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Interlink between COVID-19 and periodontal disease

Neeraj Deshpande[1*], Tapaswi Kamble[2], Monali Shah[3]
[1] Professor, Department of Periodontology, KM Shah Dental College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India
[2] Student, KM Shah Dental College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India
[3] Professor and Head, Department of Periodontology, KM Shah Dental College, Sumandeep Vidyapeeth Deemed to be University, Vadodara, Gujarat, India

Abstract
Periodontal disease is a group of chronic inflammatory disease of the tooth and its supporting structures characterized by clinical attachment loss and bone loss caused due to microorganisms in dental plaque. There is a presence of bi-directional relationships between periodontal disease and systemic conditions. In periodontal disease raised levels of some pro inflammatory cytokines which are chemotactic in nature and cause the enrolling of cells of inflammation. Coronavirus disease (COVID 19) is a current contagious disease that is spreading worldwide and targets human angiotensinconverting enzyme 2 receptor. Respiratory distress syndrome and multiple organ failure are the common outcomes of COVID 19 which finally leads to death. During COVID 19, cytokine strom takes place that is known by the release of notable amounts of pro-inflammatory cytokines including IL-1, IL-6 and TNF-alfa. This communication explores the connection between COVID-19 and periodontitis through their cytokine connection. The purpose of this text is to highlight the link between periodontal health and risk of COVID-19 and to suggest the likelihood of periodontitis as a risk factor for COVID-19 so that patient education programs and treatment strategies can be developed in early stages.

Keywords: coronavirus, cytokines, periodontal disease, povidone-iodine, Sars-Cov-2

Introduction

A pneumonia outbreak of unknown etiology befell in Wuhan, China, which ultimately evolved into a global threat [1]. Patients reported a travel history to the seafood marketplace. Later**,** sufferers now no longer having a travel history to the mark*et al*so reported with similar symptoms suggesting a human to human transmission which has unfold worldwide [2]. The outbreak was deemed as a virulent disease by the World Health Organization on March 11, 2020. The causative agent was recognized as a member of the Coronoviridae family and initially named 2019 novel coronavirus (2019-nCoV); thereafter, the virus was officially named severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2).1 SARS-CoV-2 a member of the Coronaviridae family, is an enveloped virus with non-segmented, single- stranded, positive-sense ribonucleic acid (RNA) genome [1-3]. Lately, the human population encountered three major coronaviruses that caused major disease outbreaks, first is SARSCoV appeared in 2002, followed by the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and the third and the latest: severe acute respiratory syndrome coronavirus 2 (SARS-CoV2).4 SARS- CoV-2 expresses a spike protein (S-protein) that mediates adhesion to and invasion of host cells [1].

