(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 2, Page No: 629-634
March-April 2022

IJMSCR

Viruses in Periodontology: A Short Review

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Periodontal diseases are of multifactorial origin, with various risk factors contributing their parts. The role of periodontal bacterial flora is well studied and known but their interactions with other micro-organisms, particularly viruses are being deliberated. Virus may have a direct or indirect role in periodontal pathology. Herpes simplex class of virus have shown to have direct interaction with plaque bacteria to cause rapid disease progression and attachment loss whereas HIV virus produces its effect mainly by compromising host defence mechanism. In the recent event of novel corona virus infection, the interaction and effects of SARS-CoV-2 on periodontal tissues has come in to light. The present review has discussed the possible mechanism of viruses and their importance in Periodontology.

Keywords: Periodontitis, Peridontal Diseases, Herpes Simplex Virus, HIV, SARS-CoV-2

Introduction

Periodontitis is a multifactorial disease encompassing immunological, genetic, environmental and microbiological aspect. With 1970s, comes the era which triggered research in all the insights of the periodontal diseases in an effort to find additional etiologic factors and cause related treatment for the same. Though the prime cause considered is plaque biofilm and microbial flora, the role of virus in severity of periodontal disease became intrigue. Ever since this thought, numerous studies have been conducted to evaluate and affirm the role of viruses in various forms of periodontitis.[1,2] American Academy of Periodontology in 1999 classified viral diseases such as herpetic gingivostomatitis under non plaque induced gingival lesions making a confirmation of the role of virus in the pathobiology of periodontal disease.[3]

A virus is a small infectious agent that replicates only inside the living cells of other organisms. Viruses can infect all types of life forms, from animals and plants to microorganisms, including bacteria and archaea. While not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent particles. These viral particles, also known as virions, consist of two or three parts: a) The genetic material made from either DNA or RNA, long molecules that carry genetic information; b) A protein coat, called the capsid, which surrounds and protects the genetic material; c) In some case an envelope of lipids that surrounds the protein coat when they are outside a cell.[4] Virus can gain entry in the host tissues by faeco-oral route, respiratory route or by direct inoculation via skin or mucous membrane.[5]

Viruses have emerged as putative periodontopathogens; they have shown to impair host

defence mechanisms, diminished response to bacterial challenge, substantiate growth of periodontal bacteria.[6] Hence the role of virus becomes more challenging and effective in the progression of disease, thus warranting attention.

Virus etiology of periodontal disease:

Viral diseases of oral origin have acute signs and symptoms, which include herpetic gingivostomatitis, acute necrotic ulcerative gingivitis and also oral signs of systemic infection. There can be direct or indirect role of viruses on etiology of periodontal diseases. Direct involvement or direct role of virus will produce local signs and symptoms of periodontal disease; however presence of signs and symptoms due to underlying systemic infection suggests indirect role.[5] Virus having direct role includes Herpes simplex virus, Varicella zoster virus, Kaposi sarcoma virus, Cytomegalovirus. Human immunodeficiency virus has an indirect role in periodontal disease.

Herpes Virus

Herpes simplex virus is double stranded DNA virus. It have a) core containing a large double stranded DNA genome encased within; b) icosapentahedral capsid containing 162 capsomers; c) amorphous proteinaceous tegument and surrounding the capsid and tegument; d) lipid bilayer envelope derived from host cell membranes.[6] Researchers have found approx. 120 different herpes viruses, out of which eight major types are responsible for human illnesses. These are: herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus, Epstein Barr Virus, Human Cytomegalovirus, human herpes virus (HHV)-6, HHV-7, and HHV-8 (Kaposi's sarcoma virus).

Herpes virus, once entered in the human body may remain in latent phase for years before producing symptoms. Infectious stages can be latent, subclinical or clinical depending on which phase it is: mild or asymptomatic primary phase or latent asymptomatic phase or clinical symptomatic phase.[6] The conversion of latent asymptomatic phase to clinical symptomatic phase can occur due to triggering factors such as immunosuppression, fever, menstrual period, stress and fatigue. The episodic nature of periodontal disease coincides with symptomatic stage of herpes viral disease. According to Azodo and Erhabor,[5] stage of herpes viral infection can explain the nature of periodontal diseases such as episodic progressive nature which may be due to active or latent viral infection depending on transient local immunosuppression. The localized pattern of tissue destruction in periodontal disease can be because of viral tissue tropism; the absence of severe destruction of periodontal tissues despite carrying large amount of periodontopathogenic bacteria is suggestive of absence of viral infection.[5]

