



## VIRUSES –A HIDDEN CULPRIT IN PERIODONTAL DISEASES ??

## Dental Science

**Dr.Bansi M. Bhusari**

Professor & HOD, Department of Periodontics, Y.M.T Dental College and Hospital.

**Dr. Suvidha Dere**

MDS, Department of Periodontics, Y.M.T Dental College and Hospital.

**Dr. Rohini Jadhao**

PG student 3rd year, Department of Periodontics, Y.M.T Dental College and Hospital.

## ABSTRACT

Periodontal disease is a multifactorial complex disease with various biological factors like specific nonspecific microbial species, host immune responses, genetic, epigenetic and environmental factors. The only bacterial etiology for periodontitis seems unacceptable. Few of them have suggested infectious agent like virus is involved with disease mechanism while other emphasize on host immune factor and genetic characteristics. Previously it was thought that virus is not involved with severe cases of periodontitis. After that several studies covered the strong evidences about direct virus isolation from deep focal sites. A very strong evidences in the involvement of human herpes virus, Epstein Barr virus, Human cytomegalovirus, Human Immunodeficiency Virus in both chronic as well aggressive periodontitis. The compiled information and critical aspects in the area will also help to develop suitable diagnostics and therapeutics.

## KEYWORDS:

Virus, Periodontitis, HHV Family

## Introduction:

Periodontal disease is a chronic microbial infection involving a variety of microbes that trigger inflammation, that leads to progressive destruction of the connective tissues and alveolar bone with subsequent tooth mobility and finally tooth loss.

Periodontal disease is a multifactorial complex disease with various biological factors like specific nonspecific microbial species, host immune responses, genetic, epigenetic and environmental factors.

## Figure 1:

Due to lack of proper data about infectious agents that has given rise to number of hypothesis about etiological factors in periodontitis. The probability of only pure bacterial etiology for periodontitis seems unacceptable. Few of them have suggested infectious agent like virus is involved with disease mechanism while other emphasize on host immune factor and genetic characteristics.

Viruses are well known to cause diseases in oral cavity, but their role as causative agent for periodontitis still remains unclear.

## Why Viruses Are Considered As Causative Agents In Periodontitis ??

Periodontal microbiology has a history of more than 100 years now and it continues till today. According to recently accepted hypothesis on etiopathogenesis of periodontitis, bacteria play an imperative role for development of periodontitis. The gram negative pathogenic bacteria species that elicit host defense responses resulting in inflammation and tissue destruction. Even though specific infectious agents are the key in the development of periodontitis, it is unlikely that a single agent or small group of pathogens is the sole cause or modulator of this complex disease. **Figure 2:**

It is necessary to rule out bacteria as a pure cause of periodontitis in order to answer many unanswered questions regarding the etiopathogenesis of periodontitis. (Beader N, Kardum M. 2011)

## UNANSWERED QUESTION???

## Table 1:

Hence, a pure bacterial etiology for periodontitis seems unlikely. Non-bacterial microorganisms that are found in plaque include viruses, mycoplasma, yeasts and protozoa. The development of human periodontitis may depend upon cooperative interactions among herpes viruses, specific pathogenic bacteria and tissue destructive inflammatory mediators. Individual periodontal lesions harbour millions genomic copies of Human Herpes viruses (HHV), Human Cytomegalovirus (HCMV), Epstein-Barr Virus (EBV), Human Papillomavirus (HPV), Human Immunodeficiency Virus (HIV), Hepatitis B And C Virus (HBV, HCV), and Human Enterovirus (HEV)

(Parashar A, Sanikop S, Zingade A. 2015). Out of them EBV and CMV are the most commonly researched virus in periodontology.

## Herpes viruses:

The association of herpes viruses in the etiology of periodontal diseases is suggested by their presence of higher frequency of virus detection in the gingival tissue, subgingival plaque and GCF of periodontitis sites than in healthy sites. The interaction between herpes viruses and bacteria can be bidirectional(Cappuyns I, Gugerli P, Mombelli A. 2005). The progress of periodontitis proceeds from bacteria to herpes virus and again to bacteria. **Figure 3:**

Herpes viruses are found to be more frequently present in periodontal lesions and acute necrotizing ulcerative gingivitis lesions than in gingivitis or periodontally healthy sites. Most of the time, two herpes viruses are implicated in these lesions: Epstein-Barr virus (EBV) that infects periodontal B-lymphocytes and cytomegalovirus (CMV).

