



## Correlation of periodontal disease and complications of COVID-19: an integrative review

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### Abstract

COVID-19 is a disease caused by a virus called SARS-CoV-2 that can cause damage to the lungs and other organs, of which most patients with COVID-19 have mild symptoms, however, some can develop serious illnesses such as pneumonia, edema lung disease, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndromes that can lead to death. In patients with compromised oral health who become infected with the SARS-CoV-2 virus, the virus can enter the systemic circulation of the periodontal pockets via gingival crevicular fluid (GCF) and then mix with saliva, or it can enter the systemic circulation via periodontal capillaries. In this way, the viruses associated with the periodontium can infect cells of the immune system that continually infiltrate the periodontal pocket. The literature reviews used and the observation of randomized studies were from the Bireme, PubMed, SciELO, and LILACS databases from 2007 to March 2021. To show that periodontal disease can further increase the release of cytokines via altered microflora, which cause complications in patients affected by Covid-19.

**Keywords:** Periodontitis. Covid-19. Cytokine.

### Introduction

The first cases of coronavirus disease 2019 (COVID-19) likely came from a zoonotic transmission in China in December 2019, linked to a large seafood market that also traded live wild animals [1]. For To et al., 2020 [2] rapid and accurate detection of nCoV 2019

is crucial to control the outbreak in the community and in hospitals of which, nasopharyngeal and oropharyngeal swabs are the types of upper respiratory tract exams recommended for testing 2019-nCoV diagnosis.

Paju et al., 2007 [3] report that one cubic millimeter of dental plaque contains about 100 million bacteria and can serve as a persistent reservoir for potential pathogens, oral and respiratory bacteria. Thus, periodontal diseases are a group of chronic inflammatory diseases, including gingivitis and periodontitis. These diseases are caused by various microbial agents that cause inflammation and destruction of tooth support tissues [4].

Still, according to the World Health Organization (WHO), periodontal disease affects 10% of the world's population, of which poor oral hygiene, smoking, diabetes, medication, age, heredity, and obesity have been linked to an increased risk of disease periodontal [4]. In the case of SARS-CoV-2, known and suspected affinity features of this virus for specific membrane receptors are compatible with a hypothetical affinity for periodontal cells, this may involve the outer and inner epithelial lining or gingival/periodontal ligament fibroblasts [5].

This is why periodontitis and poor oral hygiene disrupt symbiotic relationships between oral microbes and can promote the release of pro-inflammatory cytokines. Bacteria in dysbiotic biofilms further stimulate cytokine release; these cytokines in the gingival crevicular fluid (GCF) mix with saliva and, after aspiration, can induce inflammation or infection in the

lungs [6].

## Literature review COVID-19 pandemic

An outbreak of pneumonia of uncertain etiology occurred in Wuhan, China, and later became a global threat, the outbreak was declared a pandemic by the World Health Organization on March 11, 2020 [6]. SARS-CoV-2 is a virus of the Coronavirus family, for which its outbreak has caused a major coronavirus disease (COVID-19) pandemic, the primary entry of this virus is believed to be by projected droplets that lead to the first contact and colonization of cells in the oral cavity, nose or eyes [5].

Sukumar et al., 2021 [6] explain that the causative agent was identified as a member of the Coronaviridae family and initially named in 2019 novel coronavirus (2019-nCoV); thereafter the virus was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) being a single-stranded RNA virus and expressing a spike protein (S protein) that mediates host cell adhesion and invasion.

### SARS-COV-2 virus-host interaction

People with a positive diagnosis for this virus will develop variable symptoms in mild cases such as fever, cough, headache, anosmia, ageusia, etc. Moderate to severe cases such as respiratory failure can occur and can, in some cases, lead to hospitalization in the intensive care unit and eventually death [5].

Sukumar et al., 2021 [6] explain the course of the disease can be described in two or three main stages. In stage 1, individuals are mostly asymptomatic; this stage involves the activation of innate immune responses after recognition of the virus through pathogen-associated molecular patterns (DAMPs), at this stage there will be low levels of secreted IFN- $\gamma$ . In stage 2: patients have less severe symptoms. This stage mainly involves the activation of adaptive immune responses, leading to the production of specific antibodies and T cells to limit inflammatory responses. The release of DAMPs also occurs at this stage, which can further increase the inflammatory reaction. Stage 3 involves the cytokine storm, characterized by hypercoagulability, multiple organ dysfunction, and shock.

