

## Are viruses just the bystanders for Periodontal diseases?: A review

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### Abstract

Periodontal disease is multifactorial in nature. To meet long lasting therapeutic end points in treatment of it, a solid understanding of the etiology of periodontitis is need of an hour. Current research has shifted its focus from periodontitis being polybacterial infection to involvement of various viruses in the etiopathogeny of destructive periodontal disease. Discovery of the high copy counts of Epstein–Barr virus and cytomegalovirus in aggressive and chronic periodontitis, it is unlikely that these pathogenic viruses are acting merely as innocuous bystanders in pathogenesis of the periodontal diseases. These viruses probably might not act as primary periodontopathic agents but they might cooperate the specific bacteria in periodontal disease progression. The periodontal research delving more into role of virus as a causative agent for periodontal diseases can open up a whole new era in therapeutic approaches and prove to be a paradigm shift. The purpose of this review is to evaluate the evidence supporting the viral hypothesis of periodontal eitopathogenesis.

**Keywords:** Virus, Periodontitis, Periodontal bacteria, Pathogenesis, Therapy

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### Introduction

Periodontal diseases have been considered as "infections" in which micro-organisms initiate and maintain the destructive inflammatory response.<sup>1</sup> Rate of destruction in periodontal disease is unpredictable and the infectious events that trigger the progression from gingivitis to periodontitis are virtually unknown.

Despite the omnipresence of periodontopathic bacteria in saliva and gingival crevice, it remains an enigma why periodontitis tends to develop at particular sites barely affecting the periodontium of a neighboring tooth sharing the same interproximal space.<sup>2</sup> Thus considering bacteria as a sole cause of periodontitis needs to be deliberated.

It is assumed that periodontitis debuts in genetically or environmentally susceptible individuals, who are infected with virulent infectious agents. Studies on a viral cause of periodontitis in a predisposed individual has turned a page in periodontal research, which until recently was centered almost exclusively on a bacterial etiology.<sup>3</sup>

### What are Viruses???

Viruses occupy a unique position in biology. According to Slots in 2005, they are restricted intracellular agents, which are metabolically/pathogenically inert and dependant on living host cells for replication.<sup>4</sup>

Viruses are classified into two broad groups:

1. RNA viruses: They have an advantage to undergo mutation while converting viral RNA to host DNA, thus escaping immune control.
2. DNA viruses: They can directly integrate viral DNA inside host cells.

Viruses can exist in two forms:

- a. Extracellular virion particles: Most resistant to physical stress but susceptible to humoral immune control.
- b. Intracellular genomes: Maintained in host cells by limited gene expression and evade the host immune response.

### Viruses associated with periodontal diseases

Recent microbiological researches have revealed association of various viruses in etio-pathogenesis of periodontal diseases.<sup>5</sup>

They are:

1. Human cytomegalovirus (HCMV),
2. Epstein–Barr virus (EBV),
3. Human herpes virus-6 (HHV)
4. Herpes simplex virus (HSV-1 and HSV-2)
5. Human immunodeficiency virus (HIV) and
6. Human Enterovirus (HEV).

### Pathophysiology

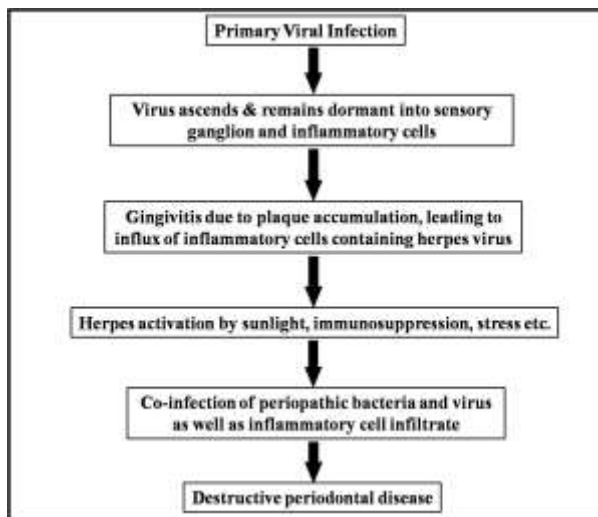
Regardless of the type of host cell, all viruses follow the same basic steps known as the lytic cycle.<sup>6</sup>

1. A virus particle attaches to a host cell.
2. The particle releases its genetic instructions into the host cell.
3. The injected genetic material recruits the host cell's enzymes.
4. The enzymes prepare multiple components.

