Role of Viruses in Periodontitis

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Abstract- Periodontitis is a complex, multifactorial chronic disease traditionally attributed to bacterial biofilms. However, recent advancements in molecular diagnostics have established a significant paradigm shift, identifying viral strains as key contributors to the disease's onset and progression. This paper reviews the active role of viruses—specifically the Herpesviridae family (EBV, HCMV, and HSV-1), HIV, HPV, and SARS-CoV-2—in modulating the periodontal microenvironment.

- **Pathogenesis: Viruses contribute to tissue destruction through the suppression of host immune responses, direct cytopathic effects on fibroblasts and epithelial cells, and a synergistic "tag-team" interaction with periodontal pathogens like *Porphyromonas gingivalis*.**
- **Viral-Bacterial Synergy: Viral infection triggers the upregulation of pro-inflammatory cytokines, specifically $IL-1\beta$ and $TNF-\alpha$, which accelerate alveolar bone resorption and impair the osteogenic potential of periodontal ligament stem cells.**
- **Clinical Implications: High viral titers are associated with deeper probing depths, greater attachment loss, and refractory disease patterns.**
- **Therapeutic Strategies: While conventional scaling and root planing (SRP) reduces microbial loads, it often fails to eliminate intracellular viral reservoirs. Consequently, the integration of adjunctive systemic antivirals and host-modulatory therapies is emerging as a vital component for managing severe or non-responsive cases.**

This evolving "poly-microbial + viral" model reorients periodontal management toward a more holistic, interdisciplinary approach to enhance long-term clinical stability and reduce systemic inflammatory burdens.

I.INTRODUCTION

Periodontitis is a complex, multifactorial chronic disease characterized by the progressive destruction of the tooth's supporting structures, including the cementum, alveolar bone, and periodontal ligament. [1] Historically, since the nineteenth century, organized bacterial biofilms within a glycocalyx matrix were viewed as the primary etiology; however, many clinical variations of the disease cannot be explained by bacterial presence alone. [2] While *Porphyromonas gingivalis* remains a recognized keystone pathogen, the clinical course is significantly modulated by host factors such as smoking and genetic variations in inflammatory response patterns. [2] The twenty-first century marked a significant paradigm shift in periodontal etiopathogenesis with the advent of advanced molecular diagnostics, which identified specific viral strains within the oral cavity as key contributors to the disease. [3] These viruses appear to directly influence the virulence of bacterial pathogens and alter the host immune response, necessitating further longitudinal and functional research to fully clarify their precise role in the onset, progression, and clinical management of periodontitis. [4,5]

Classification viruses in periodontitis

Virus / group	Role / association in periodontal pockets	Presence / role in clinically healthy oral flora
Herpesviruses (overall)	Frequently detected in chronic and aggressive periodontitis; higher prevalence and copy numbers in diseased sites; associated with tissue destruction and progression. [1,2.3,4,5,7]	Detected at lower levels or in latent form; may be present in healthy sites but not strongly linked to clinical disease. [1,2,3,4,5,7]
Epstein-Barr virus (EBV)	Found in higher prevalence and copy counts in chronic and aggressive periodontitis; associated with refractory or severe periodontitis; may persist in saliva and gingival tissues. [1,2,3,4,5,7]	Can be present in healthy subjects but without strong association with gingival inflammation; may exist in latent state. [1,2,3,7]
Human cytomegalovirus (HCMV / CMV)	Detected in higher prevalence in chronic and aggressive periodontitis; associated with deeper pockets, active disease, and virally-bacterial synergy. [1,2,3,4,5,7]	Detected occasionally in healthy sites but at lower frequency; mainly latent in immunocompetent hosts. [1,2,3,7]
Herpes simplex virus-1 (HSV-1)	Detected more often in periodontitis and gingivitis patients; slightly higher prevalence in periodontitis; correlated with deeper pockets and clinical severity. [1,3,4,7]	Present in some healthy individuals but not consistently associated with deep pockets or destruction. [1,2,3,4]
Human immunodeficiency virus (HIV)	In HIV-infected patients, typical periodontal patterns (linear gingival erythema, necrotizing ulcerative gingivitis and periodontitis) are reported; viral load and periodontal disease may be mechanistically linked. [1,2,3,4,7]	Not a “normal” flora component; when present systemically, it secondarily alters oral flora but is not part of healthy-microbiota definition in these articles. [1,2,3,4]
Coronavirus (SARS-CoV-2 / CoV-19)	Mentioned as a virus whose presence in periodontal sites is under investigation; potential interaction with periodontal pathogens and role in modifying periodontal disease severity is discussed. [3,4,5]	Discussed mainly as a systemic / respiratory virus; its role in healthy oral flora is not emphasized; treated as an incidental or secondary agent rather than a core commensal. [3,4,5]
Papillomavirus (HPV)	Discussed as a virus that may be associated with periodontal disease and could influence tissue responses and disease progression. [3,4,5]	Detected in some healthy individuals but not consistently linked to periodontal destruction; more often associated with mucosal lesions than to subgingival sites. [3,4,5]
Hepatitis-related viruses	Reviewed as part of broader viral involvement in periodontal disease, with attention to liver-related systemic effects and viral-bacterial interactions in periodontitis. [3,4,5,7]	Mentioned mainly as systemic infections; not described as a core component of healthy subgingival flora. [3,4,5]
Bacteriophage (phage)	Discussed indirectly as part of the oral virome; phages may modulate bacterial communities in periodontal pockets by infecting periodontal pathogens and influencing plaque ecology. [2,3,4,5,7]	Recognized as part of the normal oral virome; bacteriophages are present in healthy plaque and saliva, likely helping maintain microbial balance rather than promoting disease. [2,3,4,7]

