Review Article

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THE VIRUSES' AND PERIODONTITIS: AN ILLUSTRATIVE REVIEW

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ABSTRACT:

Periodontitis is a chronic infection which involves the active role of bacteria, fungi and viruses. No doubt the major etiological agents for gingivitis and periodontitis are bacteria only but to some extent, the role of viruses is equally important in the pathogenesis and progression of periodontitis, and other oral infections. Early diagnosis remains the key to success for the treatment therapy which relies upon PCR sequencing, Immunofluorescence and use of DNA probes. Since there are a lot of chances of recurrence, therefore, the ultimate aim of treatment therapy is to completely eliminate the viral infection besides controlling the bacterial infection, too. In this review, the major viruses which are responsible for causing periodontitis have been highlighted to aware clinicians about their active role in periodontal infections.

Key words: Chronic Periodontitis, cytopathic, antiviral, Mechanical debridement.

INTRODUCTION:

The human mouth harbours millions of highly diverse microbial organisms which includes bacteria, viruses, fungi and protozoa that are responsible for causing a variety of oral and systemic infections.[1]Among the oral infections, Periodontitis is the most common microbial infection that is readily observed in almost all the individuals.[2] It's progression begins at slower to moderate pace characterized by intermittent periods of rapid periodontal destruction that however, may affect either a few teeth or could involve a bilaterally symmetrical pattern involving the entire dentition (with presence of minimal plaque deposits).[3] It is established that bacteria are largely responsible for causing periodontal infections as revealed by the latest findings but they are not the sole agents.[4] It could be assumed that periodontitis debuts in genetically or environmentally predisposed individuals, who are infected with virulent infectious agents and those revealing persistent gingival inflammation and distinct immune responses. In support of this hypothesis, several studies have documented a role for viruses in the development and progression of periodontitis and other oral infections.[3-5] The role of Human cytomegalovirus (HCMV), Epstein – Barr virus (EBV) and Herpes simplex viruses (HSV-1 and HSV-2) has been revealed in the periodontitis diseases while human papillomavirus, HIV and hepatitis C virus ,too, have been linked with periodontal disease.[1,3] However, their role in periodontal

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disease is neither fully understood nor has been documented. In this review, focus has been made on the various pathogenic viruses and their active role in periodontal infections.

VIRUSES-THEIR NATURE AND CLASSIFICATION

Viruses are considered as restricted intracellular agents, which are both metabolically and pathogenically inert outside the host cells. [6-7] Perhaps, they are totally dependent upon the living cells for survival and have utilized certain immunological principles for carrying out invasion and pathogenesis. They can be broadly classified (according to genomes) into two types : extracellular virion particles and intracellular genomes. On the basis of the replication material, they can be classified as either DNA or RNA viruses.[10] Virions are known to possess better ability for bearing physical stress than genomes, but , are comparatively more susceptible to humoral immune control. They are known to survive in host cells by limiting the gene expression and in terms of this process, they are able to develop certain strategies like development of immune-regulatory proteins with homolog sequencing cellular genes.[8] These have been named as "stolen" genes . With regard to size of genome, RNA viruses are a bit advantageous in comparison to DNA viruses as the former have smaller size than latter that has the advantage of providing mutation. [6,8] The mutation acts as a protective guard from host's immune system. Earlier the role of bacteria and fungi was considered important in periodontal disease but in the past two decades , viruses have emerged as important pathogens (figure-1).[4]

