



**ORIGINAL RESEARCH PAPER**

**Dental Science**

**ROLE OF HUMAN VIRUSES IN PERIODONTAL DISEASES**

**KEY WORDS:**

Viruses; Periodontal Diseases; Herpes Virus; Human Immunodeficiency Virus; Human Papilloma Virus; Zika Virus.

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**ABSTRACT**

A virus is a non living acellular infectious organism which replicates only inside host's living cell. When a virus infects a host cell, the latter is forced to replicate into thousands of identical copies at an extraordinary rate. All types of life forms, from animals and plants to microorganisms, including bacteria and archaea can be infected by a virus. Until recently, specific bacteria were considered to be the main cause of periodontal diseases; but current studies show the presence of various viruses in periodontal environment and therefore it is imperative to understand the etiopathogenesis and therapeutic measures of such viruses.

Electronic database search of Pubmed, Medline, Google Scholar and Scopus was performed using MeSH terms- Viruses, Periodontal Diseases, Herpes Virus, Human Immunodeficiency Virus, Human Papilloma Virus, Zika Virus.

**INTRODUCTION**

“Viruses are acellular organisms whose genomes consist of nucleic acid, and which obligately replicate inside host cells using host metabolic machinery and ribosomes to form a pool of components which assemble into particles called VIRIONS, which serve to protect the genome and to transfer it to other cells.”

Viruses as a concept are just a little younger than bacteria – they were first described only in the 1890s – yet have probably co-existed with cellular life through nearly the whole of evolutionary history on this planet.

The term “virus” was coined by Beijerinck (1897) which means “poison” in Latin. <sup>2</sup> They were discovered as an excluded entity rather than by being seen or cultured, due to the invention of efficient filters: the fact that cell-free extracts from diseased plants and animals could still cause disease led people to theorise that an unknown infectious agent – a “filterable virus” – was responsible. While people were aware of diseases of both humans and animals now known to be caused by viruses many hundreds of years ago, the concept of a virus as a distinct entity dates back only to the very late 1800s. Although the term had been used for many years previously to describe disease agents, the word “virus” comes from a Latin word simply meaning “slimy fluid”. <sup>1</sup>

**Classification of Viruses**

Viruses do not obey the conventional binomial system of nomenclature. They can be named after the diseases they are responsible for (eg. Measles virus, smallpox virus), after the places where the disease first reported (eg. Newcastle disease virus, Ebola virus, Norwalk virus), Host and signs of disease (eg. Tobacco mosaic virus, cauliflower mosaic virus), Latin and Greek words (eg. Coronaviridae – “crown” Parvoviridae – “small”), Virus discoverers (eg. Epstein-Barr virus), how they were originally thought to be contracted (eg. Dengue virus :“evil spirit”, influenza virus: the “influence” of bad air, or a combination of the above (eg. Rous Sarcoma virus).

David Baltimore classified viruses as on the basis of genome and the method of replication as Class I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses), Class II: ssDNA viruses (+ strand or "sense") DNA (e.g. Parvoviruses), Class III: dsRNA viruses (e.g. Reoviruses), Class IV: (+)ssRNA viruses (+ strand or sense) RNA (e.g. Picornaviruses,

Togaviruses) Class V: ( )ssRNA viruses ( - strand or antisense) RNA (e.g. Orthomyxoviruses, Rhabdoviruses), Class VI: ssRNA-RT viruses (+ strand or sense) RNA with DNA intermediate in life-cycle (e.g. Retroviruses) and Class VII: dsDNA-RT viruses DNA with RNA intermediate in life-cycle (e.g. Hepadnaviruses).<sup>2</sup>

**Characteristics**

Viruses are non living, acellular structure. It contains a protein coat called the capsid and has a nucleic acid core containing DNA or RNA (one or the other - not both). It is capable of reproducing only when inside a host cell. Some viruses are enclosed in a protective envelope and may spikes to help attach to the host cell. Most viruses infect only specific host cells. Outside of host cells, viruses are inactive. They cause many common illnesses/ diseases. Some viruses may cause some cancers like leukemia.

