

COVID-19 and Periodontal Disease-The Link

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ABSTRACT

COVID-19 is a pandemic and a global emergency declared by World Health Organization (WHO) in the year 2020. It leads to a life threatening pneumonia and severe acute respiratory distress syndrome (ARDS). It has been found that the virus causes development of a hyperinflammatory state characterised by a release of a variety of chemical mediators. This is responsible for cardiomyopathy, disseminated blood clots, stroke, neurologic problems, thrombosis and multiorgan failure of heart, kidney and brain. Patient related factors such as hypertension, diabetes, obesity, aging etc. are suggested to increase the risk of COVID-19 complications. Periodontal disease is a chronic inflammatory disease of the tooth supporting structures characterised by clinical attachment loss and bone loss which is caused by microorganisms in dental plaque. It is also characterised by release of several chemical mediators as a result of the interaction between periodontal pathogens and the individual host response that becomes dysregulated. Periodontal disease is also related to other systemic disorders such as cardiovascular disease, endocrine disorders, respiratory diseases etc. through the release of periodontal pathogens and chemical mediators via the bloodstream that reach distant sites in the body. Therefore periodontitis patients may present as a high risk group for SARS-Cov-2 infection. The purpose of this article is to highlight the link between periodontal health and risk of COVID-19 and to suggest the possibility of periodontal disease as a risk factor for COVID-19 so that patient education programs and treatment strategies can be developed.

Key words: Periodontitis, COVID-19, Cytokines, Inflammation

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INTRODUCTION

The COVID-19 outbreak started from the Hunan Seafood market in Wuhan, China. Patients reported pneumonia of unknown etiology and a travel history to the seafood market. Later, patients not having a travel history to the market also reported with similar symptoms suggesting a human to human transmission which has spread worldwide. Usually patients report with

mild symptoms such as fever, cough, sore throat, headache, difficulty in breathing, severe acute respiratory distress syndrome and sometimes death [1]. Due to the alarming rise in COVID-19 cases, it is prudent to develop prevention strategies to cease the transmission and treatment protocols for reducing the severity of already affected cases and preventing death. The prevalence of COVID-19 in India has reached up to a mark of 7 million cases with approximately 104K deaths in the country in 2020 as of today.

Periodontal disease is a chronic inflammatory dysbiotic state in the human oral cavity which is characterized by destruction of tooth

supporting structures and an intense host-inflammatory response between the individual and the periodontal pathogens [2]. The worldwide prevalence of periodontal disease is approximately 10% [3]. Periodontal disease and SARS-Cov-2 infection have some common risk factors such as age, smoking, diabetes, hypertension, obesity etc. [4]. This article discusses the possible correlation between periodontal disease as a risk factor for severe COVID-19 infection due to these shared risk factors.

The cytokine storm

COVID-19 is characterized by an exaggerated and hyperactive immune response inducing the release of a variety of interferon's, interleukins, tumor necrosis factor (TNF), chemokine's etc. This leads to a deregulated host immune response and organ shutdown. This is referred to as the "Cytokine storm" implying the role of cytokines in injury to host cells. Reports suggest that patients admitted for serious complications of COVID-19 have elevated levels of cytokines such as IL-2, IL-7, IL-17, TNF- alpha and an elevated Th-17 response. Therefore, anti-inflammatory drugs such as corticosteroids, monoclonal antibody drugs and interleukin inhibitors are now suggested for the treatment of COVID-19.

Cytokines play an important role in the tissue destruction seen in periodontal disease. They are responsible for the bone loss seen in periodontitis. Periodontal disease is also characterized by ulceration in the pocket epithelium which could be around 40cm wide. This leads to the spread of these cytokines and microorganisms into the bloodstream. Since these same inflammatory induced by-products exacerbate the symptoms of COVID-19 and periodontal treatment has shown to reduce the levels of inflammatory markers, can the control of inflammation in the oral cavity and maintenance of oral hygiene contribute to reduction in disease severity and morbidity is the need of today's research. This common pathway of inflammatory response suggests a possible association between periodontal disease and COVID-19 [5].