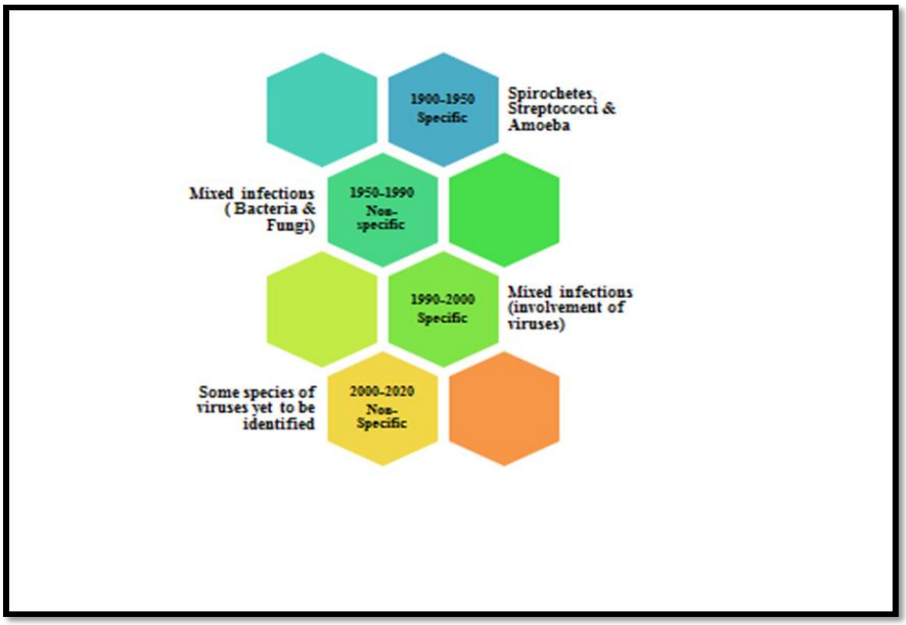

Fig.-1. Showing the involvement of bacteria, fungi and viruses in periodontitis (source-Parashar et al, 2015).

ROLE OF VIRUSES IN PERIODONTAL DISEASE

Viruses can cause severe, acute oral and oro-facial diseases, producing oral signs of systemic infection and have the potential to be transmitted to the patients and dental staff. As mentioned earlier, certain studies have supported the active involvement of viruses in progression of periodontal infections.[5,9,11] The effects of viruses can be broadly classified as direct and indirect. Direct effects are related to local expression of viral infection while indirect effect refers to secondary involvement owing to systemic infections.[4,7]

Table 1- **Studies supporting the role of viruses in periodontal infections**

Periodontal disease	Conclusion	Reference
27 patients suffering from chronic periodontitis.	1. High prevalence of HCMV (59%), EBV-1 (37%), EBV-2 (22%), HSV (26%), HIV (4%) in periodontitis sites was found as compared to HCMV (18%), EBV-1 (22%), EBV-2 (18%), HSV (7%) and HIV (0%) in gingivitis sites.	Contreras and Slots (1996) .[14]
Periodontitis (Clinical attachment loss) in HIV infected population (Senegal) who did not received antiviral or antimicrobial therapy.	It was found that the number of subjects with sites of 6 mm of attachment loss were significantly higher in HIV infected groups as compared to HIV-non-infected groups.	Ndiaye et al (1997). [9]
30 patients with advanced periodontitis and 26 patients with gingivitis.	HCMV was detected in 60% of periodontitis patients while in gingivitis group, it was observed in only 31% of patients. Among the periodontitis cases, the following viruses were detected: EBV (30%), HSV(20%), HPV(17%) & HIV (2%).They were not detected in gingivitis group.	Para and Slots (1999).[10]
Periodontitis lesions in Down syndrome patients.	Presence of HHV (26% of study lesions), EBV (37%) and CMV (37%) was found.	Hanookai et al (2000). [9]
16 subjects with juvenile periodontitis.	HCMV exhibited close association with *P. gingivalis* while EBV-CMV co-infection showed, *P. gingivalis* & *D. pneumosintes* dual infection which later, revealed bleeding on probing.	Kamma et al (2001).[9]
Gingival recession in a 26 year old patient.	HSV-1 causing gingival recession which was associated with sudden onset, pain and disappearance after antiviral	Pini-Prato et al (2002).[13]

