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Association Between Periodontitis and COVID-19

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Abstract

Purpose of Review Periodontitis has been linked to various systemic diseases and conditions. Given their shared comorbidities, extensive research has been carried out to explore the link between periodontitis and COVID-19.

Recent Findings A growing body of evidence suggests that periodontitis could increase the risk of COVID-19 infection and its complications. It has been suggested that the association between the two diseases could be due to immunological, coagulation, genetic, and microbiological reasons. The effect of periodontitis on the immune system could increase the expression of receptors used by SARS-CoV2 to infect cells (transmembrane protease, serine 2 [TMPRSS2], and angiotensin-converting enzyme 2 [ACE2]) and prime the immune system to an exacerbated immune reaction against the virus. Moreover, there is evidence indicating that periodontitis could also increase the risk of COVID-19 complications by altering the coagulation pathways, and periodontal pathogens were identified in the respiratory system of patients suffering from severe COVID-19. In addition, it was also found that patients suffering from both diseases share some genetic similarities, suggesting that both diseases could be linked through common genetic pathways.

Summary In this review, we discuss the above-mentioned associations and make the case for the prevention and treatment of periodontitis to avoid SARS-CoV-2 infection and complications.

Keywords Periodontitis · COVID-19 · SARS-CoV-2 · Cytokines · Coagulopathy · Inflammatory cytokines · Coagulopathy · Genetics

Introduction

The coronavirus disease of 2019 (COVID-19) is a contagious infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is characterized by mild respiratory illness in most patients; however, some patients can become seriously ill, especially those with comorbidities [1–3]. Severe COVID-19 occurs not only due to viral burden but also due to deregulated immune and inflammatory response [1]. In moderate-to-severe COVID-19, there is an exacerbated innate host response that results in the release of pro-inflammatory cytokines into the peripheral bloodstream, particularly interleukin (IL)-6, IL-10, IL-2, and IL-17 [2, 3].

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Periodontitis is an infectious/inflammatory disease of tooth-supporting structures, which is caused by host-microbial interaction leading to an infectious-inflammatory response and subsequent destruction of tooth-supporting structures [4, 5]. Besides its local effect, periodontitis also involves the release of pro-inflammatory biomarkers and periodontal pathogens into the bloodstream [6, 7], resulting in low-grade endotoxemia and systemic inflammation [8, 9]. This leads to the reprogramming of hematopoietic stem and progenitor cells (HSPCs), an altered responsiveness of immune cells [10], and increased formation of neutrophil extracellular traps (NETs) [11]. The low-grade periodontal inflammation can also affect overall health and aggravate other systemic conditions such as diabetes mellitus, cardiovascular diseases, adverse pregnancy outcomes, respiratory diseases, and dementia [12, 13].

COVID-19 infection and complications have been associated with many of the above-mentioned systemic conditions. Moreover, severe COVID-19 shares many inflammatory biomarkers with periodontitis. For these reasons, researchers have hypothesized since the early days of the COVID-19

pandemic that there could be an association between the two diseases [14, 15]. This includes two separate possible associations, firstly, the risk of increased initial SARS-CoV-2 infection in individuals with periodontitis, and, secondly, the risk of increased COVID-19 severity in those with periodontitis. So far, several clinical studies have corroborated the hypothesis. In this review, we summarize the available evidence on the association between COVID-19 and periodontitis as well as the possible mechanisms responsible for this nexus.