Until recently, specific bacteria were considered to be the main cause of periodontal diseases; but current studies show the presence of various viruses in periodontal environment.

**The Role of Viruses in Periodontal Tissue Destruction Herpes Virus**

Various species of Herpes Virus are Simplex 1 (HHV-1), Simplex 2 (HHV-2), Varicella (HHV-3), Epstein-Barr (HHV-4), Cytomegalovirus (HHV-5), HHV-6, HHV-7 and Kaposi's sarcoma virus (HHV-8). It leads to severe types of periodontitis. It's structure consists of a double stranded DNA contained in capsid. This capsid is covered by Tegument. The outermost layer is envelope. Glycoproteins are present on the surface of envelop.

Possible mechanism of periodontal destruction by Herpes Virus is that accumulation of bacteria on the surface of teeth leads to influx of inflammatory cells containing Herpes virus in the gingival sulcus. The marks the beginning of clinical evidence of gingivitis. The virus gets activated and presents periodontopathic properties which causes destruction of periodontal tissues. <sup>3</sup>

**Herpes Simplex Virus:**

They are of 2 types HSV- 1 & 2. HSV- 1 is most commonly transmitted by saliva while HSV-2 is transmitted via sexual contact. Common infections involve skin, eye, oral cavity, and genital tract. In healthy individuals the disease may be mild

and self-limiting but in immunocompromised and newborn, the infection may be severe and life threatening. The infections caused by these viruses can be primary infection, non-primary 1<sup>st</sup> infection or recurrent infection and are manifested clinically as Skin vesicles and shallow ulcers small, 2-4 mm vesicles that may be surrounded by an erythematous base which ruptures to causing ulcers in a few days. Most infections are asymptomatic or unrecognized as small skin fissures.

It causes acute oropharyngeal infections which includes Recurrent herpetic gingivostomatitis and Chronic herpetic gingivostomatitis. Herpes gingivostomatitis most often affects children 6 months to 5 years. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever. The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including on the gums, lips, tongue, palate, tonsils, and pharynx. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. Tender submandibular, submaxillary, and cervical lymphadenopathy are common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.

• **Epstein-Barr Virus (EBV):**

It affects over 90% of humans. It is transmitted by oral secretions or blood and replicates in epithelial cells or B cells of oropharynx. EBV is responsible for causing infectious mononucleosis which presents clinically as oral ulcers, palatal petechial, Periodontitis, recurrent aphthous stomatitis. It also causes Hairy Leukoplakia.

• **Human Cytomegalovirus (HCMV):**

It is the largest virus in Herpesvirus family. It infests mainly in t- lymphocytes and is the most common cause of natal and perinatal infections. It infects epithelial cells, endothelial cells, smooth muscles, and granulocytes, hence causing various periodontal diseases. It can be transmitted through direct contact to body fluids, sexual contact, breast milk of an infected mother, placenta from infected mother to her unborn child or during birth and blood transfusions and organ transplantations.

Saygun et al. confirmed the frequent presence of HCMV in crevicular samples of chronic periodontitis lesions, and suggested a strong relationship between the HCMV and EBV-1 in subgingival areas and the measurements of probing depth and probing attachment loss.<sup>4</sup> Contreras et al. suggested that HCMV and possibly other herpesviruses contribute to the onset and/or progression of acute necrotizing ulcerative gingivitis in malnourished Nigerian children.<sup>5</sup> In another study done by Parashar et al., he concluded that coinfection of two viruses like EBV and CMV is also responsible for progressive periodontitis. HHV also cooperate with specific bacteria in periodontal tissue breakdown.<sup>6</sup>

**Human Immunodeficiency Virus (HIV)**

The world first became aware of AIDS in the early 1980's. Researchers aren't sure exactly when and how HIV developed. The most likely theories assume that HIV-1 was transmitted to humans from chimpanzees sometime in the early 20th century. It is responsible for causing AIDS (Acquired Immunodeficiency Syndrome). There are 2 forms of the virus, HIV 1 & 2. It can be transmitted via sexual contact, pregnancy, childbirth & breast feeding, injection & drug use, occupational exposure blood transfusion and organ transplant. The virus attacks host CD4 cells and enters into its nucleus where it combines with the host DNA and replicates to form new copies of HIV.