Frequent occurrence of herpes virus in various types of severe periodontal disease makes their participation in the etiology of periodontitis as a possibility. Recent researches suggest that high load of EBV and CMV is statistically with associated aggressive periodontitis and HSV with chronic periodontitis.

## Cytomegalo Virus:

CMV infection due to a variety of viral properties can impair periodontal defenses, thus permitting the overgrowth of periodontopathogenic bacteria. Further depending on the latent or active phase of CMV infection in periodontal tissue can partly explain periods of remission and exacerbation of periodontal disease(Beader N, Kardum M. 2011).

## HIV:

Several studies show a clear association between HIV infection and some distinct forms of periodontal infection, i.e. necrotizing lesions. Furthermore, reports of increased prevalence and severity of chronic periodontitis in HIV-positive subjects suggests that HIV infection predisposes to chronic periodontitis. (Slots J. 2010)

## Viruses – Immune Modulators !!!

As per the literature available, a latent herpes virus infection may up-regulate the activation state of the innate immunity and shows resistance to the bacterial pathogens thereby providing immune benefits for the host. However, the herpes virus induced protection against bacterial infection seems to be transient, lasting only a few months. But in few situations, further impaired immunity permits overgrowth of pathogenic bacteria causing bacterial infection.

## Virus and Bacterial Co-infection:

Many bacterial infections in humans occur as super-infections of viral diseases. The best-known example of serious viral-bacterial co-infections respiratory disease showing bacterial complication in influenza outbreaks and are frequently attributed to a secondary bacterial pneumonia mainly due to *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae*.

This is similar to the situation of viral-bacterial interactions in the oral cavity. Recently, it was suggested that certain viruses might also influence the development and severity of periodontal disease. The periodontal immune response to herpes viral and bacterial infections is bi-functional with both tissue protective and tissue-destructive effects. The virus infection may be primary infection causing bacterial periodontitis as a super-infection or it may be the bacterial host response resulting in reactivation of latent virus then affecting the severity and progression of periodontitis.

**Diagnostic Value:**

The detection of the viruses, which include culture methods, DNA-DNA hybridization technique and various types of polymerase chain reactions (PCR) such as Hot Stuart PCR, multiplex PCR, nested PCR, reverse transcriptase and real time PCR Studies from various countries have found genomic copies of Epstein-Barr virus and cytomegalovirus to be present in most periodontitis lesions and to be less prevalent in gingivitis and healthy periodontal sites. Decrease in the counts of viruses in treated sites with periodontal disease can indicate the quantification of herpes virus in periodontal sites as a prognostic importance. The detection of virus within periodontal pockets by various studies proves that virus do have a role to play in periodontitis.

Despite virus diagnosis being a challenging task, detection of virus of utmost importance to show the association between presences of viruses in periodontitis. (Kolliyavar B, Setty S, Patil A. et al. 2013)

**Pathogenesis of Virus-Associated Periodontitis:**

In the case of HHV it was reported that after having a lytic cycle viral presence remains in latent form throughout the life of host. After a periodic interval, reactivation of this virus may occur due to stress or change in host immune status which may lead to serious concern. It triggers a release of pro-inflammatory cytokines that have potential to activate osteoclasts and matrix metalloproteinases which impairs antibacterial immune mechanisms causing an up-growth of periodontopathic bacteria. **Figure 4:**

According to the current idea of the pathogenesis of periodontitis & the concept of a herpes virus-bacterial co-infection, periodontitis may develop stepwise in a series of simultaneous or sequential events –

- a) a high herpes virus load in periodontal sites,
- b) activation of periodontal herpes viruses,
- c) an insufficient antiviral cytotoxic T-lymphocyte response,
- d) the presence of specific periodontal pathogenic bacteria, and
- e) An inadequate antibacterial antibody response.

These five suggested pathogenic determinants of periodontitis may collaborate in relatively infrequently and mainly during periods of suppressed cellular immunity. Thus herpes viruses may play a major role as activators of the disease process.

