

Role of Viruses in Periodontal Diseases - A Research Study

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Abstract

Background: Periodontitis is an inflammatory disease affecting supporting tissues of the teeth. However, questions in understanding of this disease remain unanswered as to what initiates change of gingivitis to periodontitis, biologic basis for disease remission, and relapse and what causes site specificity. Viruses are well known to cause disease in oral cavity, but its role as a causative agent in periodontal diseases remains unclear. A deep understanding regarding the etiopathogenesis of these diseases is important for the development of suitable preventive and therapeutic measures. The diverse opinion about the role of viruses in etiology of periodontal diseases has led to various clinical studies. The review focuses on the studies of viral cause for periodontal diseases marking a turning point in periodontal research, which until recently was centered almost exclusively on bacterial etiology.

Aim: The aim of this study was to compare levels of herpes viruses in gingival crevicular fluid (GCF) of periodontitis and healthy periodontium subjects.

Materials and Methods: A total of 30 patients with periodontitis, 30 patients with gingivitis, and 30 with healthy gingival tissues were selected. GCF samples were analyzed using quantitative real-time polymerase chain reaction to detect and quantify herpes simplex virus (HSV). Levels of HSV were compared between healthy and diseased subjects.

Results: The prevalence of HSV 1 was slightly higher in periodontitis subjects in comparison to the control group with a significant correlation with clinical parameters of the periodontitis.

Conclusion: The prevalence of the HSV viruses in the GCF and its correlation between the clinical parameters of periodontitis may represent an association with the host responses in periodontitis.

Key words: Gingiva, Herpes simplex virus, Periodontitis

INTRODUCTION

Periodontitis is a multifactorial, chronic disease that progresses by the destruction of supporting structures of teeth such as cementum, alveolar bone, and periodontal ligament. The main cause of periodontitis is the oral biofilm, with multiple microorganisms present such as bacteria and viruses. The uncertainty about the infection

and clinical events of periodontal breakdown has given rise to a number of hypotheses regarding the etiopathogenesis of the disease. The understanding of etiopathogenesis has come a long way from doctrine of calculus to non-specific and specific plaque hypothesis, host-bacterial interaction model, and now, recently to keystone pathogen concept which entails the conversion or a symbiotic relationship of normal flora and host to a dysbiotic state.

The microbes are essential but not sufficient to cause periodontal disease. These have to interact with the host to elicit disease. The transformation of commensals from a symbiosis to dysbiosis can be attributed by immunosuppression caused by keystone pathogen.¹ Much focus has been eyed on *Porphyromonas gingivalis* as a keystone pathogen, but the balance is tipping in favor

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of non-cultivable and new pathogens; viruses being the prime suspects.

Viruses are known to infect inflammatory cells of the periodontium, and they are present more frequently in diseased sites than in healthy sites. Most human viruses known to cause oral diseases are DNA viruses that are contracted in childhood or early adulthood through contact with blood, saliva, or genital secretions.²

Recently, it was suggested that certain viruses might also influence the development and severity of periodontal diseases though the cause of gingivitis and periodontitis is credited to bacteria and initiating the major mechanisms of periodontal destruction.³ It is obvious that other factors beyond biofilm are important in the pathogenesis of periodontitis, such as tobacco smoking and genetically determined variations in inflammatory response patterns. However, viruses can also interfere on immune responses through immune modulators encoded within viral genomes, which include proteins that regulate antigen presentation, function as cytokines or cytokine antagonists, inhibit apoptosis, and interrupt the complement cascade.⁴ Thus, a situation of viral-bacterial interaction could occur in the oral cavity without a denial of the argument for a major etiological role of bacteria in human periodontal disease.

The viruses are one of the smallest forms of microorganisms, which can only multiply inside living cells. These are epitome of instability and uncertainty when it comes to structure, function, and site of inoculation.⁵

Among all the groups of viruses known, Herpesviridae family is the most studied one and has shown potential link with periodontal diseases. The species of this family are divided into three subfamilies according to pathogenicity and type of cell, which they were infected with and their properties of growth (Table 1).⁶

Another virus which has gained attention in relation to periodontal disease is human immunodeficiency virus in acquired immunodeficiency syndrome patients, who have

shown typical patterns of periodontal disease in the form of linear gingival erythema, necrotizing ulcerative gingivitis, and periodontitis.

