

Herpes Viruses and Periodontal Disease – A Review

Yendluri Durga Bai¹, Aditi R², Prathypaty Santha Kumari³, Jyothsna M⁴

ABSTRACT

Periodontal disease which is the most prevalent of the microbial diseases among humans, is a complex inflammatory disease of the chronic type. Traditionally most of the research carried out to understand the microbiology of this disease has always focused on bacteria such as *Porphyromonas gingivalis*. In recent times, the herpes virus has been proposed to be involved with the pathogenesis of periodontitis. The bacterial etiology solely does not explain the various clinical aspects adequately. Herpes viruses have been linked positively in etiology of periodontitis. The present model of pathogenesis of periodontitis needs to be reconsidered considering viruses as a factor. The coinfection caused by both bacteria and viruses to some extent explains why some individuals are more affected by periodontitis than the others. In this review the role of herpes viruses in the development of chronic periodontitis has been discussed.

Keywords: Periodontitis, Herpes viruses

INTRODUCTION

Periodontitis is one of the most complex infectious diseases of the human body.¹ It is a disease attributable to multiple infectious agents and interconnects cellular and humoral immune responses and environmental factors.² The evolution of periodontal disease depends upon, periodontopathic properties such as virulence factors and anaerobiosis, local host immune responses that activate innate immune system cells which include killer cells, neutrophils, osteoclasts and humoral response via B-cells, oral cavity environmental changes such as smoking, diabetes and nutrition. Although, periodontal disease is based on infection caused by multiple infectious agents, different studies have shown that the host response factors such as inflammatory reaction and activation of the immune system are critical to the pathogenesis of periodontal diseases.³

The viruses are known to be immunosuppressive and facilitate establishment of subgingival pathogens and have been detected in the Gingival Crevicular Fluid (GCF). The viruses like inclusions have been identified in the gingival inflammatory cells from Localised Aggressive Periodontitis (LAP). They are known to infect the inflammatory cells of the periodontium. They are present more frequently in the diseased sites than in healthy sites.³ They are restricted intracellular agents which are metabolically and pathogenically inert outside the host cell. They depend on the lining cells for replication.² Thus reactivation of these viruses may initiate or accelerate periodontal tissue destruction by lytic activity against periodontal cells, immune mediated tissue destruction and immune suppression, which enhances the susceptibility of the host to bacterial attacks and increases the virulence of local pathogenic bacteria.⁴

Traditionally most of the research carried out to understand

the microbiology of this disease has always focused on putative bacteria such as *Porphyromonas gingivalis*, the herpes virus is suggested to play an intricate part in the pathogenesis of periodontitis because bacterial etiology alone does not explain various clinical aspects such as – the episodic pattern of progression of disease and rapid destruction of periodontium with minimal plaque; site specificity in periodontal disease.⁵ Since the 1990's, herpes viruses have been suggested to emerge as supposed pathogens in various types of periodontal diseases.⁶ Herpes viruses are the most important DNA viruses. The most distinctive feature of herpes virus infections is immune impairment.^{3,6}

PREVALENCE

Herpes viruses exist at a high prevalence in low- income countries than highly developed countries. The seroprevalence of herpes viruses in high-income countries reveals remarkable racial, educational and socio-economic discrepancies, starting at an early age and persisting into middle age.¹

STRUCTURE

The herpes name is derived from Greek word 'herpein' which means to creep. It is a member of family – Herpesviridae and has a 4 layered structure of the 'virion': envelope, tegument, capsid and genome.³ (Fig 1)

Envelope consists of lipids derived from host, proteins of viral origin and glycoproteins which stick out of the surface of the virus and act as a key to recognise the cell to be infected and invade it. The tegument is a protein layer between the envelope and capsid and consists of virally encoded proteins and enzymes involved in the initiation and replication. The capsid is a protein coat and is a doughnut shaped capsomere of about 100-200nm in diameter. The genome is a nucleic acid. It is double stranded DNA in herpes virus. The size of the genome is 120-250kbp. The cytomegalovirus has the largest genome.⁶ the nucleic acid with its capsid is referred to as the nucleocapsid which is icosahedral in herpes virus.³

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There are more than 130 herpes viruses in which 8 herpes viruses types are known to infect humans. They are Herpes Simplex Virus (HSV) 1 and 2, Human Herpes Virus (HHV) -6, 7 and 8, Epstein Barr Virus (EBV), Varicella Zoster Virus (VZV), Human Cytomegalovirus (HCMV).² Studies have demonstrated that HCMV and EBV occur with high frequency in actively progressing periodontal lesions and they seem to play an important role in the etiopathogenesis of human periodontitis.³