	therapy.	
Periodontitis in 11 cases and 10 healthy subjects.	Presence of TTV (a new DNA virus) isolated from Japanese subjects which was associated with periodontitis cases	Rotundo et al (2004). [9]
37 year old patient of localized aggressive periodontitis (who was also suffering from Guillain-Barre syndrome).	Presence of Cytomegalovirus which was responsible for development of localized periodontitis.	Tabanella & Nowzari (2005).[19]
3 and 6 years old siblings suffering from severe gingivitis & periodontitis (Presence of Kostmann syndrome also).	Supra-gingival plaque demonstrated high counts of Epstein– Barr virus.	Yilidrim et al (2006).[9]
Chronic and aggressive periodontitis patients.	100 % association of herpes virus in chronic periodontitis was found as compared to 57% in aggressive periodontitis patients.	Billichodmath et al (2009).[11]
Chronic periodontitis cases.	Strong association between P. gingivalis, T. forsythia, EBV-1, CMV and chronic periodontitis was found.	Chalabi et al (2010).[12]

DIRECT ROLE IN PERIODONTAL DISEASE

Viruses like Herpes simplex ,Cytomegalo virus and Varicella-zoster are responsible for causing direct effects on the oral cavity. Their role in progression of periodontal infections have been shown in following lines.

Herpes virus : Herpes viruses are composed of three main groups: (1) Alpha herpes virinae (herpes simplex virus group, consisting of herpes simplex virus [HSV] 1 and 2 and Varicella zoster virus [VZV]), (2) Beta herpes virinae (cytomegalovirus group, consisting of human cytomegalovirus [HCMV] and human herpes viruses 6 and 7), and (3) Gamma- herpes virinae (lymphoproliferative group consisting of Epstein-Barr virus [EBV] and human herpes virus 8 or Kaposi's sarcoma-associated herpes virus). [17]

Herpes Simplex: Herpes simplex virus is of two types: HSV-1 and HSV-2. They are causative agents of skin and mucous membrane infections. Herpes simplex virus-1 infections occur in the oral cavity while HSV-2 infections affect the genital area. But, they can cause infections in either area or at any other site in the body. There is a direct cytopathic effect on inflammatory cells (poly-morphonuclear leukocytes, lymphocytes, macrophages etc.) and other cells such as fibroblasts, endothelial cells and bone cells. The induction of Herpes virus cause

cytopathic effects which debilitate tissue turnover and repair.[7,8]

These viruses can be easily carried in body fluids or in fluid from herpes lesions.[3,5] The association of HSV-1 & HSV-2 has been found in Chronic periodontitis (57 %- Bilichodmath et al, 2009 & 17 %- Saygun et al, 2004) & Aggressive periodontitis (100 & 16 %- Bilichodmath et al, 2009).[11,12,15]

Varicella zoster virus: The vesicular stomatitis virus or human herpes virus-3 (HHV-3) is known to cause Chicken pox, which is the primary infection of VZV.[16] It is followed by latent period. After that, there can be recurrence which clinically manifests as herpes zoster. Association of varicella zoster has been linked with apical periodontitis and irreversible pulpitis (**Sigurdsson et al, 1995)**.[17]

HHV-8 virus: It is popularly known as Kaposi sarcoma virus since it is believed to have a significant role in the induction and/or maintenance of Kaposi's sarcoma. Occurrence of this virus in oral lesions could be attributed to the immunodeficiency state **(Hanookai et al, 2008-26 %).**[2,9] A flow chart has been depicted showing factors and effects of Kaposi' sarcoma virus (Fig-2).

