

Covid-19 And Periodontium- An Interplay Cytokine Connection- A Review

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ABSTRACT

Periodontal diseases include the category of diseases involving the inflammation process which affects the tooth supporting structures resulting in bone resorption, tooth loss on later stages which might on a longer run be able to be associated with systemic complications. There are varying systemic disorders and conditions being reported with periodontal disease which include diabetes, hypertension, cardiovascular diseases, obesity although the complete association between the risk factors shared has not been explored completely. The outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) signaled a cross species transmission which spread across the globe in the beginning of 21st century. As COVID-19 disease shares a common mechanism of triggering the dysbiosis and inflammatory reaction as periodontal disease, there can be possible association between periodontal diseases and COVID-19 disease which on further research could establish a strong relation between COVID-19 and periodontal disease. This article aims to review the possible connecting mechanism linking periodontal disease and COVID-19.

Key words: *Corona virus, Periodontitis, Inflammation, Virus, Cytokine*

I. INTRODUCTION

The novel coronavirus disease is a condition which occurs due to Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), which is been transmitted from one person to other either through direct or indirect contact. ^[1] Coronavirus disease has been declared as a pandemic along the globe by the WHO, as it has affected almost every country's health care framework, economy across the globe. Periodontitis being one of the most common oral health diseases occurs as a result of multi-factorial origin. ^[1] Microorganisms comprising bacteria plays a major role in development and progression of the disease. ^[2] Not only bacteria, there are viruses which as well play an established role in development of periodontitis. ^[2] Hence, periodontal pockets also act as reservoir pool for different pathogens. ^[2]

The first and foremost oral manifestation of COVID-19 is dysguesia. ^[3] The other various oral manifestations of the novel Corona virus disease include ulcers, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. ^[3]

There are various cytokines which plays an important pathophysiological role in COVID-19 disease which include Interleukin -2, Interleukin-7, Interleukin10, Inducible Protein-10,

Granulocyte-Colony Stimulating Factor, Macrophage Inflammatory Proteins-1 A, Monocyte Chemoattractant Protein1 and Tumour Necrosis Factor alpha. ^[4] The pathogenesis of periodontitis as well establishes its significance on cytokines especially interleukin 17 whose levels are markedly increased during active periodontal destruction and its levels in saliva and gingival crevicular fluid are reduced during non-surgical periodontal therapy. ^[5]

This interlinking pathophysiology shows there is a correlation existing between periodontal disease and COVID-19 which is further explored in this upcoming review article.

II. CORONA VIRUS- AN EMERGING PANDEMIC

The 2019 Novel Corona Virus disease (2019 n-CoV) is the fourth most strain of viral disease following H5N1, H1N1 and Middle East respiratory syndrome coronavirus (MERS-CoV) which spilled from animal population into humans which emerged in December 2019 ^[6]. The first patient cluster presented with the symptoms of fever, myalgia, dry cough in Wuhan city, Hubei province, China. ^[6] There was huge number of cases linked to the Human Seafood Wholesale Market where there was variety of mammals available for sale. ^[6] During the initial days of pandemic onset, there were no confirmed human to human transmission suspected, but the transmission of virus was later identified in the mid-week of January, 2020. ^[7] As there was an exponential increase noted in the number of cases reported it was much more evident that the virus facilitated human transmission where each patient approximately was spreading the infection to more than two other people. ^[7] Researchers as well identified that that the infected individuals could infect the virus without showing any symptoms either they were in presymptomatic or asymptomatic state. ^[7] As cases started hitting a higher number, the World Health Organization (WHO) declared this as an emerging pandemic and the countries affected started to implement lockdown aiming to slow down the disease transmission. ^[7]