**Future Directions and Implications:**

The updated information in literature justifies presence of Herpes, EBV, HCMV and herpes viruses as a likely contributing etiological agent for human periodontitis. The bacteria-herpes virus presence in periodontitis provides a reason for consideration of new therapeutic approaches to disease prevention and treatment.

Conventional mechanical debridement has showed suppressed subgingival viral load and this could be due to reduction in the inflammation and virally-infected inflammatory cells. Drugs such as acyclovir and valacyclovir have been studied for their potential use in limiting the virus infections.

The scope of development of herpes virus vaccines in the future will open up new therapeutic modality for treatment of periodontitis. It would bypass the current periodontal therapeutic methods of surgery and use of antibiotics and may also provide a low-cost prevention of periodontitis. Further research in the identification of viruses in different severity of periodontitis and use of antiviral therapy and

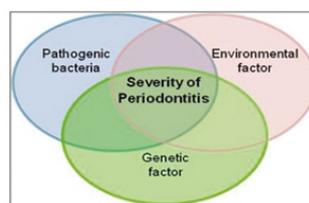
vaccines can certainly benefit large groups of individuals suffering from periodontitis.

**Conclusion:**

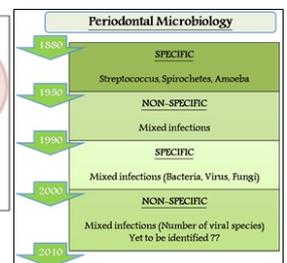
As of now it has been considered that the pathogenesis of periodontitis is based mainly on the bacterial infection that colonize tooth surface and gingival sulcus, different studies have shown that the host immune modulatory factors such as inflammatory reaction and activation of the innate immune system are also critical to the pathogenesis. Several studies have been undertaken to detect whether the viruses are present in destructive periodontal diseases & if so then to determine what is the correlation of these viruses with clinical parameters. Few studies have also demonstrated an association of herpes viruses as an immune modulator with periodontal disease wherein viral DNA has been detected in gingival tissue, GCF & subgingival plaque from periodontally diseased sites also markers of herpes virus activation have been demonstrated in the GCF from periodontal lesions. Decrease in the counts of viruses in treated sites with periodontal disease can indicate less prevalence of viruses in healthy sites.

Till date research has implied that herpes viruses such as HSV-1, CMV & EBV are frequently involved in the etiopathogenesis of periodontitis. The ability of an active herpes virus infection to alter the periodontal immune responses may constitute a crucial pathogenic feature of periodontitis. It appears that a high periodontal load of active EBV or CMV is statistically associated with aggressive periodontitis, and latent herpes virus infections are preferentially found in chronic periodontitis and gingivitis sites. Thus Herpes virus play major role as activators. Indeed, herpes viruses may be a key missing piece of the periodontopathic jigsaw puzzle that would explain the transition from gingivitis to periodontitis. Detection of high copy-counts of EBV and CMV in aggressive periodontitis, it is highly unlikely that these pathogenic viruses are acting merely as innocuous bystanders. However, herpes viruses are probably not stand-alone periodontopathic agents, but in collaboration with specific bacteria in periodontal tissue breakdown. Thus, 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.

In spite of research in the past two decades, few cases end up showing resistance to convention periodontal treatment and do not respond well. In such scenario, a definite understanding of the etiology and pathogenesis of periodontal disease is critical for developing therapeutic strategies which are more effective and ensure long term disease control. Ongoing research on viral infections of the periodontium has stream lighted towards prevention and treatment of virus induced periodontitis.



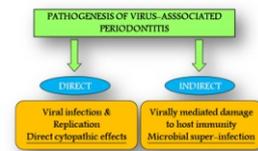
**Figure 1**



**Figure 2**



**Figure -3**



**Figure -4**

- why in some individuals only few teeth are affected despite the omnipresence of periodontopathic bacteria
- why some teeth show alveolar bone loss up to apical area whereas the destruction is minimal in adjacent teeth and how some form of diseases have bilaterally symmetrical pattern and although subjects with poor oral hygiene develops gingivitis, not every

- gingivitis progresses to attachment loss.
- why the propensity of periodontitis to proceed with periods of exacerbation and remission

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