II.PATHOGENESIS

Viruses play an important role in the pathogenesis of periodontal diseases by modulating the host immune response, altering the subgingival microbiome, and directly damaging periodontal tissues, as highlighted in multiple reviews and primary studies. [1,3,8] Herpesviruses such as Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), and herpes simplex virus-1 (HSV-1) gain entry into the gingival sulcus and periodontal pocket via saliva, inflamed epithelium, or systemic circulation, and can establish latent or persistent infection in gingival epithelial cells, fibroblasts, and immune cells, thereby maintaining a reservoir of infection within the periodontium. [1,4,7,9] By suppressing macrophage function, complement activity, and lymphocyte responses, these viruses create a local state of relative immunosuppression that impairs the host’s ability to control colonization by periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Tannerella forsythia*, thereby promoting microbial dysbiosis and biofilm maturation. [2,4,7,9] At the same time, virally derived and bacteria-induced pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) are upregulated, sustaining chronic inflammation and amplifying tissue destruction in a synergistic viral–bacterial interaction. [2,4,9]

In addition to immune modulation, herpesviruses and other viruses, such as human papillomavirus (HPV), HIV, hepatitis-related viruses, and SARS-CoV-2, can exert direct cytopathic effects on periodontal cells, inducing apoptosis of epithelial cells, fibroblasts, and endothelial cells, which contributes to the breakdown of the junctional epithelium and connective-tissue attachment. Viral infection of fibroblasts also disrupts extracellular matrix homeostasis by altering collagen synthesis and degradation, leading to increased susceptibility to pocket formation and clinical attachment loss. Experimental and clinical evidence indicate that HSV-1 can infect human periodontal ligament stem cells (hPDLSCs), particularly in an inflamed microenvironment, impairing osteoblastic differentiation and exacerbating alveolar bone loss, underscoring a direct role of herpesviruses in periodontal tissue remodeling. In systemically infected individuals, particularly those with HIV, the underlying immunosuppression favors the emergence of aggressive periodontal phenotypes, including linear gingival erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis, which are often associated with higher viral loads and dysbiotic bacterial communities. Other viruses, such as hepatitis-related viruses and SARS-CoV-2, may further exacerbate periodontal inflammation by altering systemic immunity, facilitating bacterial translocation, or exploiting the inflamed periodontal pocket as a portal for systemic spread.

