Review Article

Role of Periodontal Disease in the Pathogenesis and Prognosis of COVID-19

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Abstract

Since the outbreak of coronavirus disease 2019 (COVID-19) in late December 2019, it has brought significant harm and challenges to over 200 countries and geographic regions around the world. COVID-19 affects people in different ways, with patients exhibiting a range of symptoms and severity. Risk factors such as age, gender and comorbidities have been highlighted as increasing the risk of complications and mortality. These risk factors, however, do not account for the other 52% of deaths arising from COVID-19 in seemingly healthy individuals. This review examines the interplay between periodontal disease and development of severe complications of COVID 19. Periodontal infections alter the natural course of systemic conditions, due to the presence of a constant low grade systemic inflammatory state in the body. Correlating these two entities is the main focus of this review and how maintaining good oral health may reduce the risk of complications of COVID-19.
Key words: Periodontitis, Inflammation, COVID-19.

INTRODUCTION

Periodontitis has been defined as an infectious disease resulting in inflammation within supporting tissues of the teeth, progressive attachment loss, and bone loss. Periodontal disease is the pathological manifestation of the host response against the bacterial challenge that stems from a polymicrobial biofilm at the biofilm-gingival interface. All forms of periodontal disease share certain common pathobiological principles as polymicrobial, biofilm mediated, and chronic inflammatory diseases at the biofilm gingival interface.

Environmental, physical, social, and host stresses may affect and modify the disease expression through a multitude of pathways. Evidence has also shed light on the converse side of the relationship between systemic and oral health: the potential effects of inflammatory periodontal disease on a wide range of organ systems [1-3].

Corona viruses are positive-sense RNA viruses having an extensive range of natural hosts and affect multiple systems. SARS-CoV-2 is a strain of the severe acute respiratory syndrome related coronavirus (SARr CoV), member of the Coronaviridae family and the etiologic agent of the disease referred as 2019 coronavirus disease (COVID 2019). Coronavirus can manifest clinically as common cold, more severe respiratory diseases like SARS and MERS or anything in between. It has caused a pandemic situation worldwide, leading to disease outbreaks that have not been brought under control till date, although exhaustive efforts have been made to counter this virus [4].

While most patients with COVID 19 present with mild symptoms[5], nearly 14% of confirmed cases, mainly those with existing comorbidities, develop severe sequelae requiring hospitalization and oxygen support, 5% need admission to intensive care units and around 2% end up deceased[6]. Severe cases are usually complicated by acute respiratory distress syndrome (ARDS), Middle East respiratory syndrome (MERS), sepsis and shock, leading to multiple organ failure [7].

Periodontal disease and COVID 19: Systemic link

Periodontal disease is a well-established associative link for several systemic comorbidities like cardiovascular disease, cerebrovascular disease, peripheral arterial diseases, respiratory diseases, as well as low birth weight of newborns. This is because

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gingival and periodontal pathogens provide a constant source of low grade infection [8]. Also, chronic untreated periodontal disease has been widely accepted as a probable risk of increasing the complications of diabetes, insulin resistance, rheumatoid arthritis, obesity, osteoporosis, complications of pregnancy, and possibly severity of symptoms of COVID 19[9].

Bi-directional relationship exists between Diabetes Mellitus and Periodontal disease. It has been well documented that most of these conditions in turn can increase the severity and brings down the prognosis of periodontal conditions, by altering the body's natural immune defence against periodontopathic microorganisms. Metastatic spread of oral, especially periodontal infections, is mainly due to the transient bacteremia, circulating inflammatory mediators like cytokines, interleukin 6, TNF α, as well as metastatic inflammation caused by immunological injury induced by oral microorganisms[10].

Believing periodontal disease to be localized to the teeth is erroneous. It is never just confined to the teeth and periodontium. It always has some sort of a widespread systemic effect. In many young, healthy, and relatively disease free individuals, systemic manifestations of periodontal disease are not clinically evident. In susceptible individuals, however, periodontal infection may act as an independent risk factor for systemic disease, and it may also be a causative agent for these conditions. This is of very high significance in analyzing the morbidity, and mortality of COVID 19 during this pandemic, which in itself shows increased severity with existing and/or uncontrolled systemic disorders [3].