### Cytokines

Angiotensin-converting enzyme-2 (ACE2) has been considered the main receptor for virus entry into target cells. Furin, a proprotein convertase, is implicated in virus infection by the cleavage of viral envelope

glycoproteins. ACE2 is expressed by various cell types such as lung cells, nasopharyngeal cells, salivary gland cells, etc. In recently published preprint data, cells in the oral cavity were found to highly express ACE2, in a manner comparable to lung cells. Furthermore, in addition to ACE2, Furin is also expressed in oral epithelial cells [5].

For Paju et al., 2007 [7] the cytokines and enzymes induced from the periodontal tissues inflamed by the oral biofilm can also be transferred to the lungs, where they can stimulate local inflammatory processes that precede the colonization of pathogens and the actual pulmonary infection.

Changes in oral microbial communities can affect the microenvironment with an increase in pathogens and overstimulation of the immune system. Co-infection of the SARS-Cov-2 virus with established risk factors and comorbidities may play a role in enhancing the inflammatory response and cytokine storm [3].

Sukumar et al., 2021 [5] explain that viral replication in host cells leads to the activation of the NLRP3 inflammasome, resulting in the release of pro-inflammatory cytokines. This inflammatory response is further enhanced by the release of damage-associated molecular patterns (DAMPs) after cell death, hyperresponsive hosts exhibit an exaggerated release of cytokines, known as cytokine storm or cytokine release syndrome. In the early stages of viral infection, penetration of the virus into the epithelial layer leads to the activation of innate immune responses. When the virus enters tissues, it can infect macrophages, dendritic cells, and neutrophils and further increase viral spread. The virus activates adaptive immune responses, resulting in increased release of cytokines and leading to the differentiation of naive T cells. Increased vascular permeability also plays a role in a cytokine storm, allowing the infiltration of effector cells and thus enhancing the release of pro-inflammatory cytokines.

### Periodontitis x COVID-19 infection

Periodontal disease has long been considered a silent pandemic that has a complex multifactorial pathophysiology with evidence-based claims of immune-mediated pathogenesis. There has been a demonstration of an increase in IL-17-producing cells in the gingival tissue of patients suffering from gingivitis and periodontitis compared to healthy controls, not only that but high levels of IL-17 were found in the serum of patients suffering from periodontal disease also [8].

Badran et al., 2020 [4] report that the possible sources of initial viral infection from the infection of periodontal tissues can be the following direct infection of gingival epithelial cells exposed to the oral cavity,

migration of the virus through the bloodstream or infected immune cells in the periodontal inflammatory infiltrate. These earlier observations point to the fact that periodontal diseases are incompatible environments for viral infection and survival.

Furthermore, with the ongoing inflammatory response associated with periodontal pockets, immune cells potentially infected with viruses could reach the periodontal connective tissue and migrate to the subgingival area. The viral presence detected with conventional methods, mainly PCR was found in many locations of periodontal pockets: gingival tissues, subgingival plaque, and in gingival crevicular fluid (GCF), the latter is an inflammatory exudate generated in periodontal tissues and released into the periodontal pocket to “release” the subgingival space. Furthermore, the composition of gingival crevicular fluid (GCF) is rich in epithelial and immune cells, antibodies, microbial metabolites, biomarkers, etc. If crevicular gingival fluid could harbor SARS-CoV-2 released from infected periodontal cells or terminal capillary complexes in periodontal tissues, the viruses could reach the oral cavity [4].

Sukumar et al., 2021 [5] explain that persistent periodontal disease leads to host hyperresponsiveness and results in the release of inflammatory cytokines, these cytokines can enter the systemic circulation, or the virus can be transferred via the gingival crevicular fluid (GCF) into the saliva and then into the systemic circulation.

Bacteria can 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 increase the release of cytokines and alter the respiratory epithelium, predisposing it to inflammation, infection, and respiratory complications such as acute respiratory distress syndrome. Lung injury activates the NLRP3 inflammasome and results in the release of damage-associated molecular patterns (DAMPs), further increasing cytokine release, elevated cytokine levels in patients with periodontitis may exacerbate the inflammatory effects of severe acute respiratory syndrome infection by coronavirus 2 (SARS-CoV-2) [5].