Herpes viruses triggers or affect a number of tissue destructive mechanism constituting to pathogenesis of periodontal diseases. This includes:

a) Direct cytopathic effect: Herpes virus down regulates host immunity by hampering the function of polymorphonuclear leukocytes, lymphocytes, macrophages and other cells such as fibroblasts, endothelial cells and even bone cells.[7] They also affect MHC class I and class II pathways impairing antigen presentation.[8]

b) Cytokine and chemokines release: Viral infection up regulates the release of pro-inflammatory and inflammatory mediators such as interleukin (IL)-1β, IL-6, IL-12, tumor necrosis factor (TNF)-α, interferon (IFN)-α⁄ β, and IFN-γ and prostaglandin E2 (PGE2).[9]

c) Interference with the immune system of host: Herpes viruses infect B and T lymphocytes, monocytes and macrophages; this results in increased virulence of periodontal pathogens.[10]

d) Immuno-pathologic responses: Viruses have a direct effect on cell mediated immunity suppressing antigen specific T-lymphocyte functions.[5]

e) Promotion of bacterial colonization: Viral proteins help in generation of bacterial binding sites and enhanced bacterial adhesion by acting as bacterial receptors.[11]

Herpes viral–bacterial model of periodontitis: It is hypothesized that the presence of active herpes infection can cause quiescent periodontal infection to clinically active disease by cytopathogenic effects in immunologically deficit patient; whereas immuno-competent patient reacts via cellular or humoral

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immune responses to viral infection aided periodontal disease.[6] Figure 1 explains the possible mechanism of herpes and bacterial interaction in periodontitis. The presence of active or latent disease, site tropism are dependent on the presence or absence of virus or/and at the active or latent stage of virus and its interaction with periodontopathic bacteria.

Herpes and periodontal disease:

Herpes viruses and pathogenesis of various periodontal diseases are interlinked. Numerous studies have been performed in regard to this.

Aggressive periodontitis: Gingival specimens obtained from patients of aggressive periodontitis have shown high levels of T suppressor cells and Langerhans cells which are carriers of HCMV genome.[10] It is hypothesized that puberty-related hormonal changes in localized aggressive periodontitis patients causes reactivation of periodontal herpes viruses, this results in proliferation of resident periodontopathic bacteria and active diseased state.[12] Ting et al studied the relationship between HCMV activation and disease-active versus disease-stable periodontitis in patients with aggressive juvenile periodontitis. The presence of mRNA of the HCMV major capsid protein was detected in deep pockets of HCMV-positive patients with early disease and not in any shallow test sites.[13]

Chronic periodontitis: Herpes virus was found in higher counts in deep subgingival pockets than in shallow sites, biopsies of gingival tissues confirm the same.[14,15]

Herpes and Periodontal Abscess: Presence of herpes virus and its activation impairs host defence, this results in breakdown of gingival tissue resulting into abscess formation.[16]

Herpetic Gingivostomatitis: It is an infection of early age caused by herpes simplex virus type 1. It commonly affects infants and young children but it is also seen in adolescents and adults. Symptoms include lesions or vesicles which are clustered, diffuse, erythematous and shiny on the gingiva and adjacent oral mucosa, with varying degrees of edema and gingival bleeding. These vesicles eventually rupture forming painful ulcers with a red, elevated, halo-like margin and a depressed, yellowish or greyish white central portion. This is accompanied by general malaise, fever and difficulty in eating. The ulcers heal in 7-10 days.[17]

Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) is a lentivirus which is a subgroup of retrovirus. The genome of HIV virus is composed of two identical single stranded RNA virus. It has a particular affinity for CD4 receptor cells on T-helper lymphocyte resulting in weakening of immune system of the host, instigating opportunistic infections and is referred to as Acquired Immunodeficiency Syndrome (AIDS).