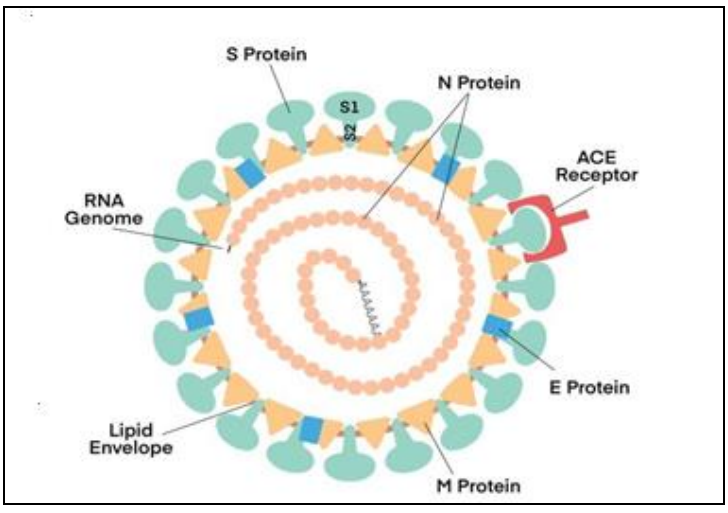

Fig 1: Structural components of Corona virus

SARS-CoV-2 also enters the human body via the oral mucosa through the Angiotensin Converting Enzyme II (ACE2) receptor, which is highly expressed in the oral mucosa (mostly in the epithelial cells of the tongue) and in the salivary glands, additionally ACE2 receptor is expressed in the lungs and kidneys [5, 6]. Currently, a new and more virulent variant of SARS- CoV-2, D614G, is spreading worldwide [1]. A study by Pascolo *et al*. has demonstrated the necessary co-expression of ACE2 and trans-membrane serine protease (TMPRSS2), to enable the entry of SARS-CoV2 into host cells. Indeed, the TMPRSS and furin serve to cleave the virus S protein and subsequently spread the infection [5, 8].

Focus on periodontitis Periodontal diseases are a group of pathologies of an inflammatory nature in which a host response is induced by microbial etiologic factors that mediate inflammatory events, which lead to tissue destruction in susceptible subjects. The global prevalence of severe periodontitis in 2017 reached almost 800 million people.7 Periodontitis is defined as "a chronic, multifactorial inflammatory disease, associated with dysbiotic plaque biofilms and characterized by the progressive destruction of the tooth-supporting apparatus"5 and is classified by staging and grading systems.9 In recent years there has been particular interest in probable associations between periodontal infection and systemic diseases. Periodontal pathogens, as well as their toxins, such as cytolitic enzymes and lipopolisaccharide (LPS) may have access to the blood stream through the compromised and/or ulcerated epithelium of the periodontal pocket. Moreover, within the inflamed gingival tissue a number of inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, prostaglandin E2 (PGE2), and γ-interferon are produced; these can enter the blood stream and contribute to the global inflammatory load. Thus, the systemic exposure to periodontal pathogens, their toxins, and periodontal derived inflammatory mediators may determine pathologic consequences in different organ or systems. Three main mechanisms by which periodontal infection may influence systemic health have been described:

1. Metastatic infection caused by translocation of Gram-negative bacteria from the periodontal pocket to the bloodstream
2. Metastatic injury, such as vascular lesions from the pro-inflammatory mediators and effects of circulating microbial toxins
3. Metastatic inflammation due to the immunological response to the periodontal pathogens and their toxins.10

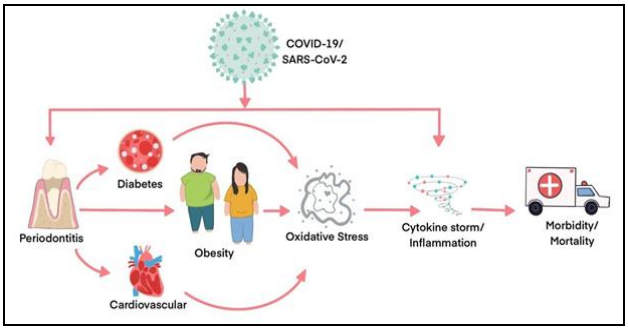

Fig 2: Potential link between periodontitis and Covid-19 with systemic disease

Cytokine Storm Syndromes (CSS) and Immunosuppression

COVID-19 is characterized by an exaggerated and hyperactive immune response inducing the release of a variety of interferon's, interleukins, tumour necrosis factor (TNF) and chemokine's. This leads to a deregulated host immune response and organ shutdown. This is referred to as the "Cytokine storm. Cytokine Storm Syndrome (CSS) is a systemic inflammatory reaction that can be triggered by a multiplicity of factors such as some medications and infections. 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. On the other hand, chronic periodontitis, one of the most prevalent chronic inflammatory diseases of human and is characterized by cytokine hyper-reactivity, with influence on systemic inflammatory-immune responses [11].

Cytokines play an important role in the tissue destruction seen in periodontal disease. Primarily responsible for the bone loss seen in periodontitis. Periodontal disease is also characterized by ulceration in the pocket epithelium which may be possibly 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.