5. The new components are assembled to form new viruses.
6. The new viruses break free from the host cell.

As the saying goes 'An insufficient virus kills its host but a clever virus stays with it'. All viruses possess specific protein on their outer coat or envelope that recognizes the host cells. This protein aids in attachment of the virus to host cell membrane. Since both the virus envelope and the cell membrane are made of lipids, few enveloped viruses can dissolve through the cell membrane of the host. Once inside the host cell, these viruses release their contents such as enzymes and genetic material etc. The viruses that do not enter the cell inject their contents (genetic instructions, enzymes) into the host cell.

In either case, the end results are identical. For Herpes viruses, it is reported that after a lytic cycle, virus remains latent throughout host's life. Stress or change in host immune status re-activates it. (Fig. 1)



**Fig. 1: Possible role of virus and their activation in periodontal diseases**

In HHV-infected periodontal sites, tissue breakdown occurs more frequently and rapidly. According to Contreras and Slots, HHV is assumed to cause direct cytopathic effects on fibroblasts, keratinocytes, endothelial, inflammatory and bone remodeling cells. Due to impaired defense cells, the host is predisposed to microbial superinfection.<sup>7</sup>

HCMV<sup>8,9</sup> and EBV<sup>10,11</sup> can infect or alter functions of immune cells mainly monocytes, macrophages and lymphocytes. Probable mechanisms by which they cause periodontal destruction:

1. HCMV possibly induce up-regulation of interleukin 1-beta (IL-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) gene expression of monocytes, macrophages and matrix metalloproteinases (MMPs). This is thought to be responsible for periodontal destruction.
2. HCMV and HHV reduces cell surface expression of MHC (Major Histocompatibility Complex) class I molecules, thereby interfering T-cell recognition. This induces cell-mediated immunosuppression.

### **Exploring the untold saga of virus-bacteria interaction, two daggers in one scabbard!!!**

Melissa Ly et. al.<sup>12</sup> in 2014 demonstrated that human saliva and gingival crevice are persistently inhabited by communities of viruses. Contrary to past assumptions, most of these oral viruses are bacteriophages.

They infect the specific periopathogenic bacteria and thus could play a significant role in shaping oral bacterial community. (Fig. 2) This may establish association between specific virome and periodontal disease.

Many of the phages encountered at all oral sites are predicted to be:

- a. **Siphoviruses:** They generally have lysogenic lifestyles by integrating into their host genomes. Lysogenic oral viruses are highly persistent members of the human oral microbiome.
- b. **Myoviruses:** They are frequently isolated in subgingival crevice in subjects with periodontitis. They are lytic in nature. They possess increased virulence for their host bacteria which ultimately leads to local bacterial diversity in oral biofilm.

Interestingly, when periodontally diseased subjects were compared with healthy subjects, number of "bacterial hosts" was in abundance. It simply means due to abundance of bacterial hosts in periodontitis sites, viruses were able to infect them more easily and establish a co-infection when compared to periodontally healthy subjects. Thus according to the authors, presence of bacteria is a prime requirement for virus to initiate the disease.