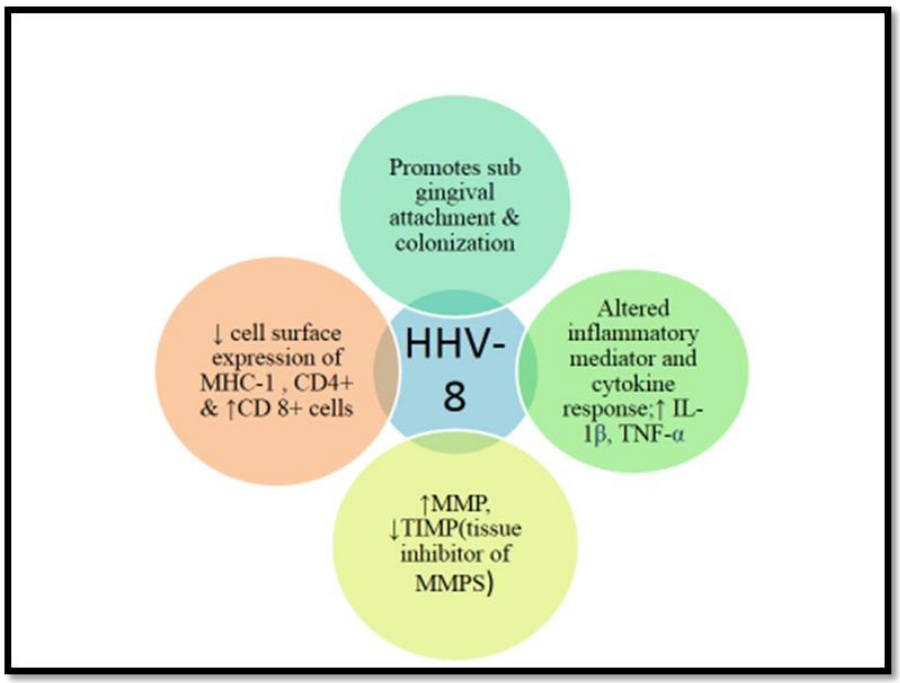

Fig 2: Impairment of immune system by HHV-8

Cyto megalo virus infection

Cytomegalovirus or HHV-5 is a kind of herpes virus that affects many people at some or the other time. Even in Infancy, the virus tends to infect the human body by entering through the placenta, during delivery or through breast feeding. It is followed by transmission which occurs

during adolescence by various means like sexual activity, blood transfusion and organ transplantation.

Patients with weakened immune system are prone to develop secondary infections through this virus (Hanokai et al, 2008; Chalabi et al, 2010). [9,12] There is a direct involvement of Cytokines which are polypeptide products of cell types that function as mediators of inflammation and immune response.[16]

The major cytokines in acute inflammation are TNF, IL-1, IL-6, and a group of chemoattractant cytokines called chemokines. Even, chemokines are actively involved in viral pathogenesis. Bacteria like *A.actinomycetemcomitans* are able to progress in this viral infection.

This mechanism of reactivation of viruses during the root development and up -regulation of inflammatory mediators suppressing the immune response of host is depicted in following figure (Fig.3).[18]