Therefore, it is important to account that chronic periodontal disease is a persistent intense inflammatory infiltrate in the connective tissue with activation of T and B cells through cytokine discharge and determine the progression of the disease. There is a dysregulation of T cells in the periodontitis with activation of subtypes Th1, Th2, and Th17 cells with production of a variety of pro-inflammatory cytokines, such as IL-1β, IL-17E (IL-25) and IL-17, that trigger other immune cells such as neutrophils, dendritic cells and B cells [12]. Then, T cells and B cells stimulated can induce the release of the receptor activator of nuclear factorκB-Ligand (RANKL), prompts the osteoclasts and cause alveolar bone resorption, resulting in tooth loss. Moreover, the activation of B cells by T cells can result in clonal activation of B cells, with antibodies production against bacterial components; though, production of auto antibodies to fibronectin, collagen, and laminin with gingival tissue damage. Also, B cells stimulate secretion of IL-8 and IL-1β and could contribute to chronic systemic inflammation. A crucial role of cytokine storm plays an important role in the pathogenesis of severe acute respiratory syndrome coronavirus-2 of the genus betacoronavirus (SARSCoV-2) human infection. The virus may attack the targeting organs that express Angiotensin-Converting Enzyme II (ACE2), such as the lungs, heart, renal, gastrointestinal tract after access lungs and peripheral blood [18]. During the infection process, the inflammatory cytokines persistent to increase, whereas T cells and B cells are decreased [19]. Thus, the COVID-19 infection triggers a respiratory failure from Acute Respiratory Distress Syndrome (ARDS) and, secondary under-recognised

Haemophagocytic Lymphohistiocytosis (sHLH) with a hyper inflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with multi organ failure [14].

Study of Zhou *et al*. showed that the Angiotensin-Converting Enzyme II (ACE2) is probable the cell receptor of 2019-nCoV. It has been identified that high ACE2 expression is in alveolar cells of lung, epithelial cells of esophagus, myocardial cells and kidney cells [20]. and, these organs should be considered as high risk for COVID-19. Regarding this finding, a recent study revealed that the oral mucosa could express the ACE2 and was higher in tongue than other oral sites [13]. They also display that oral epithelial cells are ACE2-positive, which indicates that oral cavity might provide possible routes of entry for the coronavirus. Interestingly, it has been demonstrated that the ACE2 is expressed in lymphocytes within oral mucosa, like found in lungs, and SARS-cov-2 attacks the lymphocytes and consecutively reduce the immune defense [13].

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 [15]. Both condition share risk factors such as chronic tobacco, smoke exposure and age [14].

Periodontal maintenance to limit systemic cytokine levels

Use of mouthwash and nasal spray by patients with confirmed or suspected COVID-19 as well as healthcare workers pre and post-treatment could minimize the risk of disease transmission [16] In vitro studies have demonstrated that povidone iodine gargling solutions were effective against SARS-CoV and MERSCoV [17]. Oral rinses can potentially alter the viral lipid envelope to help reduce disease transmission and viral load. The American Dental Association recommends using 0.2% to 0.5% povidone solutions or 1% hydrogen peroxide to reduce viral transmission. In hospitalized individuals, oral hygiene measures and reducing plaque build-up can minimize bacterial loads, which prevents aspiration of oral pathogens, and reduce the risk of pneumonia or respiratory illness. There is a higher risk of mortality in COVID-19 individuals with bleeding gums and concluded that mortality risk was higher in patients with periodontal disease. Hence, it is essential to assess oral health status in patients with COVID-19 to prevent adverse outcomes.

Conclusion

The theoretical evidence suggests a possible biological pathway evidencing two-way relationship among 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. The provided rationale could be used to design an observational study. The phenomenon of immune dysregulation, inflammation and dysbiosis needs to be more fully understood in this era of pandemic. Periodontal disease could further enhance cytokine release via altered microflora, expression of multiple viral receptors, bacterial superinfection, and aspiration of periodontal pathogens. Meanwhile it is recommended that oral hygiene should 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. So it is essential to maintain good oral hygiene and periodontal health to preserve overall health.

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