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# Nexus between COVID-19 and periodontal disease

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**Abstract**

Over the past several decades, studies have demonstrated the existence of bi-directional relationships between periodontal disease and systemic conditions. Periodontitis is a polymicrobial and multifactorial disease involving both host and environmental factors. Tissue destruction is primarily associated with hyperresponsiveness of the host resulting in release of inflammatory mediators. Pro-inflammatory cytokines play a major role in bacterial stimulation and tissue destruction. In addition, these cytokines are thought to underlie the associations between periodontitis and systemic conditions. Current research suggests that increased release of cytokines from host cells, referred to as the cytokine storm, is associated with disease progression in patients with coronavirus disease 2019 (COVID-19). An intersection between periodontitis and pulmonary disease is biologically plausible. Hence, we reviewed the evidence linking COVID-19, cytokines, and periodontal disease. Plaque control is essential to prevent exchange of bacteria between the mouth and the lungs, reducing the risk of lung disease. Understanding these associations may help identify individuals at high risk and deliver appropriate care at early stages.

**Keywords**

Coronavirus disease 2019, periodontitis, severe acute respiratory syndrome coronavirus 2, cytokine, cytokine storm, inflammation

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## Introduction

A pneumonia outbreak of uncertain etiology occurred in Wuhan, China, and subsequently developed into a global threat. The outbreak was deemed a pandemic by the World Health Organization on March 11, 2020. The causative agent was identified as a member of the Coronoviridae family and

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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 is a single stranded RNA virus and expresses a spike protein (S-protein) that mediates adhesion to and invasion of host cells.[2] The SARS-CoV-2 S-protein binds specifically to angiotensin-converting enzyme 2 (ACE-2) expressed in the lungs and kidneys and on myocardial cells. ACE-2 also found intra-orally, especially on salivary glands and the tongue. Currently, a new and more virulent variant of SARS- CoV-2, D614G, is spreading worldwide. The S-protein of this variant contains a replacement of G614 for D614.[3]

Periodontitis is a multifactorial disease leading to destruction of supporting structures. The relationship between periodontal disease and systemic conditions has been widely studied. Especially in respiratory diseases, plausible linking mechanisms include: (i) direct aspiration of oral pathogens into the lungs, (ii) alteration of mucous surfaces in the respiratory tract, favoring adhesion and invasion of pathogens; and (iii) hydrolytic enzymes secreted by periodontal pathogens inhibiting innate immune responses by degrading cytokines and other inflammatory mediators released from periodontal tissues, altering the respiratory epithelium and resulting in enhanced adhesion of pathogens.[4] Scannapieco et al. [5] concluded in a systematic review that there was a significant association between poor oral hygiene and nosocomial pneumonia. Another systematic review by Azarpazhooh et al.[6] suggested that antimicrobial oral hygiene measures could minimize the incidence of respiratory disease in elderly adults in nursing homes and intensive care units (ICUs). A recent systematic review and meta-analysis by Gomes-Filho et al. [7] reported moderate to strong associations between periodontitis and respiratory diseases including asthma (odds ratio [OR] 3.54, 95% confidence interval [CI] 2.47–5.07), chronic obstructive pulmonary disease (COPD) (OR 1.78, 95% CI 1.04–3.05), and pneumonia (OR 3.21, 95% CI 1.99–5.17).

Consequently, the infectious and inflammatory links between respiratory disease and periodontitis could also represent potential factors associated with exacerbation of coronavirus disease 2019 (COVID-19) respiratory distress. Alteration of cytokine profiles could be part of the potential mechanism responsible for the association between periodontal disease and COVID-19.

## Data collection

A literature search was performed using MEDLINE/PubMed, the Cochrane Library, Embase, Scopus and Google Scholar. Articles were selected if they included the following key words: COVID-19, periodontitis, SARS-CoV-2, cytokines, or cytokine storm. Articles were then analyzed and included based on their relevance to the topic. The search was limited to peer reviewed articles published from January 2020 to December 2020.