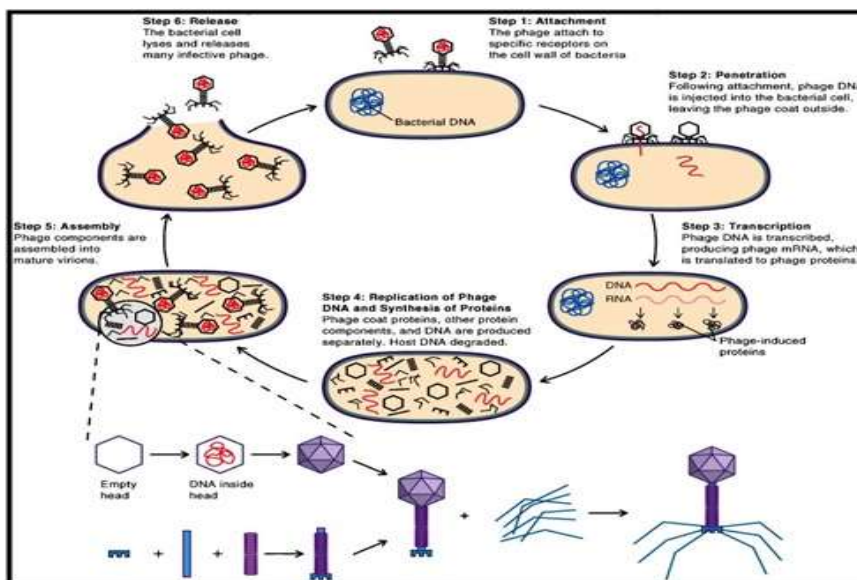


Fig. 2: Role of Bacteriophages in periodontal diseases

**Association of viruses in various periodontal infections**

**Gingivitis (Fig. 3):** Inconsistency in numbers; makes one impossible to conclude!

2. Human immunodeficiency virus (HIV)
3. Human T-lymphotropic virus type 1
4. Hepatitis B virus
5. Hepatitis C virus and
6. Torqueteno virus

Virus	Healthy	Gingivitis	Author (Year)
Herpes simplex virus- 1	0%	0%	Grenier et al. (2009)
	20%	53%	Imbronito et al. (2008)
Epstein-Barr Virus	23%	0%	Grenier et al. (2009)
	0%	20%	Imbronito et al. (2008)
	21%	20%	Wu et al. (2008)
Cytomegalovirus	8%	25%	Grenier et al. (2009)
	57%	40%	Imbronito et al. (2008)
	42%	49%	

Fig. 3: Association between gingivitis and viruses

**Chronic Periodontitis:** Jørgen Slots<sup>13</sup> in 2010 reviewed available data showing an association between chronic periodontitis and presence of various viruses. He reported a wide variation of viral load among the cases:

1. Herpes simplex virus in 13–100%,
2. Epstein–Barr virus in 3–89%
3. Cytomegalovirus in 3–83%

Fig. 4 can be a possible explanation to this wide range of viral load.

Additionally, author<sup>13</sup> also reported association between periodontal lesions and various other viruses such as:

1. Papilloma viruses

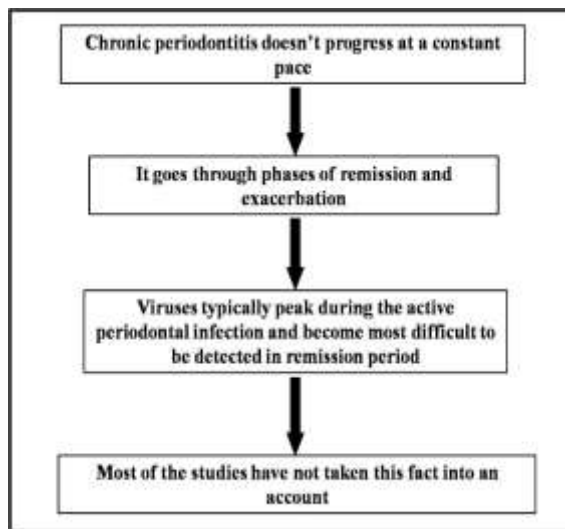


Fig. 4: Possible explanation for variation in viral among various studies

**Aggressive Periodontitis:** Ting et. al.<sup>14</sup> in 2000 hypothesized that primary cytomegalovirus infection at the time of root development of permanent incisors and first molars may affect the developing periodontium of these teeth resulting in cemental dysplasia. During puberty, latent HCMV virus is assumed to be reactivated due to hormonal changes. This may suppress antibacterial immune defenses leading to overgrowth of specific genotypes of *Aggregatibacter actinomycetemcomitans* at these sites. This ultimately results in attachment loss at these specific sites.

Teughels W et. al.<sup>15</sup> in 2007 has given possible explanation for this phenomenon:

1. *A. actinomycetemcomitans* has affinity for colonizing cytomegalovirus-infected epithelial cells.
2. Antiviral pro-inflammatory cytokine response to cytomegalovirus leads to periodontal tissue breakdown. This in turn allows gingival tissue invasion of *A. actinomycetemcomitans* leading to overall periodontal attachment and alveolar bone loss.