Saliva as protective armour

Saliva is a very complex fluid having the composition of various antimicrobial agents which have been shown to be effective against

other viruses causing respiratory disease. Hypo salivation, therefore, could predispose the patient to COVID-19. However, large randomized controlled clinical trials are required to prove this association [6].

Pneumonia

Pneumonia is a serious respiratory infection caused by viruses or bacteria where the tiny sacs in the lung get inflamed and filled with fluid. It is a leading cause of death in patients with risk factors immunocompromised state, underlying medical disorders, smoking and poor oral hygiene.

Periodontal pathogens present in dental plaque, the primary etiological factor for periodontal disease, have been implicated in aspirational pneumonia and viral respiratory infections. These microorganisms can enter the lung via bloodstream and cause pneumonia [7]. Respiratory diseases, on the other hand, predispose the patient to develop bacterial super infections that complicate the treatment. These super infections are also comprised of oral bacteria.

Evidence suggests the presence of these bacteria in the breathing tubes of intubated ventilated patients which results from high microbial load in the mouth travelling down these tubes and complicating the treatment. Therefore good oral hygiene will prevent the serious course of this disease [8].

Oral hygiene and COVID-19

A healthy oral cavity is an indicator of good overall health. Oral prophylaxis reduces the microbial load in the oral cavity which reduces the risk of many systemically related diseases including COVID-19 [8].

COMMON RISK FACTORS FOR PERIODONTAL DISEASE AND COVID-19

Aging

Aging is characterized by inevitable degenerative changes in the tissues of the human body. It is a known associated factor for developing periodontal disease due to compromised oral hygiene habits, systemic diseases, medications, altered mobility and dexterity [9]. Individuals more than 65 years of age are categorized as high risk patients due to the comorbidities and reduced immunity present at this age [10]. Thus

elderly individuals are a high risk category group for both periodontal disease as well as COVID-19.

Gender

Studies have suggested that males are more prone to develop periodontal disease when compared to females [11]. The reasons for this were proposed to be related to immunity, behavioural and environmental differences. COVID-19 is also more prevalent in men when compared to women, immunity levels being the reason [12]. Thus, gender is another shared risk factor between COVID-19 and periodontal disease.

Stress related factors

The global pandemic of COVID-19 has caused tremendous rise in the stress levels of individuals financially as well as psychologically [13]. Stress is recognized as a risk factor for development of periodontal disease. Elevated levels of stress may lead to release of neuropeptides such as substance P from sensory nerves which have an effect on the activity of immune system a release of cytokines. Through the hypothalamus-pituitary- adrenal (HPA) axis, stress leads to modulation of immunity by regulating the release of cytokines from immune cells and blocking the activation of macrophages. This leads to depressed immunity making the individual susceptible to develop periodontal disease [14]. Thus, stress is the interlinking factor between COVID-19 and periodontal disease.

Cardiovascular disease (CVD)

CVD is responsible for majority (approximately 45%) of deaths in the world with ischemic heart disease, stroke and hypertension being the major cause of CVD related deaths. Epidemiological studies have shown an association between periodontal disease and CVD [15]. Periodontitis also has a high prevalence of 11.2% of the world's population, being the sixth most common human disease. CVD is also one of the comorbidities with increased severity of COVID-19 infection [4].

Diabetes

Diabetes is a metabolic disorder characterized by high blood glucose levels due to reduced secretion of insulin from the pancreas or insensitivity of body cells to insulin. There is a two way relationship between diabetes and periodontal disease. That is, diabetes increases the possibility of having periodontal disease

and presence of periodontal disease worsens the glycaemic control of diabetic individuals [16]. Diabetes is also related to severe COVID-19 infections due to already compromised immune system in diabetics and a suitable environment of high blood glucose for the survival of the coronavirus [4].