III. STRUCTURE OF CORONAVIRUS

Coronaviruses are named after their spikey projections on their surface which mimic a crown that in Latin language means corona. ^[8] These corona viruses are enveloped single stranded non segmented RNA viruses which have important proteins that include spike (S), envelope (E), membrane (M) and nucleocapsid (N). ^[8] They possess higher tendency of mutation and recombination which allows them to adapt with the new hosts and newer ecological niche. ^[8] There are four main subgroups of coronavirus which include alpha (α), beta (β), delta (δ) and gamma (γ) which among alpha and beta strains infect humans. ^[8] The recent coronavirus is SARS-Co-2 which is stealthier virus infecting humans. ^[8]

IV. VIRUSES IN PERIODONTAL DISEASE

Periodontal diseases which include gingivitis and periodontitis are classified as chronic inflammatory diseases caused by pathogenic bacteria resulting in inflammation and destruction of periodontium.^[9] There are increasing risk factors associated with periodontal diseases which include poor oral hygiene, smoking, diabetes, age, heredity, obesity, certain medications and systemic diseases which predispose the individual to periodontal disease.^[9] These diseases induce a series of host responses which mediate the inflammatory events, leading to periodontal tissue destruction and breakdown.^[9]

From mid-1990s, viruses have been described as associated pathogens related to periodontal disease, which include Epstein-Barr virus type 1 (EBV-1) being detected in almost 43% of periodontal sites.^[10] The other viruses associated include the herpes simplex virus and human cytomegalovirus have been described as positive organisms found in periodontal pockets of periodontal disease individuals.^[10]

Furthermore, there are studies which quote that periodontal pockets serve as a favorable site for virus replication and survival. Therefore, this would draw an additional focus of infection in COVID-positive patients.

V. PERIODONTAL POCKETS AS A SOURCE OF VIRAL REPLICATION

The initial stage of viral infection in periodontal tissues could be initiated either from direct transfer from oral cavity or it could be the circulating immune cells that could transmit the infection. Hence mononuclear cells could reach the periodontal tissues from the site of infection.^[11] Thus, the gingival crevicular fluid present in the periodontal pocket could be a reservoir of virus arriving from infected mononuclear cells which can further mix with the patient's saliva.^[11]

As angiotensin-converting enzyme-2 (ACE-2) has been considered the important receptor for the SARS-CoV-2 virus entry into human cells, and they are widely distributed not only in lungs but also in saliva, nasopharyngeal mucosa and saliva, this results in major viral load in the oral cavity (especially in saliva and gingival crevicular fluid).^[12] This has been counteracted by the dental practitioners by the use of anti-microbial povidine-iodine based mouth rinses which has been showing promising results in killing the viruses.^[12]

VI. INFLAMMATORY MECHANISMS LINKING COVID-19 AND PERIODONTAL DISEASE

There are various studies which quoted that cytokines are increasing in multiple folds in serum levels of patients suffering from the novel corona virus disease. These cytokines include IL-1 beta, IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, GM-CSF, G-CSF, IFN- γ , and TNF- α , MIP1A, MIP1B, MCP1 and IP10.^[13] This is referred to as cytokine storm.^[13]

Periodontal disease has long term linkage with immune mediated cytokines. There are studies which have established increased IL-17 producing cells in gingival tissue in periodontal diseased patients. This elevation of cytokines detected in locally inflamed gingival tissue indicate that there exists a common pathway of inflammatory response points towards a possible association between Periodontitis and COVID-19 related adverse outcomes. This has as well substantiated the fact that the possibility of the presence of periodontal disease predispose to COVID-19 related adverse outcomes.^[14]

Moreover, Osteopontin a noncollagenous, calcium-binding, glycosylated phosphoprotein, which is commonly found in the mineralized phase of bone matrix, which is mainly synthesized by pre-osteoblasts, osteoblasts and osteoclastic cells and has been shown to be elevated in periodontitis. There are studies which have demonstrated osteopontin and its down regulating products enable the SARS-CoV-2 virus to infect the host cells.^[15] This indicates that there are various non-collagenous proteins, protease inhibitors which play a major role both in COVID-19 disease and periodontal disease thus both sharing common pathways of disease progression.

