Dentistry 3000

Vol 13, No 1 (2025)
ISSN 2167-8677 (online)
DOI 10.5195/d3000/2025.938

Emerging Role of Viral Infection in Periodontal Disease

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Abstract

Periodontal disease is primarily linked to a bacterial infection, such as dental plaque, which harbors a broad microbial community and can induce numerous inflammatory responses in periodontal tissue. In numerous instances, the local bacterial incursion and host-mediated immune reactions result in severe alveolar bone resorption. While researchers mainly concentrate on identifying periodontopathogenic bacteria, recent investigations have suggested that several viruses may also play a role in the onset and advancement of periodontitis. Human viruses can induce cytokine release from both inflammatory and non-inflammatory cells, hence compromising periodontal immune protection. This review investigates the potential role of viral infection in the pathogenesis of periodontal disease.

Open Access
Citation: Izzat AW, et al. (2025) Emerging Role of Viral Infection in Periodontal Disease. Dentistry 3000. 1:a001 doi:10.5195/d3000.2025.938
Received: May 7, 2025
Accepted: May 31, 2025
Published: June 27, 2025

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Introduction

Periodontal disease, or gum disease, comprises a series of inflammatory disorders that impact the tissues encircling the teeth [1,2]. In its initial phase, termed gingivitis, the gums exhibit swelling, redness, and potential bleeding. It is regarded as the primary cause of tooth loss among adults globally. In its advanced stage, known as periodontitis, the gums may retract from the tooth, resulting in bone loss, and potentially causing teeth to become loose or dislodge [3]. Halitosis (bad breath) may also occur [4]. Periodontal disease results from microbial infection, which causes inflammation and loss of connective tissue attachment as well as alveolar bone around the teeth [3]. Bacterial plaque is a primary etiologic factor of periodontitis. In most cases, the bacteria are proteolytic, Gram-negative species that produce pathogenic factors that trigger host defense responses, causing inflammation and tissue damage. Microbiological culture and culture-independent genetic investigations have recognized around 1200 bacterial species and 18,000 phylotypes in the oral cavity and a minimum of 400 bacterial species in subgingival locations. Nevertheless, despite the extensive enumeration of many bacteria associated with periodontitis, fewer than 20 species are classified as principal periodontal pathogens. Plaque contains non-bacterial microorganisms, including viruses, mycoplasma, yeasts, and protozoa [5]. Multiple studies indicate that human viruses may contribute to the etiology of periodontitis by modifying immune defenses, triggering harmful host responses, or exerting direct lytic effects on periodontal tissues [6]. Several immune-compromising factors, including smoking, inflammation, stress, trauma, and immunosuppressive disorders, may reactivate latent viruses residing in the body [7]. In numerous clinical studies, human viruses such as human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), and human immunodeficiency virus (HIV) have been implicated in the pathogenesis of periodontal disease [8]. In this research, we chose to shed light on the involvement of viruses in periodontal disease due to the scarcity of previous studies on them and their importance in understanding the basic mechanisms of immune responses to viral infection in the etiopathogenesis of the disease.

Material and Methods

For this review, the authors executed an electronic search across many pertinent scientific databases, including SCOPUS, Google Scholar, PubMed, and Web of Science. The preliminary evaluation comprised 46 publications published between 2015 and 2025 that had the terms “periodontal disease,” “herpes viruses,” “periodontopathogenic

bacteria," and "inflammatory response." Eligibility criteria: This study included recent papers, reviews, and case-control studies; all articles included in this review were published in English.

Results/Discussion

Figure 1 shows the workflow of this work. 46 articles were analyzed.

Periodontal Diseases

Periodontal infections represent one of the world's most prevalent chronic infectious conditions. Periodontitis is still one of the most common causes of tooth loss in adults. The primary etiological component of periodontitis is subgingival bacteria and their toxins; however, the destruction of tissue that occurs is a result of host response activities that are induced by microbial factors [9]. Periodontitis is characterized by bone resorption, loss of attachment, and tooth mobility [10]. The periodontal diseases affect 20%-50% of the population in the world. They are associated with a wide spectrum of chronic systemic disorders, including diabetes, cardiovascular, renal, neurodegenerative diseases, in addition to immune-mediated rheumatic diseases, obesity, neoplastic disorders, hypertension, and adverse pregnancy, chronic obstructive pulmonary disease [11]. According to several researchers, untreated periodontal diseases has been linked to higher medical care costs for non-oral diseases. A periodontal disease is a risk factor for a variety of systemic diseases, including cardiovascular diseases and diabetes. The mechanisms underlying this observation are unknown, but it is apparent that inflammatory cytokines represent a significant link between periodontal and systemic diseases [12]. Many variables, including genetic, metabolic, immunological, and inflammatory elements, are linked to the progression of periodontitis. Chronic periodontitis is an inflammatory disease induced by bacteria, wherein the immune response significantly contributes to the degradation of alveolar bone. Appropriate cytokine production is thought to result in protective immunity, whereas inappropriate cytokine production results in tissue death and disease development [13]. Moreover, it is widely acknowledged that the regulation of the T helper 1 (Th1)/T helper 2 (Th2) cell equilibrium is critical to periodontal disease immunoregulation [11].