Evidence Suggesting Viral Association in Etiopathogenesis

The criteria to ascertain various microbes as putative periodontal pathogens were postulated. Dilemma still exists whether viruses are active or prime periodontal pathogens or mere passive inhabitants of periodontal pockets.⁷ A pathogen is said to be associated with a disease if it is prevalent in higher numbers in diseased sites as compared to the healthy sites, a number of studies have confirmed a high prevalence of viruses detected in dental plaque and periodontally compromised sites. It has been seen that as many as 1 million herpes virus genome copies can be present in a single site of chronic periodontitis patients.⁸

Herpes simplex virus (HSV), CMV, and EBV have been detected in higher numbers in chronic and aggressive periodontitis patients. Nuclear body type structures, virus-like inclusions, and raised immunoglobulin G titer are indicative of herpes virus infection and were detected in periodontitis patients.⁹⁻¹¹

Table 2 summarizes the various types of viruses and their prevalence with periodontal disease.¹²⁻¹⁶

Although abovementioned studies indicated an association between viruses and periodontal diseases, certain facts need to be pondered over before reaching to any conclusion. The mere presence of viruses in periodontitis sites does not justify their role in the disease as viruses have also been detected in the healthy sites. The periodontal health was found to be associated with a median genomic detection rate of 8% for EBV and cytomegalovirus. There are certain studies, which have not detected viruses in periodontitis patients. Nibali *et al.*¹⁷ concluded that prevalence of herpes viruses in plaque sample of periodontitis subjects is not universal. Viruses have been detected in latent stages in various periodontal patients indicating their role as mere innocent bystander. Saygun *et al.*¹⁸ concluded that periodontal pockets might act as a main source of viruses in the saliva of periodontitis patients where viruses grow owing to immunosuppression caused by bacteria.

Viruses were not detected at all sites and in all studies. This might be explained by various factors. Scientific evidence states “Association is not causation.” Thus, the second

Table 1: Clinical parameters of control group and periodontitis group

Parameter	Mean±SD		P
	Control group	Periodontitis group	
PI	0.71±0.73	1.23±0.76	0.016
Gingival index	1.19±0.72	2.09±0.67	0.000
Bleeding on probing	1.23±0.79	2.37±1.19	0.000
Pocket depth	1.98±0.02	4.13±2.67	0.000
Clinical attachment loss	0.00±0.00	5.58±2.40	0.000

SD: Standard deviation

Table 2: Herpes viruses in periodontitis group of patients according to the pocket depth and CAL

Periodontitis group	Pocket depth >6 mm	CAL 3-6 mm	P
HSV-1	6	10	0.009

criterion of “elimination” further substantiates criteria of association.

If the removal of an organism leads to resolution of the disease/lesion, causality may be surfaced. The synergistic pathogen concept reveals that microbes show great interdependence in periodontitis. The effect of the removal of one organism on the other microbes should not be overlooked. Modulation of viral prevalence by therapeutic intervention leads to the improvement in periodontal conditions and might confirm their role as putative pathogens.¹⁹

Various studies have pointed out considerable improvement in periodontal parameters along with combined bacterial and viral load reduction after mechanical periodontal therapy.^{18,20-23} This authenticates a synergistic role played by both pathogens or this might assign primary role to bacteria, whose removal led to decrease of the viral load simultaneously and vice versa. A cause-and-effect relationship between viruses and periodontal disease can be pointed out by proving the efficacy of antiviral therapy alone in achieving periodontal health.²¹

Host Response to Organism and Specific Pathogen Mechanisms

A microorganism is said to be pathogenic if it elicits immune response in host and possesses certain virulence factors, which can be implicated in tissue damage cascade. Herpes virus pathogenicity in periodontal scenario is complex and is executed through direct virus infection and replication or through a virally induced alteration of the host immune defense.