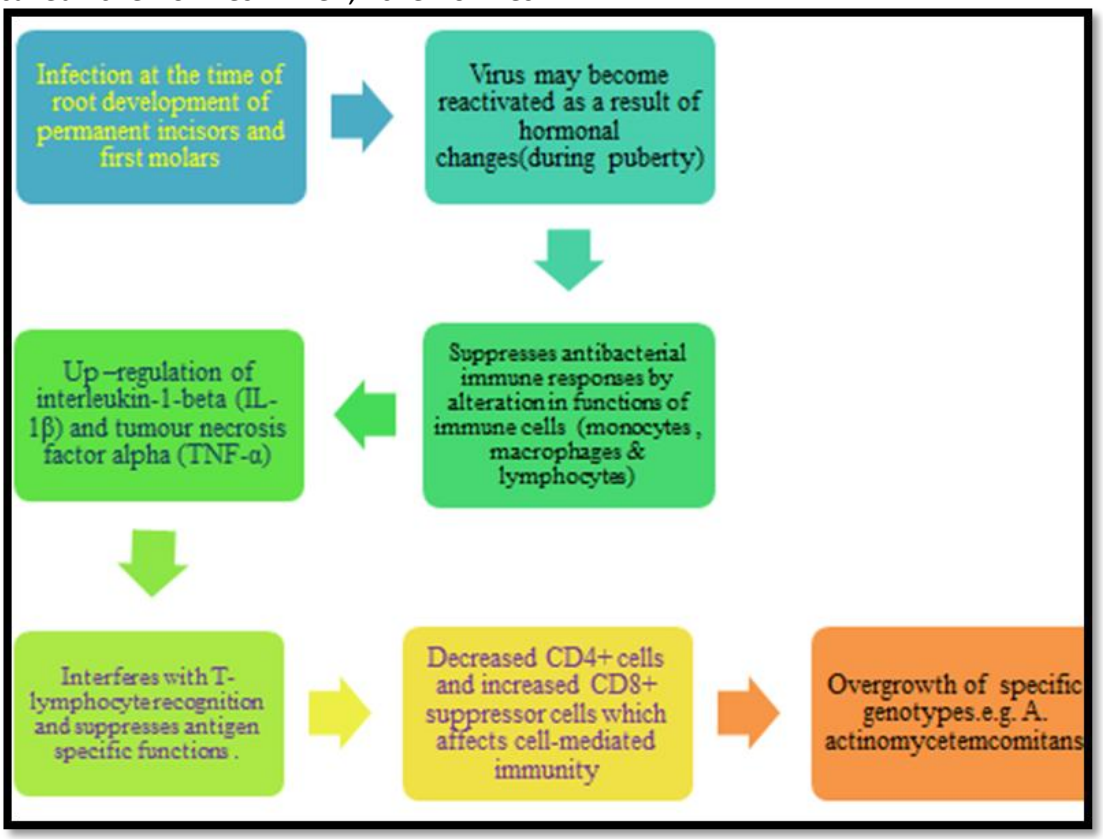

Fig 3: Proposed mechanism for the pathogenesis of HCMV (Source-Ting et al 2000)

- As proposed by **Ting et al (2000),** HCMV causes up -regulation of inflammatory mediators like TNF-α and Interleukin-1β which causes

suppression of immune responses of individuals and cause dreadful diseases like Chronic and aggressive periodontitis.[18]

- HCMV could be responsible for inducing cell-mediated immunosuppression by interfering with cytotoxic T-lymphocyte recognition through the down-regulation of cell surface expression of major histocompatibility complex class I molecules.[3] It is followed by interference with the major histocompatibility class II antigens , thereby, inhibiting natural killer cell activity.

EBV or Ebstein-barr virus infection- it is a causative agent of kissing's disease and nasopharyngeal carcinoma. It is associated with irreversible pulpitis and apical periodontitis.[17] EBV is familiar with infecting periodontal B-lymphocytes in periodontitis lesions (Contreras & Slots, 1997;Li et al,2008). [8,14,17] EBV infection results in down regulation of above mentioned immune cells which could be responsible for causing bacterial super-infection which results in increased virulence of resident bacteria EBV may induce proliferation of cytotoxic T lymphocytes whose main purpose is recognition and destruction of virally infected cells.

Indirect role in periodontal disease

Indirect role refers to secondary infections occurring which manifests at a very later stage in the form of oral infections. It means directly that there are no oral signs or symptoms but after primary systemic infections, oral lesions that begin to start. A classic example is HIV or human-immuno-deficiency virus infection.