VIRAL MULTIPLICATION

Due to a lack of its own biosynthetic enzymes, virus depends on the synthetic machinery of the host cell for replication. The viral multiplication cycle is divided into six phases and the phases may sometimes overlap.⁶ (Fig 2)

ASSOCIATION BETWEEN HERPES VIRUSES AND PERIODONTAL DISEASE

Mahmoud YM Taha et al, in their mini review stated that many viruses including herpes viruses are present in periodontal pockets suggesting a role for the existing viruses in the progression of periodontal disease.⁴ Simona Grigoras et al, in their research article sustain the hypothesis that the clinical situation of certain severe periodontal infections depend on the specific presence of herpes viruses and pathogens.⁷ Ayako Kato et al, conducted a study in Japanese patients with chronic periodontitis and established for the first time that more EBV DNA is found deeper in the periodontal pockets of chronic periodontitis and the result suggested that DNA may serve as a pathogenic factor leading to chronic periodontitis among them.⁵

Gulden Eres et al, conducted a study in pregnant patients with gingivitis which indicates that pregnancy increases the risk of the presence of subgingival EBV in pregnant women by 3,647 times more than in non-pregnant women.⁸

PATHOGENESIS OF HERPES VIRUS ASSOCIATED PERIODONTAL DISEASE

Herpes viruses are very complex and more than 90% of the world's population is infected with these viruses. They usually occur in childhood via infected secretions such as saliva. Primary infection by reactivated under various conditions. The main cause of reactivation is immune suppression.⁹ Herpes virus may cause periodontal pathology either as a direct result of virus infection and replication or as a result of virally induced impairment of periodontal host defences.³

Herpes virus may exert pathogenic potential through at least 5 mechanisms operating alone or in combination.³

1. By direct cytopathic effects- Since fibroblasts, keratinocytes, endothelial cells, inflammatory cells such as neutrophils, lymphocytes, macrophages and bone cells are key constituents of inflamed periodontal tissue, herpes virus – induces cytopathic effects which may hamper tissue turnover and repair.³
2. By impairing cells involved in host defense, thereby predisposing to microbial superinfection. CMV and EBV-1 can infect and / or alter the functions of monocytes, macrophages and lymphocytes.³
3. By stimulating subgingival attachment and colonization

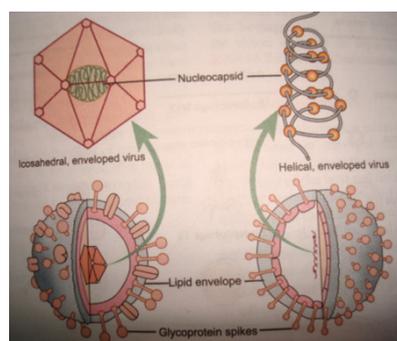


Figure-1: Structure of Herpes Virus

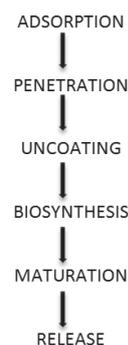


Figure-2: Viral Multiplication

of periodontopathic bacteria, viral proteins act as bacterial receptors and induce loss of virus damaged epithelial cells which can expose the basement membrane and the surface of regenerating cells leading to formation of new bacterial binding sites.³

4. By altering inflammatory mediator and cytokine responses. For example HCMV upregulates IL-11 β and TNF- α gene expression of monocytes and macrophages which increase the production of proinflammatory cytokines such as IL-11 β and TNF- α which in turn upregulates MMPs and down regulates TIMPs causing periodontal tissue destruction and disease.³
5. By inducing cell-mediated immunosuppression HCMV and HSV can induce cell mediated immunosuppression by reducing the cell surface expression of major histocompatibility complex class 1 molecules, thereby interfering with T-lymphocyte recognition.³

HCMV induces metabolic abnormalities in lymphocytes and monocytes and suppresses antigen – specific cytotoxic T- lymphocyte functions resulting in reduction in circulating CD4 cells and increase in CD8 cells leading to global impairment of cell mediated immunity. The active infection with certain herpes viruses, decreases the resistance of the periodontal tissues, thereby permitting subgingival overgrowth of periodontal pathogenic bacteria.³

The active infection with Herpes virus is associated with an increased risk of progressive periodontal disease as tissue breakdown is more frequently seen in Herpes infected periodontal sites than in herpes virus free sites.^{4,6,7} Herpes viruses are commonly found in the periodontal pockets and may establish or accelerate destruction of the periodontal tissues by lytic activity against periodontal cells, immune mediated tissue destruction and immune suppression which increases the sensitivity of the host to bacterial attacks and increases

virulence of local pathogenic bacteria.⁴ Transient immunosuppression is caused by Herpes virus reactivation in periodontal tissues which explains the episodic progressive nature of human periodontitis.³