Most cases of periodontitis are historically classified as either aggressive periodontitis or chronic periodontitis. Recently, it has become clear that insufficient evidence supports this classification based on factors such as varying clinical presentation and scientific investigations. A deficiency of distinct pathobiology-based differentiations among the specified categories, diagnostic ambiguity, and obstacles in therapy execution. In periodontology, a new classification was introduced despite the 1999 classification have been used for the previous 17 years [14]. Biological and clinical discoveries have revised the periodontal, peri-implant illness, and status classification system, resulting in the 2017 World Workshop Classification [15].

Pathophysiology of periodontal diseases

Dental plaque is a microbial biofilm that accumulates on the teeth and gingiva, which is the first stage of gingivitis. In the absence of treatment, gingivitis can advance to periodontitis, a condition characterized by deep periodontal pockets that reflect the illness and may result in the loss of teeth [16]. Interestingly, Studies estimate that a human host may have up to 150 different types of microbes in their biofilm. In addition, human dental plaque contains over a thousand species [17]. Research on the healthy residential microbiome using current DNA methods reveals an overabundance of Gram-positive microbes, despite the existence of periodontal pathogens [18]. This makes them symbionts, or obligate inhabitants of the subgingival and submarginal regions of the dental biofilm formation. Further spirochetes, viruses, and Gram-negative anaerobic bacteria are all possible causative pathogens [19]. Particularly, Treponema denticola, Porphyromonas gingivalis (P. gingivalis), and Tannerella forsythia are members of the red complicated collection of anaerobic microorganisms thought to be the effective bacterial species affecting the onset and progression of periodontal disease within the many different and extensive range of bacteria residing in subgingival biofilm formation. It is possible that microbial biofilm presence alone is insufficient for PD development. The disease develops when a microbial biofilm and its host have lost their equilibrium due to dysbiosis brought by the presence of "keystone" bacteria or an excessive response of the immune system in the host to the existence of microbes [20].

Moreover, inflammation is triggered when the host reacts to the typical residing plaque as it builds, which alters the microbial ecology and dysbiosis. An "ecological catastrophe" can be brought by a pathological malfunctioning of the immune response. An upward cycle of escalating dysbiosis feeds on itself. In particular, the immune cell remnants (after apoptosis), the complete spectrum of host immune elements encompasses immunoglobulins, complement, serum proteins, and cytokines. chemokines and collagen breakdown products are elevated during inflammation. Furthermore, serum exudates are present in inflamed pockets due to enhanced capillary permeability. There is an increase in anaerobic bacteria because an anoxic environment occurs in inflammatory situations. Therefore, given the new environmental circumstances, certain symbionts become pathobionts, i.e., commensals become potentially pathogenic due to an aberration in homeostasis. Pathobionts' proliferation (such as *P. gingivalis*) can further provoke and exacerbate host inflammatory responses. A transcriptome investigation of subgingival microbiomes in periodontitis demonstrated elevated expression of genes encoding proteolytic enzymes, iron acquisition, and lipopolysaccharide synthesis; this strongly suggests that numerous saccharolytic, anaerobic, and Gram-negative bacteria in periodontal inflammation take advantage of ecological alterations for their nourishing and enormous requirements [21]. As periodontal inflammation worsens, the bacterial biomass of biofilms is associated with human periodontitis development. Thus, the dysbiosis and inflammation encourage one another, creating a vicious cycle that could continue periodontal inflammation and the disease's development [14].