## COVID-19 and the cytokine storm

Most SARS-CoV-2-infected individuals are asymptomatic although a few develop mild to moderate symptoms. Less than 5% of individuals develop serious symptoms like acute respiratory distress syndrome (ARDS) and multiple organ failure requiring ICU support. Viral replication in host cells leads to activation of the NLRP3 inflammasome, resulting in release of pro-inflammatory cytokines. This inflammatory response is further enhanced by release of damage associated molecular patterns (DAMPs) following cell death. Hyper-responsive hosts show exaggerated cytokine release, referred to as a cytokine storm or

cytokine release syndrome.[8,9] In the early stages of viral infection, penetration of the virus into the epithelial layer leads to activation of innate immune responses. When the virus enters tissues, it can infect macrophages, dendritic cells and neutrophils and further enhance viral spread. The virus activates adaptive immune responses resulting in enhanced cytokine release and leading to differentiation of naïve T cells. Increased vascular permeability also plays a role in the cytokine storm, permitting the infiltration of effector cells and thereby intensifying proinflammatory cytokine release.[10]

Hypercytokinemia is a common consequence of SARS-CoV-2 infection and causes acute lung injury, followed by ARDS as its severe form, in a large proportion of patients. Local inflammation can spread to the systemic circulation causing sepsis, thrombocytopenia, leukopenia, and hyperthermia. Increased cytokine production enhances systemic levels of C-reactive protein (CRP), haptoglobin, fibrinogen, serum amyloid A, and $\alpha$1-antitrypsin. Moreover, increased cytokine production leads to enhanced vascular permeability, altered coagulation mechanisms, and enhanced complement activation. Cytokine production can induce excessive proliferation of monocytes/macrophages and excessive apoptosis of lymphocytes, leading to immunodeficiency.

Individuals infected with SARS-CoV and Middle East Respiratory Syndrome-CoV (MERS-CoV) had elevated levels of pro-inflammatory cytokines and chemokines.[11] Patients infected with MERS-CoV had elevated levels of interferon (IFN)-$\gamma$, tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)-15, and IL-17.[12] Earlier studies showed that serum pro-inflammatory cytokine levels in patients infected with SARS-CoV were also elevated, especially IFN-$\gamma$, IFN-$\gamma$-induced protein 10, IL-1$\beta$, IL-6, IL-12, and monocyte chemoattractant protein (MCP-1).[13]

## SARS-CoV-2 virus-host interactions

The course of the disease can be described by two or three main stages. In stage 1, individuals are mostly asymptomatic; this stage involves activation of innate immune responses following recognition of the virus via pathogen associated molecular patterns (PAMPs). At this stage there will be low levels of IFN-$\gamma$ secreted. At stage 2, patients present with less severe symptoms. This stage mainly involves activation of adaptive immune responses, leading to production of specific antibodies and T cells to limit inflammatory responses. Release of DAMPs also occurs at this stage, which may further enhance the inflammatory reaction. Finally, stage 3 involves the cytokine storm, characterized by hyper coagulability, multiorgan dysfunction and shock.[14]

Patients with COVID-19 show altered clotting cascades, as reflected by moderate to severe thrombocytopenia ($<50 \times 10^9$ platelets/L), increased D-dimer levels, prolonged prothrombin and partial thromboplastin times, and decreased fibrinogen ($<1.0$ g/L). Deterioration of these parameters over time, especially elevated D-dimer levels ($>0.5$ µg/L fibrinogen equivalent units), is indicative of severe disease. Changes in clotting cascade molecules are also associated with high mortality rates. Elevated levels of serum ferritin were also noted in patients with COVID-19, which are indicators of hemolytic events caused by hypercoagulation.

In a retrospective study, Chen et al. [15] evaluated the clinical and immunological features of patients with COVID-19. Among the 21 participants, 11 patients who were severely ill presented with significantly higher levels of CRP, lactate dehydrogenase, ferritin, alanine aminotransferase, D-dimer, IL-10, IL-6, and TNF-$\alpha$, as well as reduced CD4+ and CD8+ T cells counts compared with 10

patients who were moderately ill. Expression of IFN-$\gamma$ by CD4+ T cells declined in patients who were severely ill. The cytokine profiles of patients with COVID-19 were evaluated by Huang et al.[16] and showed elevated levels of pro-inflammatory cytokines. The authors also compared cytokine release in patients with COVID-19 treated in ICUs with release in patients who did not require ICU support. The results showed enhanced release of IL-1$\beta$, IFN-$\gamma$, chemokines (CCL2 and CXCL10), IL-6, IL-10, and TNF-$\alpha$ in patients admitted to the ICU compared with those with less severe infection. This evidence indicated the activation of Th 1 cell responses, which may be associated with the cytokine storm seen in patients who were severely ill.