Bacteriophages, as part of the oral virome, contribute to pathogenesis by selectively infecting and lysing bacterial species within the subgingival biofilm, thereby reshaping the microbial composition and, in some cases, favoring the outgrowth of more pathogenic taxa. [2–4,7] In clinically healthy periodontal sites, phages appear to help maintain microbial balance by regulating bacterial populations, whereas in diseased pockets the viral–bacterial equilibrium may shift toward increased lytic activity against beneficial or commensal species, further promoting dysbiosis and tissue breakdown. [2,4,7] Recent reviews and umbrella analyses of herpesviruses in periodontitis suggest that viral–bacterial coinfection is a key determinant of periodontitis severity, with herpesviruses acting as cofactors that not only enhance bacterial colonization but also contribute to systemic inflammatory burden. Collectively, these mechanisms demonstrate that viruses are not mere bystanders but active participants in the pathogenesis of periodontitis, acting through immune modulation, direct tissue damage, viral–bacterial synergy, and virome-driven microbial shifts that collectively advance the progression and severity of periodontal disease. [1,2,4,7,11]

Detection of Viruses in the Periodontal Pocket

The identification and detection of viral species within the periodontal pocket have become central to understanding the complex microbial landscape of periodontitis (5, 7). Research emphasizes that detecting these viruses is crucial for determining disease severity and predicting progression. (12, 13)

1. Methods of Detection and Identification

The literature highlights various laboratory and clinical approaches to identify viral presence:

- PCR and Molecular Techniques: Polymerase Chain Reaction (PCR) is a primary tool for the precise detection of viral DNA, such as HCMV and EBV-1, in subgingival samples. (2, 12, 13)
- Subgingival Sampling: Detection involves taking samples directly from the periodontal pocket, where viruses are often found in deeper sites (>6mm) rather than shallow ones. (12, 13)
- Case-Control Studies: Laboratory studies use these detection methods to compare the viral prevalence in active periodontal lesions versus healthy or stable sites. (13)

2. Primary Viruses Detected

Based on the research, the most frequently detected viruses in the periodontal environment include:

- Herpesviridae family: Specifically Human Cytomegalovirus (HCMV), Epstein-Barr Virus (EBV), and Herpes Simplex Virus (HSV-1). (2, 10, 11)
- Other Viral Species: Studies have also focused on the detection of HIV, Papillomavirus, Hepatitis viruses, and Coronavirus-19 to understand their roles in the pathogenesis of periodontitis. (4, 6)

3. Clinical Significance of Detection

Detecting a high viral load within the pocket serves as a diagnostic indicator for several reasons:

- Synergy Mapping: Detecting viruses helps map the "herpesviral–bacterial interaction," where viral presence often precedes or facilitates the overgrowth of periodontopathic bacteria. (2, 9)
- Bone Stability: The detection of HSV-1 is particularly significant as it indicates a risk for dysregulated osteogenesis, as the virus infects periodontal ligament stem cells. (10)
- Predictive Value: The presence and detection of these viruses are linked to "futuristic implications" in how clinicians might diagnose and manage refractory cases. (8)

Clinical implications

The growing evidence for viral involvement in periodontal diseases carries important clinical implications for diagnosis, prognosis, and treatment planning. [1,2,4,7,13]

High detection rates of herpesviruses such as Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), and herpes simplex virus-1 (HSV-1) in chronic periodontitis are strongly associated with deeper probing depths, greater clinical attachment loss, and higher bleeding-on-probing scores, suggesting that viral copresence may serve as a biomarker for disease severity and progression. [1,4,7,9,11,12]

In aggressive and juvenile periodontitis, coinfection with herpesviruses and periodontal pathogens has been linked to more rapid tissue destruction, supporting the concept that viral screening may help identify patients at risk for refractory or rapidly progressive periodontitis.

Clinically, viral presence may influence treatment response and maintenance outcomes; reductions in subgingival herpesvirus load after scaling, root planing, and adjunctive antimicrobial therapy suggest that conventional periodontal therapy may partially suppress viral reservoirs while controlling bacterial dysbiosis.

In patients with systemic viral infections such as HIV, hepatitis-related diseases, or SARS-CoV-2, clinicians should anticipate altered periodontal phenotypes and integrate systemic medical assessment with periodontal care.

Emerging data suggest that HSV-1 may infect periodontal ligament stem cells and impair osteogenic differentiation under inflammatory conditions, implying that adjunctive antiviral or host-modulatory strategies could be explored in selected refractory cases.