The altered ecology then promotes the outgrowth of pathobionts, which might exacerbate inflammatory reactions and prolong the disease's course. In addition to the subgingival bacterial biofilm on the tooth root surface and epithelial lining (a), genetic predispositions and epigenetic modifications (b), lifestyle-related risk factors (c), systemic diseases (d), and other factors (e) have been recognized as causal risk factors for periodontitis [22].

Regarding the degradation of bone and connective tissue in periodontitis, the host response is thought to play a crucial role. Antigens of microbes and virulent elements trigger inflammation and immunological responses. These reactions include both innate and adaptive immune responses. Furthermore, there is individual diversity in response due to differences in cytokine and other antimicrobial responses and the individual's environmental circumstances and genetic predispositions. The host's reaction to bacterial invasion entails activating and stimulating various inflammatory cell types and resident tissue cells [23].

Role of viruses in periodontal disease

Herpesviruses

The Herpesviridae family, including EBV-1, HCMV, and herpes simplex virus (HSV), has been associated with several types of periodontal disease [24,25]. Research indicates that these viruses can infect and modify the functioning of polymorphonuclear leukocytes, lymphocytes, and macrophages, resulting in a reduced capacity to combat

bacterial challenges [26]. This may augment the virulence of periodontopathogenic microbiota. In contrast, the dysfunction of polymorphonuclear leukocytes at periodontal sites can promote the proliferation of periodontopathic bacteria and the following progression of destructive periodontal disease. Periodontal sites associated with the herpes virus typically exhibit increased concentrations of periodontopathic bacteria, such as P. gingivalis, Tannerella forsythia, Dialister pneumosintes, Dialister invisus, Prevotella intermedia, Prevotella nigrescens, Treponema denticola, Campylobacter rectus, and Aggregatibacter actinomycetemcomitans [27].

The presence of periodontal HCMV, EBV, and maybe other viruses, local host immune responses, and periodontopathic bacteria constitutes a fragile equilibrium that may result in periodontal damage [28].

The pathogenicity of the herpes virus is intricate, either through direct viral infection and reproduction or by a virally mediated modification of the host's immunological system. The initial stages of periodontitis in immunologically naive hosts may primarily entail cytopathogenic occurrences, while most clinical manifestations in immunocompetent individuals are attributable to cellular or humoral immune responses [29].

Herpes viruses may exhibit periodontopathic potential through the following mechanisms: Herpes viruses can directly elicit cytopathic effects on keratinocytes, endothelial cells, fibroblasts, and inflammatory cells, including polymorphonuclear leukocytes, lymphocytes, macrophages, and possibly osteocytes. EBV and CMV can infect and alter the functions of monocytes, macrophages, and lymphocytes in periodontal lesions. Aggressive periodontitis lesions, potentially due to a herpes virus periodontal infection, exhibit a reduced number of viable cells, an increased presence of T-suppressor lymphocytes, and a higher concentration of B lymphocytes (EBV impact) compared to chronic periodontitis lesions or healthy periodontal sites. Cytopathic effects generated by the herpes virus may impede tissue turnover and repair [30].

2. An infection with the periodontal herpes virus may augment the virulence of the periodontal microbiota. Proteins of the herpes virus synthesized on eukaryotic cell membranes may function as innovative bacterial binding sites. Cytomegalovirus can enhance the adherence of A. actinomycetemcomitans to primary epithelial cells from periodontal pockets and HeLa cells [31,32].

Herpes viruses may cause dysfunctions in the phagocytosis, adherence, chemotaxis, and bactericidal functions of polymorphonuclear leukocytes, which are crucial for managing periodontopathic bacteria. Active Epstein-Barr virus infection can produce anti-neutrophilic antibodies, resulting in neutropenia, and can polyclonally increase the proliferation and differentiation of B cells. The pathogenic processes of herpesviruses synergistically worsen illness; hence, a dual periodontal infection involving cytomegalovirus and EBV, or CMV and HSV, is likely to manifest in severe forms of periodontitis [33].

Epstein-Barr virus (EBV)

The Epstein-Barr virus, a common γ-HHV, infects around 95% of individuals asymptomatically and is generally transmitted by blood or oral secretions. The virus proliferates in oropharyngeal epithelial cells or B lymphocytes. Nearly all seropositive individuals actively excrete viruses in their saliva [34]. While EBV infection in children is typically subclinical, EBV infection in adults causes infectious mononucleosis. Fever, lymphadenopathy, and pharyngitis are the predominant symptoms of infectious mononucleosis. Oral ulcers, palatal petechiae, and, less frequently, gingival ulcerations may arise [33]. The most common EBV-related lesion is oral hairy leukoplakia. Its presence usually indicates a relatively advanced stage of immunosuppression, such as in HIV infection. HIV-infected patients' T cells suppress EBV-infected B cells less effectively than immunocompetent people's T cells. Thus, HIV patients have 10–20 times the number of circulating EBV-infected B cells as healthy people [26]. According to the EBV status, there may be two dissimilar mechanisms involved in the pathogenesis of BL: virus-driven and mutational coding [35].