IL-6 levels were used to assess the systemic cytokine load. IL-6 is considered a highly predictive indicator of COVID-19 mortality in older patients and patients with comorbidities.[17] COVID-19 associated cytokine responses most commonly involve elevated levels of macrophage associated cytokines such as IL-6, IL-10, and TNF-$\alpha$. Hence, IL-6 could be a predictor for COVID-19 mortality. Herold et al[18] assessed IL-6 levels in patients with COVID-19 who were critically ill to identify patients at high risk of respiratory failure requiring mechanical ventilation. The study showed a strong association between IL-6 levels and requirement for mechanical ventilation. The cut off value of IL-6 was 80 pg/mL; beyond this value the risk of respiratory failure was 22 times higher compared with patients with low IL-6 levels. Mandel et al. [19] evaluated the cytokine profiles of patients with COVID-19, including levels of IL-6, IL-1$\beta$, IL-8, and TNF-$\alpha$, to predict 30-day mortality in hospitalized patients. The authors suggested a cut-off value for predicting mortality; using this cut-off, only IL-6 significantly predicted 30-day mortality in patients with COVID-19. The cut-off value was 163.4 pg/mL with 91.7% sensitivity and 57.6% specificity. In a meta-analysis, Coomes et al. [20] suggested that there were 2.9-fold higher levels of IL-6 in patients with COVID-19 who were critically ill compared with patients with mild or moderate disease. Increased levels of IL-6 were significantly associated with adverse outcomes. IL-6 could be considered a potential target to regulate host responses and minimize COVID-19-associated adverse events.

Th17 responses were also shown to be elevated in patients infected with SARS-CoV and MERS-CoV.[21] In patients with COVID-19, Th17-mediated inflammatory responses may also play a role in enhanced cytokine release. Infection-associated elevated production of IL-6 by the immune system triggers activation of Th17 cells.[22] Recent studies have reported increased serum levels of IL-6 in patients with COVID-19 and showed a positive correlation with disease severity. Because of the pleotropic nature of IL-6, this molecule plays a key role in the cytokine release syndrome of patients with SARS-CoV-2.[23–27] Increased production of IL-17 by gingival tissues in patients with periodontal disease compared with healthy controls was reported by Graves et al.[28] Serum levels of IL-17 were also reported to be higher in patients with periodontitis. Cheng et al.,[29] reported that serum and gingival crevicular fluid (GCF) IL-17 levels were reduced following non-surgical periodontal therapy.

## COVID-19 and the role of psychological stress

Psychological stress also induces cytokine release and may therefore account for the cytokine storm in some cases of SARS-CoV-2 infection. Stress leads to activation of the "stress system" (i.e., the hypothalamic–pituitary–adrenal axis). As a response to stress, the hypothalamus secretes

corticotrophin-releasing hormone, which acts on the pituitary gland and triggers release of adrenocorticotrophic hormone. In turn, adrenocorticotrophic hormone stimulates the adrenal cortex to secrete cortisol in the blood, impairing immune defense mechanisms. Release of pro-inflammatory cytokines and neuropeptides can result in numerous neurological manifestations including psychological disorders, anxiety, depression, and post-traumatic stress disorder.[30] Both the central and peripheral nervous system are affected in patients with COVID-19.[31] Reported neurological effects of COVID-19 include headache, encephalitis, encephalopathy, myelitis, seizures, stroke, loss of smell and taste, and Guillain–Barré syndrome. A recent systematic review concluded that the COVID-19 pandemic has had a significant impact on physical and mental health. Thus, it is essential to administer psychological interventions as part of COVID-19 treatment.[32]

A positive correlation between stress and increased risk of periodontal disease has been reported. Stress elevates salivary cortisol levels, which in turn reduces immune responses and upregulates various inflammatory markers, leading to gingival inflammation and periodontal tissue destruction.[33] Periodontal therapy can play a major role in preventing tissue damage and thereby inhibit the release of inflammatory mediators. Anti-cytokine inhibitors like tocilizumab used in COVID-19 treatment may have anti-depressant effects that could be beneficial in reversing the psychological symptoms of stress.[34]

## Nexus between COVID-19 and periodontal disease

Periodontitis and poor oral hygiene disrupt the symbiotic relationships between oral microbes and can promote pro-inflammatory cytokine release. Bacteria in dysbiotic biofilms further stimulate cytokine release; these cytokines in GCF mix with saliva, and upon aspiration, may induce inflammation or infection within the lungs.[35] Interbacterial exchange between the lungs and the mouth potentially increases the risk of respiratory infections.[36] Zheng et al.[37] reported high neutrophil counts and lower lymphocyte counts in patients with severe COVID-19 compared with those with mild symptoms. Increased neutrophil counts are commonly associated with bacterial infections but more rarely observed in viral infections. Zheng et al. suggested that bacterial super-infection may be widespread in severe COVID-19 cases, and that bacterial infections could supersede the original viral infection. This hypothesis was supported by Zhou et al.,[38] who found that 50% of patients with severe COVID-19 died from secondary bacterial infections rather than from viral infection. Patients with comorbidities (diabetes, hypertension, COPD, cardiovascular and cerebrovascular disease) were at increased risk of post-viral complications and death from COVID-19.[39] The associations between these major comorbidities and oral biofilm dysbiosis in periodontal disease have been well studied.[40–42] Hence, the links between COVID-19 and periodontitis are important to acknowledge and understand.