categorized it into 4 stages; Stage I: Acute (primary) infection (Seroconversion), Stage II: Early (asymptomatic) disease ( CD4 > 500/mm<sup>3</sup>), Stage III: Intermediate HIV infection (CD4 200-500/mm<sup>3</sup>), Stage IV : Late stage HIV disease (CD4 50-200/mm<sup>3</sup>), Stage V : Advanced HIV disease (CD4 < 50/mm<sup>3</sup>).

It effects periodontium and causes Linear Gingival Erythema (LGE), Necrotizing Gingivitis (NG), Necrotizing Periodontitis (NP), Chronic Periodontitis (CP).

According to Mataftsi et al., higher prevalence of opportunistic microorganisms has been frequently detected in the subgingival flora of HIV-infected individuals, probably due to the immune status of those patients, as colonization and overgrowth of atypical pathogenic species is facilitated by immunosuppression.<sup>7</sup> Ryder et al. suggested that the oral and periodontal conditions most closely associated with HIV infection include oral candidiasis, oral hairy leukoplakia, Kaposi's sarcoma, salivary gland diseases, oral warts, other oral viral infections, linear gingival erythema and necrotizing gingival and periodontal diseases.<sup>8</sup>

**Human Papilloma Virus (HPV)**

They are small, unenveloped double stranded circular DNA virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. It's one of the most common sexually transmitted disease. The incubation period range from 1 month to 2 years. There are more than 100 different HPV types, 40 of them can cause warts or lesions, and some of these 40 can start a carcinoma. The virus enters the host cell and controls its multiplication causing wart like lesions or the virus contained cell may burst releasing viruses causing areas of inflammation, pain and spots which allows cross infection to occur. In gingival tissues, it causes koilocytosis and proloferation of epithelial cells which leads to proliferation and migration of junctional epithelium causing periodontal breakdown. HPV mainly causes oral cancers, tumors and periodontitis.

Marketta et al. suggested that the periodontal pocket might serve as a reservoir of HPVs in oral mucosa. While having important implications in understanding the HPV transmission, this observation does not rule out the possibility that HPV may be involved in the initiation of periodontal disease.<sup>9</sup>

In another study done by Wiener et al., the researchers failed to reject the hypothesis of no association of the presence of HPV in oral rinse specimens and periodontitis.<sup>10</sup>

**Zika Virus**

Zika virus (flavivirus) belongs to the family Flaviviridae. It was first recognized in the year 1947 and was isolated from Aedes Africanus. It's clinical features include fever, cutaneous rash, arthralgia, conjunctivitis, neurological defects and adverse fetal outcomes. The virus can be transmitted through aedes mosquito as well as from mother to the fetus. It is present in the body fluids such as saliva, but there is no reliable evidence to state that it can be transmitted through this route. However, oral health providers must follow the standard infection control protocols. Currently, there is no specific treatment for the disease caused by Zika virus, hence, prevention is based on vector control.<sup>11</sup>

**Treatment**

Although most periodontal diseases of viral origin resolve spontaneously, antiviral agents such as acyclovir, ganciclovir, valacyclovir and famciclovir accelerate the healing of the lesion and reduce the duration of pain. However, these drugs must be begun early enough in treatment to be effective. They may be given by the intravenous route in the

immunocompromised patients and have been useful in the resolution of the lesions in a number of cases. Human immunodeficiency virus responds to a number of highly active antiretroviral agents. These do not result in total eradication of the virus but greatly reduce their multiplication thus helping in the clinical improvement of the patient. Kaposi Sarcoma, being a vascular neoplasm respond to the chemotherapeutic agent especially vinblastine in the control of the lesion.

### CONCLUSION

Several studies have shown the presence of virus in periodontal environment. Therefore its deep understanding regarding etiopathogenesis is required for development of suitable preventive and therapeutic measures.

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