It induces latent infection in B-cells, with occasional lytic reactivation linked to the terminal differentiation of B-cells into plasma cells. Chronic latent EBV infection is associated with lymphomas and carcinomas [36]. EBV is associated with several autoimmune disorders [37], serving as a direct cause of multiple sclerosis [38]. Recent studies revealed substantial insights into EBV's involvement in periodontitis [39]. They found that EBV commonly infects periodontal junctional Epithelial Cells [40]. Furthermore, it was determined that periodontitis lesions harbor significant plasma cells, predominantly exhibiting EBV positivity [41]. These findings provided the initial evidence of active EBV presence in periodontal lesions, indicating that it exacerbates local inflammation and contributes to the etiology of periodontitis [39].

Cytomegalovirus (CMV)

Cytomegalovirus (CMV) infects T lymphocytes, periodontal monocytes, and macrophages [42]. The global seroprevalence of CMV infection varies from 0% to 95%, contingent upon the geographic region (developed versus developing countries) [43]. The infection typically initiates during childhood or even before birth, as the placenta plays a crucial role in the transmission of CMV to the fetus. Evidence indicates that CMV has developed several techniques to circumvent the host immune response and has utilized the host immunological response to facilitate reactivation from dormancy and propagate infection [25,44].

Acute CMV infection is characterized by increased viral replication and dissemination to many organs. The pathogenesis of acute infection illustrates a correlation among viral replication levels, organ dysfunction, and disease in patients [32]. The pathogenesis of chronic infection involves a bi-directional relationship between viral gene expression and the host's inflammatory response: the host's inflammatory response facilitates viral reactivation, while the virus provokes the host's inflammatory response. In this case, the disease could be attributed to viral and host functions [45]. Consequently, CMV is frequently reactivated, leading to temporary immunosuppression and the proliferation of periodontal pathogenic bacteria. While it has been presumed that the pathogenesis of periodontitis is primarily due to bacterial infection on the tooth surface and within the gingival sulcus, numerous studies have demonstrated that host response factors, including inflammatory responses and activation of the innate immune system, are essential to the development of periodontal disease [26].

Human Immunodeficiency Virus (HIV)

Periodontal pathology in HIV-infected patients falls into three categories: (i) Linear gingival erythema, (ii) necrotizing ulcerative periodontal diseases, and (iii) enhanced progression of chronic adult periodontitis [26]. In the mid-1980s, several reports described necrotic periodontitis and intense gingival erythema in HIV-infected patients. HIV-associated periodontitis (HIV-P) was named after these acute necrotic lesions, characterized by the loss of the underlying bone, and HIV-associated gingivitis (HIV-G) was termed for a specific kind of gingival erythema that proved resistant to conventional plaque treatment. The contemporary terminology utilized by the American Academy of Periodontology classifies HIV-G lesions as linear gingival erythema and HIV-P lesions as necrotizing ulcerative periodontitis. In addition to linear gingival erythema and necrotizing ulcerative periodontitis, these conditions were more common in patients with HIV. Necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis are two periodontal conditions that have been identified in both HIV-positive and HIV-negative

patients. Necrotizing ulcerative gingivitis is characterized by interdental papilla ulceration, gingival bleeding, and severe pain. The interproximal papilla is usually described as punched out and a fibrinous pseudo membrane typically covers the affected area [46]. The only difference between necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis is that Lesions of necrotizing ulcerative periodontitis infiltrate the alveolar bone. Necrotizing ulcerative periodontitis is distinguished by exposed bone, gingival recession, and tooth movement. Additional manifestations of necrotizing ulcerative gingivitis or necrotizing periodontitis are halitosis, lymphadenopathy, pyrexia, and general malaise [26].