HIV infection is diagnosed based on:[18]

Positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay). This is confirmed by a second HIV antibody test (rapid or laboratory-based enzyme immunoassay) relying on different antigens or of different operating characteristics;

and/or;

Positive virological test for HIV or its components (HIV-RNA or HIV-DNA or ultrasensitive (HIV p24 antigen) confirmed by a second virological test obtained from a separate determination. (WHO 2007)

Periodontal diseases in HIV patients

HIV infected patients' shows following periodontal manifestation:

Linear gingival erythema: Winkler at al first described distinctive erythema of the free gingiva, attached gingiva and alveolar mucosa associated with HIV infection.[19] It appears as a distinct red band extending 2 to 3 mm apically to free gingival margin. The presence of lesion do not corresponds to presence of plaque, and is painful in some instances. It has shown equal distribution to all quadrants.[19]

Necrotizing Ulcerative Gingivitis/Periodontits: HIV related necrotizing periodontal disease manifests as loss of interdental papillae resulting in ulceration or necrosis. It can be extends up to involve entire attached gingiva in severe cases resulting in loss of bone and supporting tissues.[17]

Adult Periodontitis and Rapidly Progressive Periodontitis: The greater breakdown and rapid destruction in HIV-infected individuals is the result of immunosuppression. Steinsvoll et al showed that serum immunoglobulin G responses to specific plaque bacteria were decreased in HIV infected

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patients with immunodeficiency.[20] Because of malfunctioning and decreased immune response, opportunistic organisms, other viruses invade the gingival and periodontal tissues leading to accelerated damage in HIV-infected patients.

Periodontal Pathogens and Reactivation of Latent HIV Infection: HIV lives in cells of immune system such as helper T-cells (specifically CD4+ T-cells), these cells which function which function as memory cells and remains in the body for years.[21] HIV can integrate into dendritic cells, monocytes/macrophages and CD4+ T-cells, thus causing them to be long-lived reservoirs of the latent virus.[21]

COVID-19 and Periodontal Diseases

The world has witnessed a mysterious virus in 2020 which has baffled the physicians, scientists and researchers alike. The world is still trying to compete with it, all the while understanding its characteristics and effects. There have been studies which show that periodontal diseases and COVID-19 are interlinked.[22]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus from coronaviridae family which affects respiratory system. The symptoms include fever, throat pain, cold, dry cough, loss of taste and smell and respiratory distress. Apart from these symptoms like diarrhoea, nausea, reddening of eyes is also seen. Respiratory distress can be from mild to severe depending on the infection of lungs with pneumonia. The COVID-19 also results in cytokine storm of pro-inflammatory and inflammatory cytokines and chemokines from immune cells such as interleukin, interferons.[23]

As the research is progressing, decoding of interlink between COVID-19 and periodontitis is emanating. Both periodontitis share risk factors such as diabetes, cardiovascular diseases, obesity and oral dysbiosis.[24] Sahni and Gupta, 2020 has stated that inflammatory response between the two can be related and hence suggesting a connection between the two. They expressed that, both have shown elevated levels of Interleukin (IL) 7, Interferon gamma, TNF-alpha, GM-CSF, thus emphasizing presence of periodontal disease as predisposing factor to COVID-19.[25] Rubio et al 2020 reviewed the common risk factors amongst COVID-19 and periodontitis and hypothesized that gingival health can be a mirror of systemic health.[24] They have explained how comorbidities such as Diabetes Mellitus, Asthma, Chronic Obstructive Pulmonary Disease, Liver Diseases and malignancy in a COVID -19 positive patients have shown more complications. These factors have been closely related to poor prognosis of periodontal diseases suggesting a strong connection between the COVID-19 and periodontitis.[24] Marouf et al 2021 has conducted a case control study to investigate the possible association in this regard. The study was done on 568 COVID-19 positive patients; the results have shown that age, diabetes and smoking habits are stronger risk factors for both periodontitis and COVID-19 complications. They also observed that periodontitis was associated with increased risk of overall COVID-19 complications, death, ICU admission and need for ventilation.[22]

Apart from immunological connection, periodontal pockets can also act as reservoir to novel corona virus; this can be hypothesized based on the fact deep sub gingival environments harbour viruses such as HSV, EBV, and HCMV.[26,27] There are few studies in this regard, which have shown that SARS-CoV-2 could infect oral cells increasing the expression of Angiotensin converting enzyme-2 (ACE-2).[28] This could be the result SARS-CoV-2 and its affinity to periodontal pocket cells.[27] However, this research is still in infancy and a lot more is yet to be established.