Looking into the pathogenesis of COVID 19 infection, patients with severe COVID 19 and ARDS or MERS[11], usually exhibit an exaggerated immune response, characterized by excessive levels of proinflammatory cytokines and widespread tissue micro-edema and inflammation, preferentially called as the 'Cytokine storm syndrome'[12]. Predictors of severe lung infection and higher risk of developing complications from COVID-19 infection is not mainly due to aging itself; the presence of one or more comorbidities can predict COVID-19 severity in older patients[13]. Its mortality has also been notably associated with elevated serum levels of interleukin-6 (IL-6), C Reactive Protein (CRP), D-dimer, ferritin and many more pro-inflammatory cytokines [14].

This clearly relates disease severity and the constant state of low grade non-resolving systemic inflammatory state, proportionally increasing with the viral load, similar to what has been entrenched in periodontal disease. Furthermore, severity of COVID 19 infection has also been associated with patients' comorbidities such as hypertension, diabetes, cardiovascular disease [15], older age, obesity, etc…[16]. Nevertheless, the specific risk factors leading to poorer prognosis have not been well explained.

Periodontal disease is one of the most prevalent and commonly ignored, both by practitioners and patients alike, chronic inflammatory noncommunicable diseases (NCDs) [17]. The Global Burden of Disease (GBD) Study and other epidemiological studies have reported that 50% of adults are affected by mild to moderate periodontitis and 10% by the severe form of the disease, making it the sixth most prevalent 'systemic disease or illness' affecting general population [18].

Along with the above discussed conditions, a poorly functioning immune system has a part in determining the severity of COVID 19 complications. Superimposition of existing and/or uncontrolled comorbidities, age related declining function of immune system or immunosenescence, low grade systemic inflammation, can lead to increased severity of COVID 19 outcomes [19]. According to Del Valle et al., high IL-6 and TNF-α levels in the serum, during hospital stay, are the main indicators for severity and survival rates [20]. In this state of chronic low grade inflammation, the increased activation of NF-kB has a crucial role in modulating the secretion of proinflammatory mediators and the immune response [21]. Viral load in patients is also an important parameter in foreseeing disease severity. In patients with severe infections, it is 60 times higher than those with mild or no evident clinical infections [22].

A variety of different parameters can help segregate patients infected with COVID 19 into, low, moderate, and high risk of morbidity and mortality. Identification of these parameters can increase the efficacy of treatment. Modifications in the oral microbial colonies can affect the microenvironment, causing increased pathogenic load, overburdening the immune system [23].

A connection has been found to exist between the lung microbiota and admission to intensive care. Complications have arisen associated with bacteria belonging to gut microbiota not commonly found in the lung ecological niche. Identifying patients with initial gastrointestinal symptoms could help predict patient outcomes and help improve decision making for preventive measures and treatment plan. Therefore, it would be useful to categorise the microbiome in periodontal disease in patients with COVID-19.

Pre-existing periodontal infections can metastasize to bacterial respiratory infection via blood, directly linking these two. Aspiration of saliva and other oral fluids is also a plausible route of spread, especially to the lower respiratory tract. Either way, infected periodontal tissue is the main etiological factor. Therefore, we can say that there is a risk of lung

infections in patients with active periodontal disease [24].

Keeping in mind that the prevalence of *Porphyromonas gingivalis* infection increases with age, this periodontopathic microorganism has been noted as one of the etiological agents in aspiration pneumonia in adults and also in acute pulmonary infection using murine models[25]. Whereas periodontal bacteria can be isolated from infected lung samples [26], death occurring due to these pathogens as the sole cause is difficult to demonstrate. Nevertheless it can be established that these excessively pathogenic microbiota can aggravate pre-existing lung infection. Multiple studies have demonstrated that periodontal treatment has a beneficial effect on lung function by reducing the exacerbation of respiratory diseases, significantly lowered adverse respiratory events, improved lung function, and lower risk of death have been observed in patients with COPD after appropriate periodontal treatment, such as timely scaling, root planing, and other procedures reducing the oral microbial load [27].

Stress: Another gateway to periodontal disease and COVID 19

The pandemic has caused a high amount of stress psychologically and financially for the average person, with the introduction of quarantine, isolation, and many losing their means of livelihood. In one survey, 70% of respondents stated that the months during this pandemic have been the most stressful time in their entire lives [28]. Many studies have demonstrated interrelationship between stress and increased risk of developing periodontal disease and clinical attachment loss [29].