Conclusions

Herpes viruses may have a role in the etiopathogenesis of destructive periodontal disease. Based on research completed over the last 15 years. Active Epstein-Barr virus or cytomegalovirus infections are statistically correlated with aggressive periodontitis, while latent herpes virus infections are predominantly located in chronic periodontitis and gingivitis sites. Herpes viruses are probably not independent periodontopathic agents but instead cooperate with bacteria in the degradation of periodontal tissue. Papillomaviruses and other mammalian viruses frequently reside in periodontitis lesions. However, their involvement in the pathophysiology of the disease remains unclear. The recurrent and prolonged activation of periodontal herpes viruses in immunologically naive and immunocompromised individuals may elevate the incidence and severity of clinical exacerbations of periodontal disease.

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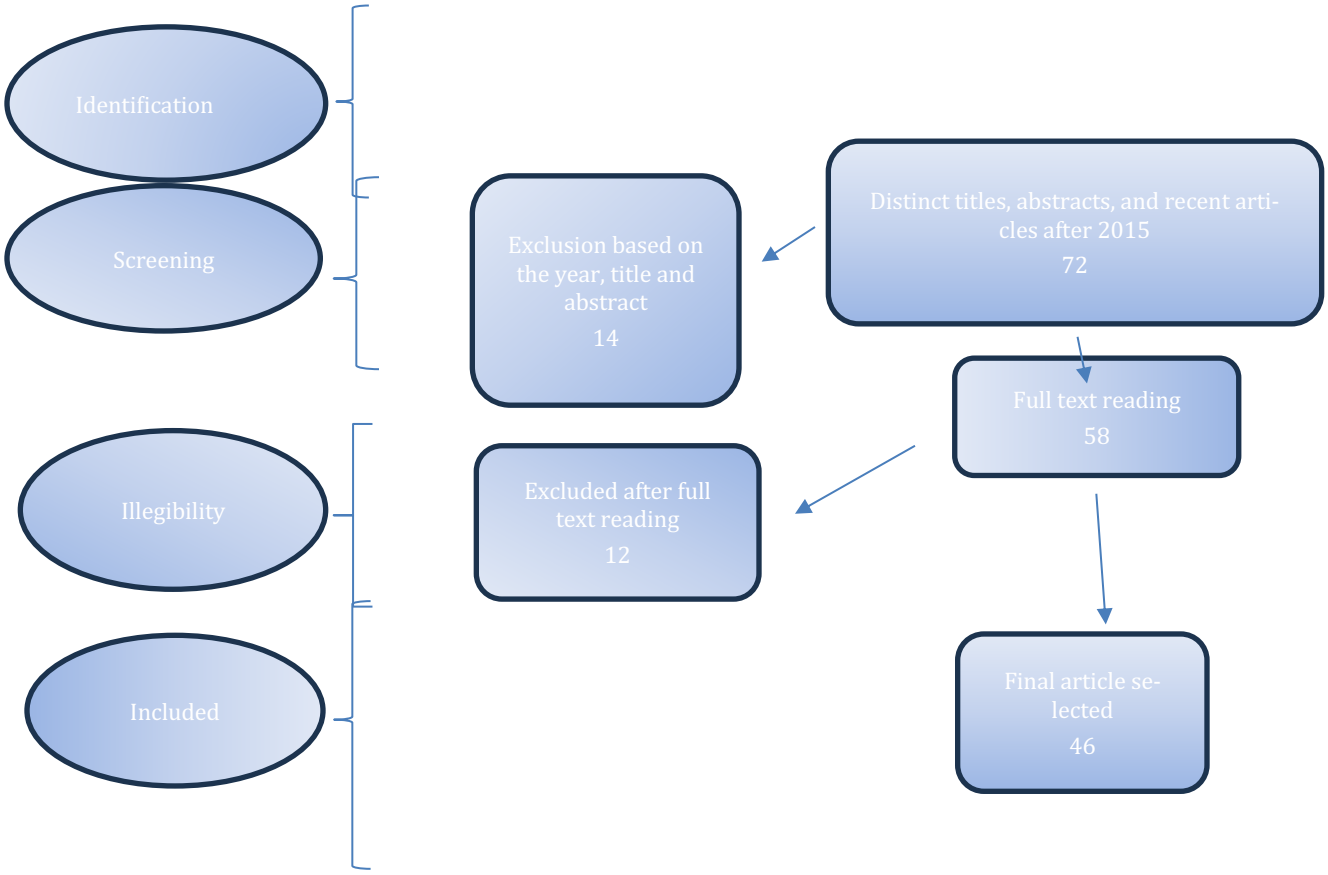

Figure 1. Progression of the search and selection procedure.