Cytopathic Effects on Host Cells

Herpes viruses can exert direct cytopathic effects on fibroblasts, keratinocytes, endothelia cells, and various inflammatory cells. It may induce abnormalities in the adherence, chemotaxis, and phagocytic and bactericidal activities of PMNs. Epstein–Barr virus active infection can also generate anti-neutrophilic antibodies and neutropenia and polyclonally stimulate the proliferation and differentiation of B-lymphocytes. They can upregulate the interleukin- β and tumor necrosis factor- α gene expression of monocytes and macrophages. Increased levels of pro-inflammatory cytokines in periodontal sites can cause enhanced risk of periodontal tissue destruction by disrupting homeostasis.⁸

Increased Bacterial Colonization

Herpes virus proteins expressed on eukaryotic cell membranes may act as new bacterial binding sites. Cytomegalovirus can enhance the adherence of *Aggregatibacter actinomycetemcomitans* to pocket epithelial cells and to HeLa cells.²⁴

Activation of Autoimmune Cascade

Periodontitis tends to be of greater severity in carriers of the HLA-DR4 alloantigen,²² perhaps because cytomegalovirus-specific CD8+T cells can cross-recognize HLA-DR4 molecules and potentially induce autoimmune reactions.²⁵

Disruption of Epithelial Barrier

Herpes viruses can disrupt oral epithelial cells. The disruption of epithelial barrier may facilitate the access of bacteria to deeper tissues and create additional sites for bacterial binding and action.²⁴

Defective Development of Periodontium

Ting *et al.*¹⁰ hypothesized that a primary cytomegalovirus infection at the time of root formation of permanent incisors and first molars can give rise to a defective periodontium and can affect morphology of teeth. Cytomegalovirus infection early in life can lead to cemental hypoplasia.²⁶

Latent Membrane Proteins (LMPs)

LMP-1 mimics receptors of the TNF receptor superfamily and activates numerous signaling pathways.⁸

Alteration of Microbiological Ecology

Oral virobiota may alter microbial ecology and hence can predispose the host to periodontal destruction. A periodontal herpes virus infection may increase the pathogenicity of the periodontal microbiota.²⁷

Integrated Pathogenicity

The integration of bacterial, viral, and fungal metatomes (interactome) together with medically compromised host as a co-factor might explain the occurrence of severe, recurrent, and refractory periodontal cases.²⁸

Clinical Implications

Implicating viruses in the initiation and progression of periodontal disease has therapeutic implications. HMV, EBV, and CMV have been shown to persist in saliva, gingival tissues, and cells of lymphoid series in latent or active stage of affected individuals. The elimination of these viruses can be done by following methods:

- Periodontal therapy
- Chemical and plaque measures
- Specific antiviral drugs such as acyclovir and valacyclovir can lead to resolution of periodontal disease.²¹

Prophylactic and Therapeutic Vaccination

Periodontal disease being a ubiquitous disease poses a great social and financial burden. Recent understanding of herpes virus-bacterial host interaction holds great promise in developing vaccines to prevent and cure periodontal disease.

Prophylactic vaccines harness the immune system of healthy subjects to prevent infection by viruses. Therapeutic vaccines stimulate the immune system into combating existing viruses and disease. Labeling of viruses as potential pathogen might also explain the missing authentic link of periodontitis-systemic disease syndrome. Therefore, these vaccines might start a new era of disease-free world.

Sunde *et al.*²¹ treated a patient, who exhibited refractory periodontitis and high Epstein–Barr virus subgingival copy counts, with the anti-herpesvirus drug, valacyclovir HCl, 500 mg twice a day for 10 days. The treatment suppressed subgingival Epstein–Barr virus to undetectable levels for at least 1 year and resulted in clinical improvement.

Anti-herpesvirus chemotherapy can also decrease the salivary viral load. A short course of valacyclovir, 2 g twice on the day of treatment and 1 g twice the following day, resulted in a significant decrease in the salivary occurrence of Epstein–Barr virus compared with controls.²⁹ Valacyclovir, 500 mg 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.³⁰ Valacyclovir therapy, 3 g 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.³¹ The orally administered acyclovir prodrug and valacyclovir can reach serum concentrations similar to those of intravenously administered acyclovir and are prescribed for a variety of herpes viral diseases.³² The US Institute of Medicine has assigned high priority to the development of vaccines against HSV, Epstein–Barr virus, and cytomegalovirus, to be given to 12-year-old children.³³

MATERIALS AND METHODS

A total of 30 patients with periodontitis, 30 patients with gingivitis, and 30 with healthy gingival tissues were selected from the OPD of the Department of Periodontics, IGGDC, Jammu. Gingival crevicular fluid (GCF) samples were analyzed using quantitative real-time polymerase chain reaction (PCR) to detect and quantify HSV virus. Levels of HSV were compared between healthy and diseased subjects.