During the initial stages of infection, the throat is a crucial region for viral replication. Recent studies showed that during the first week of infection, oropharyngeal swabs of patients infected with SARS-CoV-2 had elevated concentrations of viral RNAs, indicating active replication that peaked around day 4 post-infection.[43] The expression of ACE2 in the minor salivary glands is higher compared with the lungs. Thus, the salivary glands could act as a reservoir for SARS-CoV-2. To et al.[44] reported that live virus could be cultivated

using saliva samples from patients with COVID-19.

Nasal epithelial cells are a key reservoir for SARS-CoV-2 invasion and spread.[45] ACE2 is expressed at sites other than the nasopharyngeal region, including in the oral epithelial cells of the tongue, buccal mucosa, gingival tissues, periodontal pockets, and gingival crevices. Oral epithelial cells show higher expression of ACE2 and transmembrane protease serin 2 (TMPRSS2).[46] Trypsin like proteases such as TMPRSS2 are necessary to activate the SARS-CoV-2 S-protein to bind host cells.[47] Though these proteases were expressed in the oral cavity, periodontopathogens can also produce such proteases that may help activate the S-protein and further increase SARS-CoV-2 infectivity.[48]

Periodontal pockets provide favorable environments for replication of pathogenic viruses like human herpes simplex virus and human papillomavirus.[49] The virus may enter the systemic circulation from periodontal pockets via GCF and then mix with saliva, or may enter the systemic circulation via periodontal capillaries. Periodontium associated viruses can infect immune cells that continuously infiltrate the periodontal pocket.[50] In a recent clinical trial, Gupta et al.[51] assessed the presence of SARS-CoV-2 in GCF samples from 33 patients with COVID-19. Virus was detected only in asymptomatic carriers and patients who were mildly symptomatic, whereas individuals with poor oral hygiene had elevated inflammatory exudate levels. The authors concluded that periodontal pockets may aid in virus replication; as the viral load in GCF increases, the virus gains entry via saliva to the systemic circulation. Therefore, GCF could represent a potential mode of transmission. However, no direct association between virus levels in GCF and periodontal disease has been demonstrated. Current studies suggest that the periodontal pocket epithelium may be a focal point of infection for SARS-CoV-2,[50,52] and thus periodontal therapy could help minimize the systemic spread of viral pathogens.

Underlying systemic diseases appears to intensify infection with SARS-CoV-2. Most comorbid conditions (e.g., diabetes, hypertension, COPD, cardiovascular disease, and cerebrovascular disease) associated with COVID-19 severity also exaggerate periodontal disease. Although there is no clear causal link, periodontal disease could increase COVID-19 severity by causing microbial dysbiosis, bacterial superinfection, host hyper responsiveness, and immune system overstimulation. Together with other systemic conditions, periodontitis can play a role in enhancing inflammatory responses and the cytokine storm. Most likely, environmental, microbial, and inflammatory factors together contribute to disease progression.[53] Further clinical trials assessing periodontal status in patients with COVID-19 are needed to more firmly establish links between SARS-CoV-2 and periodontal disease (Figure 1).

## Periodontal maintenance to limit systemic cytokine levels

A recent Cochrane review suggested that preprocedural 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.[54] *In vitro* studies have demonstrated that povidone iodine gargling solutions were effective against SARS-CoV and MERS-CoV,[55] but the effectiveness of preprocedural rinses against SARS-CoV-2 remains unclear. 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