### Transmissibility of the virus

Like the other respiratory coronaviruses, SARS-CoV-2 is transmitted primarily by respiratory droplets, with a possible but unproven route of fecal-oral transmission. In infection, the average incubation period is approximately 4-5 days before the onset of symptoms, and 97.5% of symptomatic patients [1].

Respiratory pathogens such as influenza are also transmitted via airborne dispersion of small-particle aerosols ( $\leq 5 \mu\text{m}$ ) when an infected individual breathes, coughs, or sneezes, while respiratory syncytial viruses, SARS-CoV and MERS-CoV can spread. In large droplets propelled through the air and inoculated into the eyes, nose, and mouth at a short distance [6].

### Oral dysbiosis

Oral dysbiosis is the loss of homeostatic balance of oral microbial communities with the host and is associated with oral diseases such as periodontal disease. The main pathogens associated with periodontal disease are *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* (red complex), but there are more pathogenic bacteria, including species of the genera *Prevotella*, *Desulfobulbus*, and *Selenomonas*, as well as *Aggregatibacter* and others. Host factors, such as diet and the immune system, are determinants for the emergence and persistence of dysbiosis that allows the growth of pathobionts and their virulence factors in periodontal disease. Microbial communities execute a mechanism called “polymicrobial synergy and dysbiosis” that allows the interaction between bacteria to become a dysbiotic community, where pathobionts grow and stimulate inflammation and tissue damage. These pathobionts successfully escape epithelial barriers and a host immune response through mechanisms such as neutrophil manipulation, inhibition of macrophage response, or complement subversion [3].

### Discussion

Bradran et al., 2020 [4] report that periodontal pockets are isolated peculiar environments presenting adequate biological dynamics, with bidirectional interactions with the oral cavity on the one hand and the systemic circulatory system via gingival peripheral blood vessels on the other. Sahini et al, 2020 [8] and Badran et al., 2020 [4] state that several pathophysiological mechanisms have been presented to explain their behavior, one of which is the fact that their symptoms seem to be related to a 'cytokine storm' that presents as elevated serum levels of IL-1 beta, IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, GM-CSF, G-CSF, IFN-gamma, TNF alpha, MIP1A, MIP1B, MCP1, and IP10.

Underlying systemic diseases appear to intensify infection with SARS-CoV-2 of which most comorbidities (eg, diabetes, hypertension, COPD, cardiovascular disease, and cerebrovascular disease) associated with the severity of COVID-19 also exaggerate periodontal disease [5,9]. However, Sukumar et al., 2021 [5] say that although there is no clear causal link, periodontal

disease can increase the severity of COVID-19, causing microbial dysbiosis, bacterial superinfection, host hyperresponsiveness and overstimulation of the immune system. , but agreeing with other authors, along with other systemic conditions, periodontitis may play a role in increasing inflammatory responses and cytokine storm, most likely environmental, microbial and inflammatory factors together contribute to disease progression.

Furthermore, if bacterial biofilms in the periodontal pocket have been the main focus of the scientific dental community, the viral presence and its implications for periodontal health and disease have become progressively plausible over time with the cumulative knowledge gained [4].

On the other hand, Badran et al., 2020 [4] also reports that it has been shown that viruses associated with the periodontium can infect cells of the immune system such as macrophages, T lymphocytes, etc. These continuously reach the inflammatory infiltrate in the mucosal wall. This could be another potential source of viruses found in the periodontal pocket, the question of whether SARS-CoV-2 could infect these specific types of inflammatory cells is open to debate among the authors. Metagenomic analysis of patients with severe COVID-19 disease reported the emergence of the genera *Prevotella*, *Fusobacterium*, and *Veillonella*, which are associated with periodontal disease [3].

Pitones-Rubio et al., 2020 [3] agree, claiming that in addition, some research suggests that the virus recognizes the ACE2 receptor, which is located in the nasopharynx, but also in the oral mucosa, therefore, the entry of the virus can subvert the host's immune system and oral microbiota triggering a dysbiosis that allows for superinfection, explaining the association of periodontal disease with severe COVID-19.