VII. PERIODONTITIS AS A RISK FACTOR OF COVID-19

Periodontitis could be associated with severe COVID-19 illness. Previous medical history of periodontitis could be a characteristic to classify the risk group to severe COVID-19.^[16] The suggested relationship between periodontitis and severe COVID-19 illness which is discussed above could associate the link between them. There are as well more common risk factors reported in patients with severe COVID-19, also aggravate the development of periodontitis.^[16] These risk factors include the age, gender, smoking, diabetes mellitus, hypertension and cardiovascular disease, obesity, liver diseases and pregnancy.

- **AGE:**

Age is a factor which is considered to cause degenerative changes in cellular and tissue level leading to progression of autoimmune diseases, infections and inflammation which include periodontitis as well. Periodontitis affects the older age group as they have risk factors of poor oral hygiene, use of medications, other chronic diseases, and lack of timely dental treatment that alters the oral microbiota which allows the development of periodontitis.^[16]

As well people over 65 years are the highest risk group of COVID-19 disease which increases the morbidity of this group as that do not have a stronger immune response to counteract the viral response. Thus age can probably considered as a risk factor connecting periodontitis and COVID-19 disease.^[16]

- **GENDER:**

There are studies which quote both periodontitis and COVID-19 disease has a slighter male predilection than compared to females which is possibly thought to associate both the disease.^[17]

- **SYSTEMIC DISEASES:**

There are systemic diseases like asthma, chronic obstructive lung disorder (COPD), hypertension and cardiovascular disease, diabetes which are considered to be the risk factors of both periodontitis and COVID-19 disease.^[18]

- **SMOKING:**

Smoking is an established risk factor for both periodontal disease and COVID-19 disease progression as it could increase the expression of ACE-2 and smoking cessation could decrease the severity of COVID-19. Smoking promotes dysbiosis in periodontal tissue, thereby improving the virulence factor of key periodontal pathogens which impairs the immune response of the host.^[19]

- **OBESITY:**

After smoking, obesity is the next highest factor linking to periodontitis. Adipose tissue secretes low levels of pro inflammatory cytokines like IL-6, IL-8, and TNF- α which contributes to the development of periodontal disease.

Obesity is been as well implicated as a risk factor in COVID-19 disease as it could be associated with decreased expiratory reserve volume and reduced respiratory system compliance. As well periodontitis could contribute the amplification of systemic inflammatory cytokines in patients with COVID-19 disease.^[20]

VIII. PERIODONTISTS AND COVID-19 DISEASE PREVENTION

Current evidences suggest that COVID-19 virus human to human transmission is mainly through droplet spread of infected people.^[21] As dental clinics receive patients belonging to different groups of age, habits and demographies it is quite difficult to protect and prevent the professional from infection.^[21] Dentists are at higher risks of getting infected as we work in close proximity with the patient wherein we are prone to handle the infected saliva, blood and other body fluids which harbor the virus.^[21] Hence, we as a dental health care professional should follow the guidelines mentioned by the Dental Council of India (DCI) which includes use of pre-procedural mouth rinse to decrease the viral load, use of personal protective equipment (PPE), following strict sterilization and disinfection protocol and maintaining a proper temperature and saturation check of the patient entering the clinic.^[21] As there are chances of aerosol contamination existing as well, procedures involving the aerosol generation should be minimized if the patient falls under the category of suspected case of COVID-19.^[21]

There are studies which substantiate that periodontitis could be a risk factor associated with COVID-19 disease; hence proper oral hygiene maintenance along with periodic consultation with periodontist is necessary to prevent the disease rather than to treat it.

IX. CONCLUSION

Periodontal diseases and COVID-19 thus has an interlinking mechanism wherein each disease contributes to the progression of the other. As well, there are various inflammatory mechanisms shared in a common pool with each other thereby instantiating the fact that COVID-19 and

periodontal disease could be the risk factor of each other. Hence periodontists have an established role in preventing the spread of COVID-19 disease wherein proper non-surgical therapy can reduce the microbial load in the oral cavity thereby reducing the risk of COVID-19 infection. There are further more studies required to correlate periodontal diseases with COVID-19.

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