Alternatively, Michalowicz BS et. al.<sup>16</sup> in 2000 reported a synergistic role of cytomegalovirus and *Porphyromonas gingivalis* in development of localized aggressive periodontitis. The association established by an odds ratio:

1. Odds ratio of 6.6 for localized aggressive periodontitis and cytomegalovirus.
2. Odds ratio of 8.7 for localized aggressive periodontitis and *P. gingivalis*.
3. Odds ratio of 51.4 for co-infection of cytomegalovirus and *P. gingivalis* when compared with the odds of harboring neither of the two infectious agents

**Periodontal abscess:** The periodontal abscess is characterized by the localized accumulation of pus in periodontal apparatus secondary to severe periodontal breakdown. Saygun I et. al.<sup>17</sup> in 2004 studied 18 periodontal abscesses and concluded that:

1. Epstein–Barr virus was detected in 72% of cases,
2. Cytomegalovirus in 67% of cases, and
3. Co-infection with the two viruses in 56% of cases

**Necrotizing ulcerative gingivitis and Periodontitis:** Necrotizing ulcerative gingivitis/periodontitis affects immunocompromised, malnourished and psychosocially stressed individuals. Collapsed immune status and environmental conditions like these are assumed to provide conducive environment for rapid proliferation of various viruses.

Contreras et al.<sup>18</sup> in 1997 showed a possible association. They studied necrotizing ulcerative gingivitis in non-HIV-infected malnourished population and reported presence of:

1. Herpes simplex virus in 23% of lesions,
2. Epstein–Barr virus in 27% of lesions and
3. Cytomegalovirus in 59% of lesions

**Human immunodeficiency virus-periodontal diseases:** HIV virus by itself seldom causes periodontal breakdown. However HIV-induced immunosuppression may re-activate various latent viruses leading to cascade of periodontal destruction.<sup>13</sup>

1. According to Conteras in 2001, cytomegalovirus is the most commonly found virus in HIV associated periodontitis. It was found in:
  - a. 81% of HIV-associated periodontitis lesions

- b. 50% of non-HIV-associated periodontitis lesions
2. Other viruses that are associated with HIV-induced periodontal infections:
  - a. HHV-8 (Mardirossian A. et. al. 2000)
  - b. EBV-1 (Grande SR et. al. 2008)
  - c. EBV-2 (Jørgen Slots 2010)

On the other hand, latent HIV virus lodged inside the periodontal apparatus gets reactivated by inflammatory mediators from periodontal infection. Increased production of TNF- $\alpha$  and buterate/butyric acid can reactivate latent HIV virus within periodontium and elsewhere in body. This reactivation aids in dissemination of activated virions in systemic circulation.

Additionally, Jørgen Slots<sup>13</sup> in 2010 reported a list of syndromes associated with both periodontal viruses and severe periodontitis.

Disease	Periodontal Viruses
Guillain-Barré syndrome	Cytomegalovirus
Kostmann syndrome	Epstein-Barr virus
Fanconi's anemia	Herpes simplex virus, Cytomegalovirus
Papillon-Lefèvre syndrome	Epstein-Barr virus, Cytomegalovirus
Down's syndrome	Herpes simplex virus, Epstein-Barr virus type I, Cytomegalovirus

There is endless data proving an 'association' between 'presence of virus' and 'periodontal disease'. But as the saying goes 'association doesn't necessarily prove causation'. Thus there is still a long way to go to prove viruses' active role in periodontal disease initiation and progression.

Dr. Craig S. Miller<sup>19</sup> in 2014 strongly expressed his views which are similar to the above statement. According to him most of the published data fail to contribute to Koch's postulate in establishing "virus" as a causative agent of periodontal disease.

They fall short in generating evidence for:

1. Presence of Epstein-Barr virus (EBV) or cytomegalovirus (CMV) in all cases of the disease (i.e., periodontal disease);
2. The pathogen was isolated from the diseased host and grown in pure culture;
3. The pathogen from the pure culture caused the disease when inoculated into a healthy, susceptible laboratory animal;
4. The pathogen was re-isolated from the new host and shown to be the same as the originally inoculated pathogen.

### Therapeutic implications

Saygun et al. reported that antimicrobial periodontal therapy can greatly reduce the herpes viral load in the periodontium, probably because of the reduction in gingival inflammatory cells on which periodontal herpes viruses depends on. Conventional periodontal mechanical debridement can also reduce the periodontal load of viruses. Anti-herpes virus chemotherapy can also decrease the salivary viral load. Chemotherapeutics are only effective against viruses in their lytic phase, but not against viruses in the latent phase.

### Conclusion

After much of deliberation and review of literature, important question arises is whether the virus–periodontitis association is etiologically based or is merely a by-product to gingival inflammation. Studies on viral etiology of periodontal diseases face difficulties in demonstrating cause and effect. Removal of viruses by specific antiviral medication or vaccines; leading to arrest, reversal or prevention of periodontitis can prove its causal relationship. For definitive answers, periodontal research needs to delve much further into their molecular level interactions.

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