Obesity

Obesity is recognized as a risk factor for periodontal disease as it leads to alteration of microbiota present in the periodontal pocket with prevalence of periodontal pathogens. The adipose tissue secretes pro-inflammatory cytokines such as IL-1, IL-6, TNF- alpha and adipokines like leptin and adiponectin. These inflammatory mediators may contribute to periodontal disease by altering the response of gingiva to microbial biofilm. Amount of free radicals is also increased in obesity which increase the oxidative stress further deteriorating the progression of periodontal disease [17].

Factors linking obesity to COVID-19 illness could be decreased respiratory reserve, functional capacity, respiratory system compliance and heightened inflammatory state [4].

Pregnancy

Immunosuppression in pregnant patients, hormonal changes such as high progesterone and estrogen levels and the physiological adaptive changes predispose the pregnant female patient to develop periodontal disease as well as respiratory illness. COVID infection could complicate the perinatal events in the form of preeclampsia, premature rupture of membrane and low birth weight [4].

Respiratory diseases

Studies have established that periodontal disease is a possible risk factor for respiratory diseases. Respiratory diseases are responsible for significant morbidity and mortality in human populations.

Scannapieco et al. [18] has suggested some mechanisms to explain the possible role of oral bacteria in the pathogenesis of respiratory infection:

- ✓ Aspiration of periodontal pathogens (such as *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, etc.) into the lung to causes infection,

- ✓ Periodontal disease-associated enzymes in saliva may transform mucosal surfaces to support adhesion and colonization by respiratory pathogens, which are then aspirated into the lung,
- ✓ Periodontal disease-associated enzymes in saliva may destroy salivary pellicles on pathogenic bacteria to obstruct their clearance from the mucosal surface.
- ✓ Cytokines coming from host microbial may modify respiratory epithelium to promote infection by respiratory pathogens.

It was suggested that patients with COVID-19 have an increased risk of aggravation when they present COPD and patients with pre-existing COPD have a 4-fold increased risk to develop severe COVID-19 illness [19]. It was proposed that the increased risk could partly be because COPD patients present increased expression of ACE-2 in airways. Thus, the association of PD with COPD could be helpful to identify risk groups to develop severe COVID-19, since COPD increased importantly the risk of this affection.

Environmental factors- oral hygiene, smoking

Smoking is a major risk factor to develop PD, and it affects the progression, severity and response to treatments of this condition. On the other hand, smoking is a risk factor of COVID-19 progression, being 1.4 times more probable to have severe COVID-19 symptoms [20]. Additionally, as COPD, smoking could increase the expression of ACE-2.

HIV

Patients with HIV or a compromised immune function, represent a group at higher risk of systemic and oral manifestations. HIV has been considered a risk factor for COVID-19 infection [21]. There are not enough studies yet, but it is believed that the degree of immunosuppression may contribute to a higher susceptibility to SARS-CoV-2 infection.

Cancer

In recent years, PD has been identified as a risk factor that increases the development of cancer. Dysbiosis induces inflammation, systemic translocation of periodontal pathogens through the weakened periodontal epithelium, systemic immune dysregulation, and the increase in circulating cytokines and chemokines are responsible for the relationship between cancer and PD. Cancer patients are more susceptible

to COVID-19 due to immunosuppression and nutritional deficiencies [22].

Liver diseases

Liver diseases have a high prevalence around the world. There are many studies in the literature suggesting a relationship between periodontal disease and liver conditions such as liver cirrhosis, tumours of the liver, fatty liver disease etc. liver transplantation patients have to undergo a thorough oral examination before surgery due to the risk of bacteraemia and sepsis by pathogens present in the periodontal pocket [23]. The interaction between periodontal pathogens and the host generated an immune-inflammatory reaction which leads to production of several inflammatory mediators such as IL-1 β , IL-6, IL-10, IL-12, and TNF- α and INF- γ that are involved in the development of liver diseases [24]. The lipopolysaccharide from *Porphyromonas gingivalis* is known to induce liver inflammation.