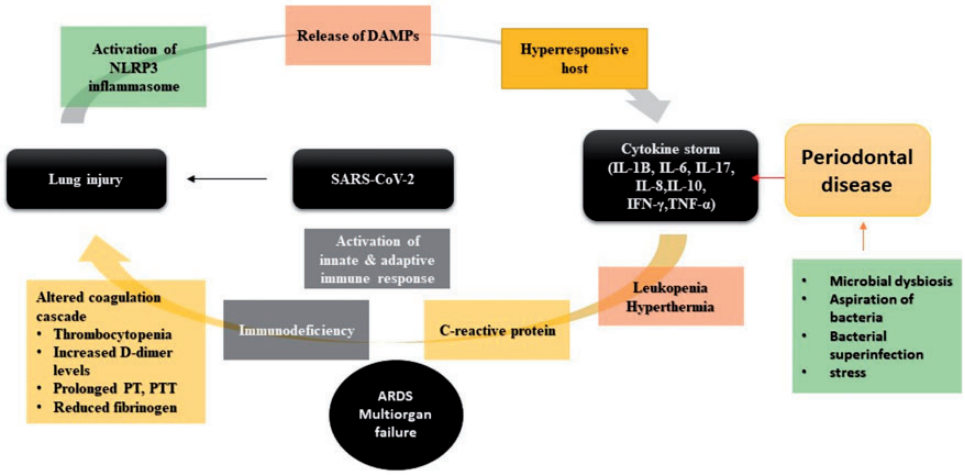


**Figure 1.** Potential links between periodontal disease and coronavirus disease (COVID-19). Persistent periodontal disease leads to hyper-responsiveness of the host and results in release of inflammatory cytokines. These cytokines can enter the systemic circulation, or virus may be transferred via GCF to saliva and then to systemic circulation. Bacteria may be aspirated and thus reach the upper or lower respiratory tract. Through all these potential mechanisms, periodontal disease can induce systemic inflammation. In addition, stress contributes to local and systemic inflammatory responses. All these factors together enhance cytokine release and alter the respiratory epithelium, predisposing to inflammation, infection, and respiratory complications like acute respiratory distress syndrome. Lung injury activates the NLRP3 inflammasome and results in release of damage associated molecular patterns (DAMPs), further enhancing cytokine release. The elevated cytokine levels in patients with periodontitis could exacerbate the inflammatory effects of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.
IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; PT, prothrombin time, PTT, partial thromboplastin time.

1% hydrogen peroxide to reduce viral transmission. In hospitalized individuals, oral hygiene measures and reducing plaque build-up can minimize bacterial loads, prevent aspiration of oral pathogens, and reduce the risk of pneumonia or respiratory illness. Larvin et al,[56] assessed the impact of periodontal disease on COVID-19 outcomes. The authors found 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.

ACE2 is the primary receptor for SARS-CoV-2. Upon viral infection and replication, ACE2 expression is downregulated, resulting in an acute inflammatory response. ACE2 helps balance cytokine levels; higher levels of ACE2 downregulate proinflammatory cytokines including IL-6, IL-7, IL-2, MCP-1, TNF-$\alpha$ and IL-1$\beta$. However, higher levels of ACE2 aid entry of SARS-CoV-2 virus into the oral cavity.[57] The ACE2-SARS-CoV-2 complex reduces ACE2 expression on the cell surface and results in increased production of cytokines. Administration of ACE inhibitors might increase ACE2 levels and enhance the anti-inflammatory response. Combinations of periodontal therapy and ACE inhibitors might reduce periodontal disease progression and thereby minimize the risk of adverse COVID-19 outcomes.[58]

Recent studies have demonstrated that a strong association between elevated levels of IL-6 and COVID-19 adverse outcomes. Thus, non-surgical periodontal therapy along with treatment using anti-cytokine inhibitors may have beneficial effects in patients infected with SARS-CoV-2. Treatment with the IL-6 antagonist tocilizumab during the early stages of COVID-19 has shown beneficial effects. A retrospective study showed that patients with COVID-19 in ICUs who received tocilizumab had reduced mortality.[59] Other agents like anakinra and siltuximab are being evaluated in clinical trials for treatment of SARS-CoV-2-infected individuals.

Early detection and treatment of periodontal disease, as well as identification of hyperresponsive individuals through cytokine profiling, may assist in selection of appropriate anti-cytokine drugs. Though promising outcomes have been reported following treatment of patients with COVID-19 with immunomodulators, further clinical trials are required to understand the efficacy and safety of these drugs according to disease stage and severity.

## Conclusion

The current evidence suggests that increased production of pro-inflammatory cytokines is the foremost cause of the adverse events related to COVID-19. Periodontal disease could further enhance cytokine release via altered microflora, expression of multiple viral receptors, bacterial superinfection, and aspiration of periodontal pathogens. SARS-CoV-2 can penetrate the blood-brain barrier via the olfactory bulb. Though SARS-CoV-2 infects cells only through ACE2 receptors, the mechanisms through which virions induce deleterious effects in the central nervous system remain unclear. The relationships between COVID-19 psychological stress and periodontal disease could be mediated by altered cytokine responses following viral replication. Further clinical trials evaluating periodontal status in patients with COVID-19 are required to determine the exact mechanisms. Because poor oral hygiene could exaggerate SARS-CoV-2 infection, it is essential to maintain good oral hygiene and periodontal health to preserve overall health.

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