Human immunodeficiency virus:

HIV infection spreads frequently by sexual contact, parenteral exposure to blood or mother to child transmission. Four forms of HIV-associated periodontal / oral diseases have been described: Linear gingival erythema, necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and necrotizing stomatitis.[1] It tends to affect $CD4^+$ helper T cells. A decrease in T helper cell count causes loss in immunity which predisposes the individual to a number of opportunistic infections including periodontal diseases and oral diseases (Ndaiye et al,1997; Para and Slots, 1999).[1,10,16]

Diagnosis : Virus diagnosis is a challenging task in periodontal cases. Culturing of virus as *in vitro* (cell lines) or *in vivo* (animal) model was considered as gold standard but still it is a time consuming procedure. Rapid diagnosis of virus is essential for effective treatment which is possible by application of molecular techniques like PCR, RT-PCR, Real time RT-PCR and sequencing.[2,4,19] However, PCR Technique has a drawback that it can detect only those viruses for which it is designed to detect. [3,7] DNA microarrays are also useful to detect simultaneously HHV, EBV and CMV (Fig.-4). It relies upon real-time PCR

techniques to quantify simultaneously the number of genome-copies .Even DNA probes, Flow cytometry and immunofluorescence staining are extensive techniques which can be used along with other diagnostic tools. [20] Still, there is a vast array of viruses in human oral cavity which are yet to be identified.

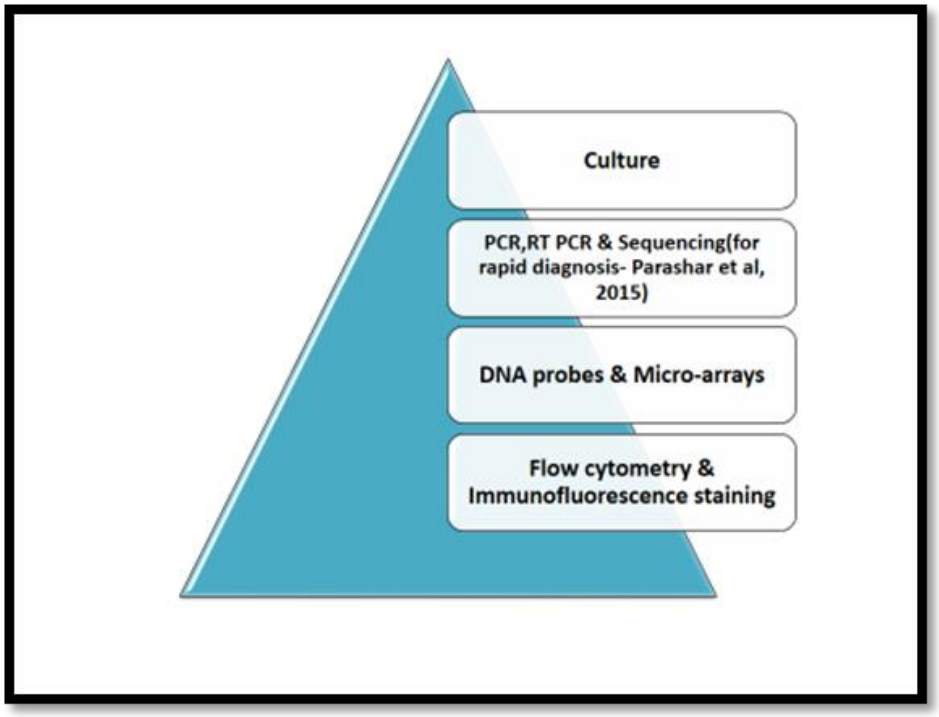

Fig.4-Showing diagnostic methods for viruses

THERAPEUTIC IMPLICATIONS AND FUTURE SCOPE OF VACCINES- Conventional periodontal therapy could probably reduce the periodontal load of herpes viruses and it has been shown that mechanical debridement could be useful to suppress sub-gingival presence of EBV.[3] Repeated debridement in periodontitis patients showed absence of CMV but there was presence of small amounts of EBV and Herpes virus suggesting that CMV is particularly vulnerable towards periodontal therapy.[2] Hence, development of herpes virus vaccines offers a new therapeutic modality for the treatment of periodontitis (Fig.-5). It would be a good alternative for current periodontal therapeutic methods (including surgery & antibiotic therapy) and might reduce the effective cost of conventional periodontal therapy.[21,22]

