antibacterial immune defenses and overgrowth of exogenous bacteria such as specific genotypes of A. actinomycetem-

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comitans, a major pathogenic species in the early phases of localized aggressive periodontitis, leading to breakdown of periodontal attachment and alveolar bone.

Accumulated evidence shows that CMV not only evades the host immune response but also exploits the host immune response to achieve re-activation from latency and disseminated infection. CMV uses nuclear factor kappa B to mediate an inflammatory response and to induce immediate early gene expression in order to drive viral replication. CMV encodes the chemokines that draw susceptible monocytes and neutrophils to the site of infection. Consequently virus induces production of IL-1 and TNF-α, which in turn may up-regulate MMPs and down regulate TIMP. MMPs are the key proteolytic enzymes responsible for cleaving interstitial collagen and degrading periodontal ligamentous attachments and bone matrix proteins. Lipopolysaccharides from resident gram-negative bacteria may act synergistically with HCMV in stimulating IL-1β gene transcription, resulting in markedly increased IL-1β levels at periodontal sites. Wu et al. (2008) identified cytomegalovirus gB-I genotype in 20% and cytomegalovirus gB-II genotype in 87% of cytomegalovirus positive subjects with periodontitis (Beader N and Kardum MI, 2011).

Epstein Barr Virus (EBV)

Epstein Barr Virus (EBV) causes oral hairy leukoplakia and infectious mononucleosis, whose symptoms include fever, lymphadenopathy, oral ulcers, multiple palatal petechiae and infrequently pericoronitis, acute ulcerative gingivitis and gingival ulcerations have been reported.

EBV is associated with various types of lymphoid and epithelial malignancies. EBV infects and replicates in oral and oropharyngeal epithelium and B-lymphocytes. Saliva is the main vehicle for EBV transmission from individual to individual. Midline granuloma is an EBV associated lymphoma which can cause severe gingival and periodontal destruction. EBV DNA is detected in 60-80% of aggressive periodontitis lesions and in 15-20% of gingivitis lesions. The periodontal presence of EBV is associated with an elevated occurrence of periodontopathic anaerobic bacteria.

EBV exhibits genotypic variability. Slots J et al. (1999) found that the EBV nuclear antigen 2 (EBNA2) genotype-1 occurs more frequently in periodontitis lesions than the EBNA2 genotype-2.

Periodontal therapy can markedly suppress the EBV load in periodontal pockets as well as in saliva, which has the potential to reduce the risk of viral transmission between close individuals. Co-infection with EBV type 1 and the cytomegalovirus gB-II genotype was associated with periodontitis, as the patients who were dually infected with these viruses tended to have deeper periodontal pocket depths and increased attachment loss (Jiyasi T, Chacko L, Abraham S, Moon N and Ali FM, 2014)

Herpes Simplex Virus (HSV)

Approximately 120 different herpes viruses have been identified out of which herpes simplex virus (HSV) type I and II are known to infect humans. HSV can be transmitted through direct contact with HSV lesions or via infected saliva or other secretions. HSV-I causes mainly oral infections and HSV-II ano-genital infections. Although HSV- I is responsible for most cases of herpetic gingival stomatitis, HSV-II may occasionally be involved.

Primary herpetic gingivostomatitis occurs most often in infants and children younger than 6 years of age but it is also seen in adolescents and adults. It appears as diffuse, erythematous, shiny involvement of the gingiva and the adjacent oral mucosa with varying degree of edema and gingival bleeding. It is characterized by the presence of discrete spherical gray vesicles, which may occur on gingival, labial and buccal mucosa, soft palate, pharynx, sub lingual mucosa and tongue. After approximately 24 hours, the vesicles rupture and form painful ulcers which heal after several days. Primary herpetic gingivostomatitis is contagious.

A recurrent herpetic episode may be precipitated in individuals with history of herpes virus infection by dental treatment, respiratory infections, sunlight exposure, fever, trauma, exposure to chemicals and emotional stress (Cappuyns I, Gugerli P and Mombelli A, 2005).

Human Papilloma Virus (HPV)

In the oral cavity, periodontitis has been associated with papillomavirus-16 related squamous cell carcinoma of the tongue. Co-infection with papillomavirus-18 and Epstein–Barr virus has also been linked to tongue carcinoma. As periodontitis lesions frequently harbour papilloma viruses and may even comprise the major oral reservoir of the virus, periodontitis sites in intimate contact with the tongue may serve as the source of oncogenic papillomaviruses. Papillomaviruses have also been associated with the potentially malignant disorders of oral leukoplakia and oral lichen planus.

In a study conducted by Hormia M et al (2005), it was found that the periodontal pocket might serve as a reservoir of HPV's in the oral mucosa and HPV may be involved in the initiation of periodontal disease.

Conclusion

A solid understanding of the etiology of periodontitis is critical for developing clinically relevant classification systems and therapies that can ensure long lasting disease control. The ability of an active virus infection to alter the periodontal immune responses may constitute a crucial pathogenic feature of periodontitis.

Research has shown that a number of viruses are involved in the etiopathogenesis of destructive periodontal disease. A high periodontal load of active Epstein-Barr virus or Cytomegalovirus is associated with aggressive periodontitis, and latent herpes virus infections are preferentially found in chronic periodontitis and gingivitis sites. Also a co-infection of active herpes viruses and periodontopathic bacteria may constitute a major cause of periodontitis and explain a number of the clinical characteristics of the disease.

Development of new vaccines for viruses involved in periodontal disease is required in future, which can provide real hope for low-cost prevention of periodontitis in large groups of individuals. Hence an effort needs to be made towards deep understanding of etiopathogenesis of disease, for the development of suitable preventive and therapeutic measures.

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