Exclusion Criteria

- The patients with known systemic diseases
 - <20 teeth present
 - Any therapy of periodontitis 1 year before the study.
- A full mouth periodontal examination was done in all patients by a single clinician trained for the specific study recording the following clinical parameters at six sites using a periodontal probe graded in mm*:

- Clinical pocket depth in mm,
- Bleeding on probing recorded as present (1) or absent (0),
- Plaque index (PI) measured along the mucosal margin and recorded as present (1) or absent (0),
- Radiographs were taken from all the diseased sites using a standardized technique.

Microbiological Sample Collection

Sterile cotton pellets removed the supragingival plaque, and micropipette is inserted in gingival sulcus/periodontal pocket. GCF was collected in small plastic tubes samples.

Quantitative Real-time PCR Assays for HSV

The PCR procedure was carried out at the Microbiology and Pathology Laboratory of Government Medical College, Jammu. Quantitative real-time PCR was performed to detect the presence/absence and quantify the HSV-1. The real-time quantitative PCR was performed with oligonucleotide primer pairs and probe specific for the type - common region of HSV-1. The primers used were HSV-FP (5'- TCC CGG TAC GAA GAC CAG-3') and HSV-RP (5'- AGC AGG CCG CTG TCC TTG-3'), and the probe was HSV-TCP (5'-FAM-TGG TCC TCC AGC ATG GTG ATG TTG/C AGG TCG-TAMRA-3'). Amplification was carried out in an Applied Biosystem Sequence Detector 7500 machine, programed for a four-step protocol: 2 min of incubation at 50°C for Amp Erase activation, 10 min at 95°C for polymerase activation and for 45 cycles: 15 s at 94°C for denaturation, and 60 s at 58°C for annealing, extension, and data collection. Each 50 µL-PCR mixture contained 10 µL of purified DNA, 840 nM concentrations of each primer, and 100 nM probe in 1x TaqMan universal PCR master mix (Applied Biosystems, Branchburg, New Jersey, USA). Negative controls were included in the extraction process between every clinical sample. All negative samples were tested twice.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences for Windows, version 15. Statistical differences between frequencies were tested with Chi-square test.

RESULTS

Within the periodontitis group, several clinical parameters showed a significant difference with different levels of virus in the GCF. Table 1 probing pocket depth and clinical attachment loss revealed higher values in the patients with HSV, while PI was lower. In addition, HSV occurred more often in deeper pockets with more clinical attachment loss (Table 2).

DISCUSSION

Grenier *et al.*²² reported a higher prevalence of HSV-1 in subjects with periodontitis than in healthy subjects. Similar results were found by Parra and Slots³⁴ in patients with chronic periodontitis than in patients with mild gingivitis. The same results were concluded by Contreras *et al.*²⁴ in gingival tissue specimens. Surprisingly, Bilichodmath *et al.*¹⁶ found a higher prevalence of HSV-1 in patients with chronic periodontitis than in patients with the aggressive form of the disease, but they explained the results as the influence of their patients' age, which is also a limiting factor of our study. However, Nibali *et al.*¹⁷ found a low prevalence of all investigated herpes viruses in both patients with periodontitis and controls.

The most important result in our study is the relationship between the presence of HSV-1 and pocket depth with the higher prevalence of HSV-1 with an increase in pocket depth. Other authors did not find correlation between the depth of periodontal pockets and HSV-1.²² Our results also showed lower values for the PI in periodontitis group subjects, which indicates the influence of HSV-1 on periodontal tissue destruction. Kamma and Slots³⁵ detected significantly higher frequencies of HSV and other viruses in active and progressive periodontitis sites.

Sabeti *et al.* presumed that viral infections contribute to immune impairment, which in turn creates a fertile ground for bacterial infections and causes shifting of gingivitis toward periodontitis. Furthermore, reactivation of viruses such as HSV coincide phases of remission and reactivation of periodontitis.³⁵

CONCLUSION

Long-term studies with adequate sample size, well-designed randomized controlled trials, more sensitive and specific technological advancements to detect latent and activated viruses may provide sufficient evidence to implicate viruses as prime pathogens. Importance of the present literature cannot be undermined as it is rightly said that "absence of evidence is not the evidence of absence." At the same time, a cause-and-effect relationship remains to be established. The possible involvement of human herpesviruses in the pathogenesis of chronic periodontitis merits further investigation.

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