Previous data related to SARS-CoV indicated that the latter can infect and replicate in mononuclear cells, but for a limited time, a similar pattern of actions has been described for T lymphocytes that infect SARS-CoV-2, but with a trigger. of apoptosis of infected cells. It remains unclear whether SARS-CoV-2 replication is deficient in all inflammatory cells and that furthermore, SARS-CoV-2 infection of endothelial cells seems possible [4].

Larvin et al., 2020 [9] and Sukumar et al., 2021 [5] state that it has been suggested that COVID-19 could be related to periodontal disease due to shared risk factors, which include obesity, age, and hypertension. Larvin et al., 2020 [9] confirm that in addition, there is increasing evidence of bacterial coinfection in COVID-19 hospitalizations, while ventilator-associated pneumonia is also a reported complication in hospitalized patients with COVID-19.

Furthermore, the association between periodontal disease and severe COVID-19 disease may be non-causal, suggesting that prevention or treatment of periodontal disease does not prevent worse progression and outcome of COVID-19. Future studies on the periodontal status of patients with COVID-19, including mild to severe forms, may allow for the timely identification of people at risk for severe disease and the generation of relevant recommendations [3,10].

## Conclusion

The recent study shows that given the hypotheses raised that periodontal disease could act as a reservoir of SARS-CoV-2 complications, it is quite relevant, as it is a common pathway of inflammatory response related to increased production of pro-inflammatory cytokines. the main cause of adverse events related to COVID-19. Therefore, understanding this association underscores the importance of keeping periodontal disease under control and the value of maintaining meticulous oral hygiene in the COVID-19 era and further points to the possibility that periodontal disease may predispose to adverse outcomes related to COVID-19, but it is worthy of further studies related to the correlation of the worsening of COVID-19 in patients with active periodontal diseases at the time of disease activation.

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No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

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## References

1. Tay MZ, Poh CM, Rénia L, Macary PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol.* 2020;20(6):363374. doi:10.1038/s41577-020-0311-8.
2. To KK, Tsang OT, Yip CC, Chan KH, Wu TC, Chan JM et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 71(15), 841– 843, 2020. <https://doi.org/10.1093/cid/ciaa149>.
3. Pitones-Rubio V; Chávez-Cortez, EG; Hurtado-Camarena A; Gonzalez-Rascón, A; Serafin-Higuera, N. A doença periodontal é um fator de risco para doença COVID-19 grave? *Med Hypotheses.* 2020; 144: 109969. doi: 10.1016/j.mehy.2020.109969.
4. Badran Z, Gaudin A, Struillou X, Amador G, Soueidan A. Periodontal pockets: A potential reservoir for SARS-CoV-2?. *Medical hypotheses*, 143, 109907, 2020. <https://doi.org/10.1016/j.mehy.2020.109907>.
5. Sukumar K, Tadepalli A. Nexus entre COVID-19 e doença periodontal. *J Int Med Res.* 2021; 49 (3): 3000605211002695. doi: 10.1177/03000605211002695.
6. Eggers M, Koburger-janssen T, Eickmann M, Zorn J. Eficácia Bactericida e Virucida In Vitro de Gargarejo de Povidona-Iodo / Colutório Contra Patógenos Respiratórios e do Trato Oral. *Doenças infecciosas e terapia*, 7 (2), 249-259, 2018. <https://doi.org/10.1007/s40121-018-0200-7>.
7. Paju S, Scannapiego FA. Oral biofilms, periodontitis, and pulmonary infections. *Oral diseases*, 13(6), 508–512, 2007. <https://doi.org/10.1111/j.16010825.2007.01410a.x>.
8. Sahni V, Gupta S. COVID-19 & Periodontitis: The cytokine connection. *Medical hypotheses*, 144, 109908, 2020. <https://doi.org/10.1016/j.mehy.2020.109908>.
9. Larvin H., Wilmott S., Wu J., Kang J. The Impact of Periodontal Disease on Hospital Admission and Mortality During COVID-19 Pandemic. *Frontiers in medicine*, 7, 604980, 2020. <https://doi.org/10.3389/fmed.2020.604980>.
10. Matuck FB., Dolhnikoff M, Maia G, Issac Sendyk D, Zarpellon A, Costa Gomes S et al. Periodontal tissues are targets for Sars-Cov-2: a post-mortem study. *Journal of oral microbiology*, 13(1), 1848135, 2020.