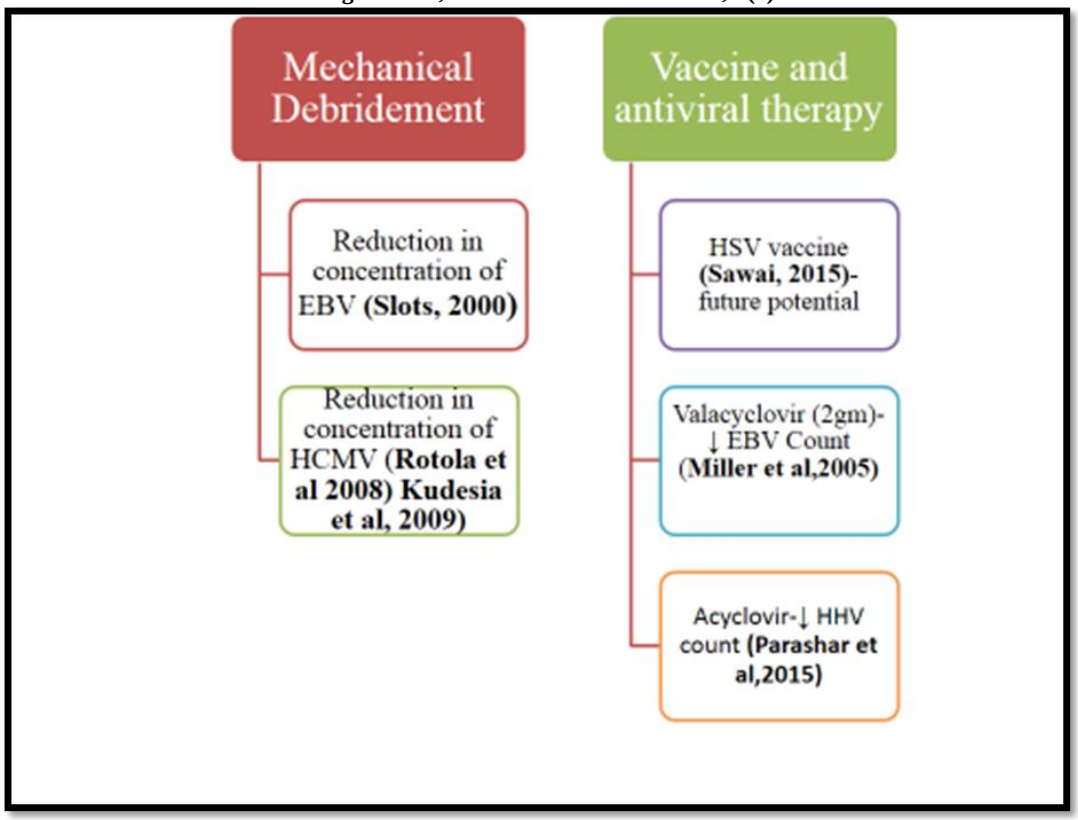

Fig 5:Mechanical debridement and antiviral therapy (along with vaccines) may be useful in the management of periodontal load of viruses.

CONCLUSION

Periodontal infections are complex in nature which involve active role of a variety of microbes. It appears that a presence of active Epstein–Barr virus or cytomegalovirus is significantly associated with aggressive periodontitis while latent herpes virus infections are preferentially found to inhabit the chronic periodontitis and gingivitis sites. Besides these, Papilloma viruses and other mammalian viruses are also known to be involved in aetiology of periodontal lesions, but the mechanism of pathogenesis still remains a daunting task for clinicians.

Hence, the current paradigm of the pathogenesis of periodontitis needs to be revisited and explored as far as the concept of viral–bacterial co-infection is concerned. The existing information has tried to stress upon the complex mechanisms and synergistic approaches of viruses and has justified their role as the contributory agents in pathogenesis of periodontal diseases. It is, therefore, expected that further studies in this context may be planned for future benefits and early diagnosis.

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