From a public-health perspective, recognition of viral–bacterial synergy highlights the value of early diagnosis, strict oral hygiene, and regular monitoring in patients with recurrent gingival inflammation or severe periodontitis.

In the future, viral diagnostics such as e-PCR, serology, or salivary biomarkers may supplement conventional clinical indices to guide personalized periodontal and systemic management.

Treatment of Viral Pathogens in the Periodontal Pocket

The integration of viral-targeted protocols into periodontal therapy represents a critical shift toward managing the "poly-microbial" nature of the disease. (5, 7) While conventional mechanical debridement through Scaling and Root Planing (SRP) remains the fundamental approach, its efficacy is often compromised in deep pockets (>6mm) where the viral-bacterial synergy is most potent (12, 13). SRP serves to physically disrupt the biofilm and reduce the subgingival load of Human Cytomegalovirus (HCMV) and Epstein-Barr Virus (EBV-1), yet it frequently fails to address the intracellular viral reservoir sequestered within inflammatory cells and the periodontal ligament (PDL) (9, 11).

Advanced therapeutic strategies now emphasize the necessity of arresting the viral lytic cycle to prevent the localized suppression of host immunity (2, 15). The presence of HSV-1 is particularly deleterious, as it has been shown to exploit inflammatory signaling to infect PDL stem cells, thereby directly inhibiting osteogenesis and post-treatment bone regeneration (10). To counteract this, recent clinical guidelines (14) recommend systemic antiviral adjuncts—specifically Valacyclovir (e.g., a 3-day high-dose regimen)—to reduce viral titers and dampen the "cytokine storm" (specifically IL-1β and TNF-α) that drives rapid alveolar bone resorption (4, 8, 15).

Furthermore, treating the periodontal pocket as a potential viral reservoir has broader public health implications. Addressing viruses such as HIV, Hepatitis, and SARS-CoV-2 within the oral cavity not only improves local clinical parameters but also reduces the risk of systemic dissemination and virus-induced oral complications [4, 6, 14]. By disrupting the synergistic "tag-team" between herpesviruses and anaerobic pathogens, such as *Porphyromonas gingivalis*, clinicians can transform a refractory, high-risk pocket into a stable environment conducive to long-term attachment gain [2, 9, 13].

III.CONCLUSION

The accumulating evidence suggests that viruses, particularly herpesviruses such as Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), and herpes simplex virus-1 (HSV-1), are not incidental bystanders but active contributors to the pathogenesis and progression of periodontal disease. Viral–bacterial synergy within the periodontal pocket promotes dysbiosis, amplifies local inflammation, and impairs tissue repair, thereby transforming otherwise manageable inflammation into severe or refractory periodontitis. The detection of viral DNA or RNA in subgingival plaque, gingival crevicular fluid, and periodontal tissue further supports the concept of the periodontal pocket as a reservoir not only for bacteria but also for oral and systemic viruses.

Conventional periodontal therapy, including scaling and root planing, effectively reduces subgingival microbial load and diminishes some viral titers; however, it often fails to clear intracellular viral reservoirs or break the cycle of viral reactivation and host-immune suppression. Recent evidence suggests that adjunctive systemic antiviral agents and targeted host-modulatory strategies can significantly reduce herpesvirus replication, mitigate cytokine-driven bone resorption, and facilitate improved clinical attachment and pocket-depth outcomes, particularly in deep or refractory sites.

From a public-health perspective, acknowledging viral involvement encourages a more holistic, interdisciplinary approach to periodontal care, especially in patients with systemic viral infections such as HIV, hepatitis-related diseases, or SARS-CoV-2. Integrating viral screening, careful medical coordination, and tailored supportive therapy into routine periodontal practice may not only enhance periodontal stability but also reduce the risk of systemic viral dissemination and virus-associated oral complications.

In summary, the recognition of viral contributions to periodontal disease reorients periodontology toward a “poly-microbial + viral” model, in which mechanical debridement, adjunctive antivirals, and host-modulatory strategies work in concert to disrupt the pathological viral–bacterial synergy and promote a more stable, regenerative periodontal microenvironment. This evolving paradigm underscores the need for further clinical research to refine dosing, duration, and indications for viral-targeted therapy while preserving the long-standing core principles of periodontal treatment.

CONFLICT OF INTEREST: Nil

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