The Coronavirus has been shown to be binding to the cells of the liver using a ACE-2 receptor. Therefore patients with liver diseases are more prone to develop COVID-19 infections. Thus, patients with liver diseases and periodontitis could indicate a higher risk group for developing COVID-19 infection.

Rheumatoid arthritis

Studies show that patients suffering from rheumatoid arthritis (RA) have a worse prognosis if they also suffer from periodontal disease and that RA and periodontal disease are closely related. A periodontal pathogen *Porphyromonas gingivalis* is known to create an enzyme that causes citrullination, and periodontal bacteria have been isolated from synovial fluid [25]. RA patients have increased susceptibility to infectious diseases such as COVID-19. The relationship between RA and periodontal disease and the associated inflammatory picture resulting from these diseases could affect the outcome in COVID-19 patients.

Recent literature on COVID-19 and oral diseases

Patel et al. has reported a case report of patient with Necrotizing Periodontal Disease (NPD) and suspected COVID-19. The author suggested that patients with SARS-CoV-2 infection have higher prevalence of *Prevotella intermedia* organism along with other periodontal pathogens

implicated in the etiology of periodontal disease. The bacterial co-infection propagated by *P. intermedia* and other anaerobic pathogens may predispose the individual to develop COVID-19 infection [26].

Riad et al. studied the epidemiological implication of potential COVID-19 oral manifestations by assessing eight case reports that reported oral lesions in COVID-19 positive patients. According to the case reports, 75% of the cases involved masticatory mucosa and 25% cases involved the lining mucosa. Causes suggested by the case reports for the appearance of oral manifestations in COVID positive patients could be a possible drug reaction, stress caused by the pandemic situation, bacterial coinfection enhancing the severity of COVID-19 or as a result of inflammatory reaction that induces vascular inflammation [27].

Nathalie et al. has suggested a hypothesis that improving oral health could decrease the severity of COVID-19 infection and reduced the associated mortality with the disease. The hypothesis was formulated on the basis of the shared common risk factors between COVID-19 infection and periodontal disease [28].

Xu et al. suggested salivary glands as the potential reservoirs for an asymptomatic infection because of the presence of ACE-2 receptors in the salivary glands to which the COVID-19 virus binds. SARS-CoV RNA can be detected in saliva before lung lesions appear which may explain the presence of asymptomatic infections. Therefore, as the source of saliva is the salivary gland, the potential of saliva to infect other individuals with SARS-CoV-2 infection should not be ignored [29].

Vieira et al. proposed that mild cases of COVID-19 infection do not show oral manifestations. They are seen in severe cases in which a persistent inflammatory status appears to act as a trigger for the coagulation cascade and is associated with increased levels of fibrinogen degradation products (e.g., D-dimer). Also, the author suggested that untreated moderate or severe periodontitis may deteriorate COVID-19. Conversely, periodontal therapy in individuals with initial COVID-19 symptoms may decrease the threat of the condition to become severe by reducing the amount of D-dimer in the plasma,

which is seen when patients with periodontitis are treated [30].

Hypothesis

Through this paper we suggest a hypothesis that COVID-19 and periodontal diseases have several shared common risk factors which may predispose the individual to develop severe complications of either of the disease. Therefore, a dentist plays an important role in diagnosing cases with higher risk of COVID-19, thereby reducing the mortality caused by this pandemic by providing early intervention to high risk groups.

CONCLUSION

Randomized controlled trials are the need of the hour to determine the link between periodontal disease and COVID-19. Also, there is a pressing necessity to study co-infections in COVID-19 patients and boost clinicians to diagnose these conditions timely, owing to their influence to mortality and intensified disease severity in historic pandemics of respiratory viral infections. Routine intra-oral examinations for COVID-19 patients should be delivered across healthcare disciplines.

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