Conclusion

The current concept critically acclaims the role of virus in periodontal disease and their interactions with periodontopathic bacteria. The role of Herpes and HIV has been an area of interest since long amongst the researchers; with the evolution of new virus, the collaboration of bacteria and virus spiked the investigators' interest.

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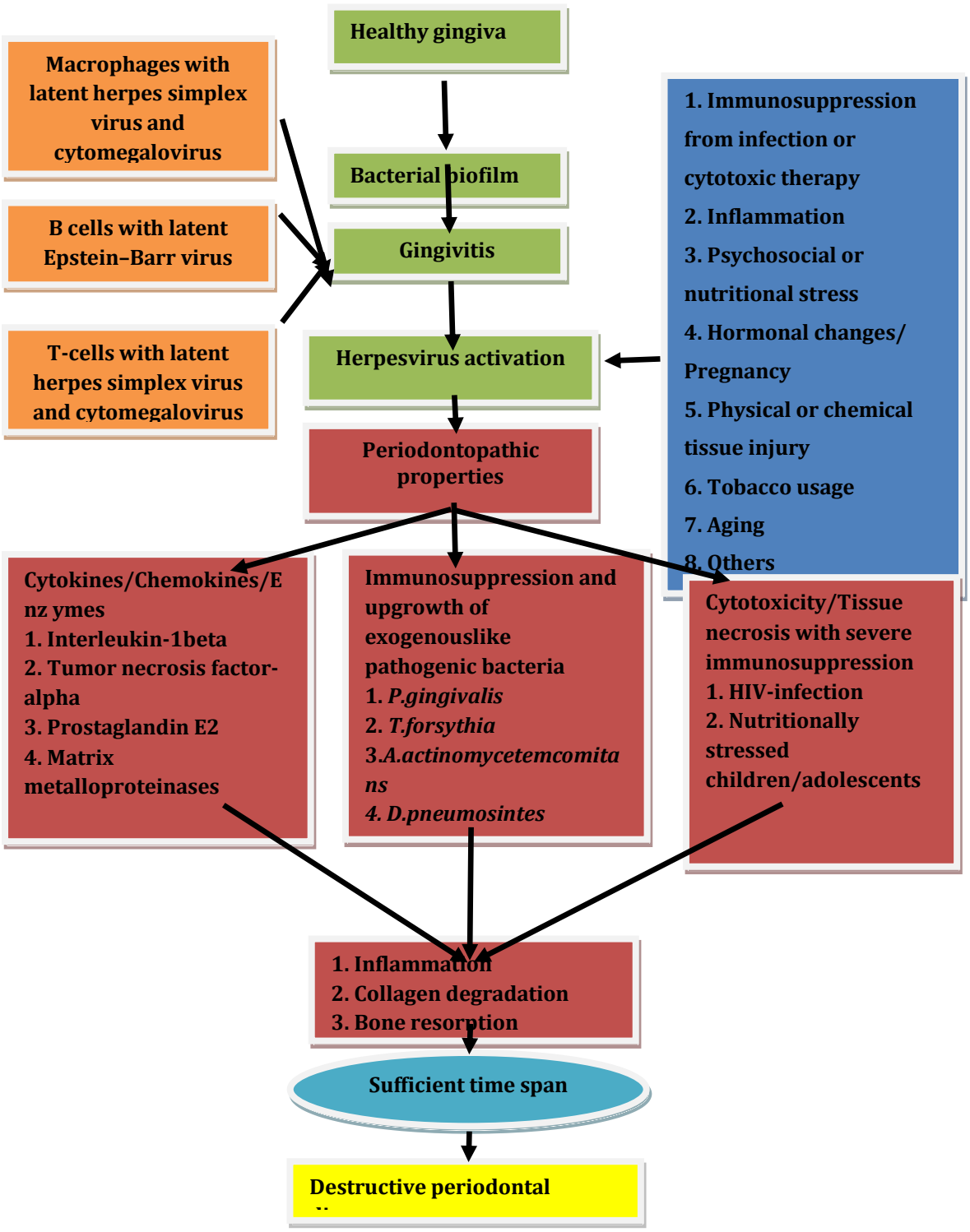
Figure 1: Herpes Viral-Bacterial Model of Periodontitis



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