The episodic progressive nature of the periodontal disease can be explained to an extent by the possibility that Cytomegalovirus infection impedes periodontal defences, and hence permits excessive periodontopathogenic bacteria. It can also be explained by the latent and active phases of infection.¹⁰ The localised pattern of destruction in many cases of periodontitis can be explained by tissue tropism of the herpes virus infection. Absence of periodontal herpes virus infection or reactivation could suggest the conditions where some individuals carry periodontopathic bacteria in their sub-gingival microbiota while maintaining periodontal health.³ The perception that periodontitis is a disease involving multiple factors such as herpes virus, bacteria and host reactivation may explain the reason for why aggressive periodontitis is relatively uncommon in majority population despite a high prevalence of individuals possessing both herpes viruses and bacterial pathogens.³

HERPES VIRAL–BACTERIAL INTERACTIONS IN PERIODONTAL DISEASE

The reciprocal action between herpes viruses and bacteria probably functions bi directionally with bacterial enzymes or other inflammation including factors having the potential to activate periodontal herpes viruses.(Fig.3)

Initially bacterial infection of the gingiva causes inflammatory cells such as periodontal macrophages with latent HSV and HCMV, T- Lymphocytes harbouring HCMV, B-Lymphocytes harboring EBV and HSV in GCF seem to originate mainly from local plasma cell synthesis rather mainly from passive transudation from serum, which indicates the presence of gingival Herpes viruses.⁶

Reactivation of Herpes from latency may occur-

- Spontaneously
- During periods of impaired host defence resulting from immunosuppression.
- Infection
- Physical trauma
- Hormonal changes

Herpes virus activating factors are also known risk factors for periodontal disease.⁶

PERIODONTOPATHIC PROPERTY

Herpes viral activation leads to increased inflammatory mediator responses in macrophages and connective tissue cells within the periodontal lesion. After reaching the critical virus load, activated macrophages and lymphocytes trigger a cytokine/ chemokine storm of IL-11 β , TNF- α , IL-6, prostaglandins interferons and multifunctional mediators, which have potential to propagate bone resorption.⁶

Herpes virus induced immune impairment allows sub gingival overgrowth of gram negative anaerobic bacteria which releases lipopolysaccharides together with HCMV, that can induce cytokine and chemokine release and may act synergistically in stimulating IL-11 β gene transcription.⁶

It is conceivable that herpes virus rely on coinfection with

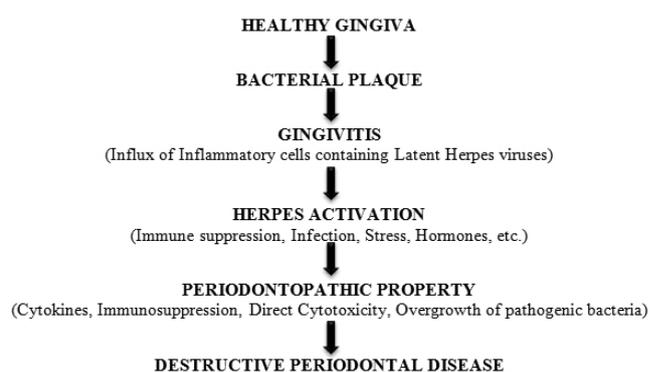


Figure-3: Herpes Viral Bacterial Model And Periodontitis

periodontal bacteria to produce periodontitis and conversely, periodontopathic bacteria may depend on the viral presence for the activation and progression of some types of periodontitis.⁶

VIRAL DIAGNOSTIC METHODS

Different diagnostic methods are available now to identify viruses in periodontitis. The presence of herpes virus in periodontium is also confirmed using flow cytometry, DNA probes and immunofluorescence staining. Other popular technique is Polymerase Chain Reaction (PCR), which is becoming the standard technique for detection and quantification of periodontal herpes virus. Several types of PCR methods are used like Nested PCR, real – time PCR and Multiple PCR. Studies reported that EBV and HCMV have been identified by Nested PCR, real-time and Reverse transcription PCR.¹¹

THERAPEUTIC IMPLICATIONS

Conventional approach for periodontal disease can reduce the herpes viruses load. Mechanical debridement has also showed suppression of subgingival EBV. The orally administered and intravenously administered acyclovir are used for a variety of herpes virus diseases. Studies are still being conducted to detect whether antiviral drugs are effective in the treatment of herpes virus or other viruses in periodontitis.¹¹

CONCLUSION

Herpes virus are positively linked in etiology of periodontitis. Current paradigm of pathogenesis of periodontitis needs to be revisited taking viruses into account. Viral bacterial coinfection pathogenesis of periodontitis partly explains why some individuals are more affected by periodontitis than others. Future treatment trends such as anti-herpes virus vaccines for periodontal disease can be developed.⁶

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