Both financial stresses and psychological stresses have been shown to double and even quadruple the risk of developing periodontal attachment loss [30]. And those constantly under stress have been found to possess high levels of cortisol in their salivary fluids. The release of chronic cortisol leads to a decreased immunity and upregulation of various inflammatory markers. The result of chronic inflammation and decreased immune function is the rapid destruction of periodontal tissue [31]. Coping mechanisms to deal with anxiety, stress, and depression can often involve poor diet, bodily neglect, and deleterious habits such as substance abuse [32]. Periodontal destruction has been shown to increase in a dose-dependent function with smoking and other deleterious habits [33].

Additionally, lack of hygiene, professional scaling and other periodontal procedures can worsen tissue destruction. Studies show that bacteria recolonized teeth as early as six to eight weeks after scaling and root planning [34]. Poor nutrition has also been shown to increase inflammation of periodontium either through the onset of insulin resistance, or in general by inducing chronic low grade systemic inflammation [35]. Many patients whose oral health was controlled under strict periodontal care prior to the pandemic can experience relapse when under stress.

Reinforcing oral hygiene practices and warranting periodontal care is the best way to halt or slow the progression of the disease. Stress management also becomes an important issue, faced by the dentist, or the physician in general, as it can lead to exaggeration of the chronic systemic inflammation, leading to increased susceptibility, or severity of periodontal disease, COVID 19 symptoms, or both in an interlinked manner.

Prevention

SARS-CoV-2 virus infects human cells using the ACE2 receptors, which are widely distributed in the upper respiratory tract and the epithelial cells lining the ducts of the salivary glands, with these being early targets of infection [36, 37]. The mouth, mainly the tongue, is a great reservoir of viruses.

Therefore, tooth brushing, interproximal hygiene and tongue cleaning are necessary to reduce the viral load in the oral cavity. Therefore oral prophylaxis by a dentist significantly reduces oral microbial, especially viral loads. Periodontal status is a potential modifiable factor in the primary prevention of infections in COVID 19 patients, especially in those with multiple comorbidities. Therefore, the diagnosis and management of periodontal disease in the population deserves better awareness. Dentists can also encourage the use of antiviral mouthrinses and other necessary oral hygiene measures can be implemented [38].

Additionally, in order to prevent cross-contamination, it is important to make sure that tooth brushes within the family members are not in the same container. After use, toothbrush becomes contaminated and, if not disinfected, can be a reservoir of microorganisms [39], including bacteria, viruses and fungi, that maintain their viability for a significant amount of time, ranging from 24 h to 7 days. Microbial survival promotes the reintroduction of potential pathogens into the oral cavity or the spread to other individuals when toothbrushes are stored together or shared. It is advisable to discard the toothbrush and the other oral hygiene aids used following recovery from COVID 19. As important as social distancing, keeping the infected belongings away is better [40].

CONCLUSION

The outbreak of COVID-19 has caused widespread concern and has disrupted education, economic and health care systems, resulting in significant damages worldwide. The development, severity and risk of complications following an episode of COVID-19 infection depend on a number of host and

viral factors that will affect a patient's immune response. While 80% of patients with COVID-19 infections have mild symptoms, 20% progress to have a severe form of infection associated with higher levels of inflammatory markers (IL-2, IL-6, IL-10), bacteria and neutrophil-to-lymphocyte count.

The connection between periodontal disease and COVID-19 complications should be investigated further for better understanding the outcomes of COVID-19. It is clear that bacterial superinfections are common in patients suffering from severe forms of COVID-19, with more than 50% of deaths occurring due to the aforementioned reason. More research should be conducted on bacterial superinfections, and the connection between the oral microbiome and COVID-19 complications, as there is an urgent requirement to establish the importance of oral hygiene and pre-existing oral disease in the severity and mortality risk of COVID-19.

Meanwhile, we recommend that oral hygiene be maintained, if not improved, during a SARS-CoV-2 infection in order to reduce the bacterial load in the mouth and the potential risk of a bacterial superinfection. Poor oral hygiene can be considered a risk to post-viral complications, particularly in patients already predisposed to altered biofilms due to diabetes, hypertension, cardiovascular disease, etc. Improved oral hygiene may play an important part in reducing the risk of complications. Increased awareness about oral health is the need of the hour.

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