Association Between Risk of SARS-CoV-2 Infection and Periodontitis

Several studies have investigated the possible association between periodontitis and the risk of SARS-CoV-2 infection. A case–control study ($N=149$) evaluated the association between periodontitis and SARS-CoV-2 infection by comparing the periodontal conditions of SARS-CoV-2-positive cases to SARS-CoV-2-negative controls [16•]. SARS-CoV-2-positive patients presented increased levels of plaque and calculus scores, tooth mobility, gingival bleeding, probing pocket depth, gingival recession, and clinical attachment loss. Another Mendelian randomization study investigating the possible causal impact of periodontal disease on SARS-CoV-2 infection found a significant association between periodontitis and SARS-CoV-2 infection risk using inverse-variance weighted (IVW) (odds ratio [OR] = 1.024, $P=0.017$, 95% confidence interval [CI] 1.004–1.055) and weighted median methods (OR = 1.029, $P=0.024$, 95% CI 1.003–1.055) [17•]. Moreover, Guardado-Luevanos et al. [18•] carried out a blinded case–control study ($N=234$) to evaluate whether periodontitis acts as a risk factor for SARS-CoV-2 infection using a self-reported periodontal disease questionnaire. They found that SARS-CoV-2-positive patients presented higher levels of self-reported periodontitis than negative patients (OR = 3.3, 95% CI 1.8–6.0). Another study was performed on UK biobank participants tested for SARS-CoV-2 who had also completed a self-reported survey of indicators on periodontal health ($N=13{,}253$). This study found no significant association between the risk of SARS-CoV-2 infection and indicators of periodontal health such as painful or bleeding gums and loose teeth (OR 1.10, 95% CI 0.72–1.69; OR 1.15, 95% CI 0.84–1.59) [19•]. Mendelian randomization (MR) analyses by using data from the OpenGWAS database showed a positive association between SARS-CoV-2 infection risk and periodontitis (OR = 1.02 (95% CI, 1.00–1.05), $P=0.0171$). Moreover, it was also found that the gingival crevicular fluid (GCF) IL-1β levels were associate with increased susceptibility to SARS-CoV-2 infection (OR = 1.02 (95% CI, [1.01–1.03]), $P<0.001$) [20•]. The above-mentioned associations between periodontitis and the risk of SARS-CoV-2 infection could be due to the increased expression of SARS-CoV-2 receptors in patients with periodontitis, such as transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2). Indeed, animal studies have shown that periodontitis seems to increase the expression of TMPRSS2 in gingival keratinocytes in a mouse model [21•]. Also, a bioinformatic model predicted that periodontitis-induced increased microRNA-146a and microRNA-155 in the oral cavity could upregulate the expression of ACE2 [22•], which is essential for SARS-CoV-2 infection, and modulate the host antiviral response.

Taken together, the results of the studies discussed above provide evidence on the possible mild association of periodontitis with increased susceptibility to SARS-CoV-2 infection.

SARS-CoV-2 in Periodontal Tissues/Pockets

In addition, some studies have investigated the presence of SARS-CoV-2 in periodontal tissues. A study on post-mortem biopsies ($N=7$) using RT-PCR demonstrated the presence of SARS-CoV-2 RNA in the periodontal tissues of deceased COVID-19 patients [23]. Another study evaluating the presence of SARS-CoV-2 in periodontal pockets of COVID-19 patients ($N=72$) using real-time polymerase chain reaction (RT-PCR) found that 41.7% of symptomatic COVID-19 cases presented SARS-CoV-2 in their periodontal pockets [24]. Moreover, a study assessing the SARS-CoV-2 RNA load in the gingival biofilm of COVID-19 patients admitted to the intensive care unit (ICU) ($N=52$) found that the presence and load of the viral RNA in the gingival biofilm were associated with longer stay in the ICU [25••]. These findings could suggest that periodontal pockets could act as a source of SARS-CoV-2 and as a reservoir for the virus.

Association Between Periodontitis and COVID-19 Severity

Several studies have investigated the association between periodontitis and COVID-19 complications. Studies assessing periodontitis through self-reported questionnaires, dental radiographic assessments, and periodontal clinical examination before and during the course of the COVID-19 infection have all reported similar results corroborating the association between COVID-19 severity and periodontitis. A case–control study assessing periodontitis using self-reported questionnaires ($N=234$) not only showed that periodontitis was associated with a higher risk of initial infection but also that periodontitis

was associated with an increased risk of developing a higher number of COVID-19 symptoms [18•]. Another study using a similar methodology ($N = 13,253$) found that self-reported oral health risk indicators such as gingival bleeding and painful gums were associated with high mortality rates (OR 1.71, 95% CI 1.05–2.72) but not with hospital admission (OR 0.90, 95% CI 0.59–1.37) [19•]. A retrospective longitudinal study on obese COVID-19 patients ($N = 58,897$) used the same method for assessment of periodontitis and found significant associations between the presence of periodontitis and COVID-19 outcomes including the hospital admissions (hazard ratio, 1.57; 95% CI, 1.25 to 1.97) and mortality (hazard ratio, 3.11; 95% CI, 1.91 to 5.06) [26••].

Studies assessing periodontitis using radiographic signs of periodontal bone loss found similar observations. A study on 87 severe COVID-19 patients that survived ICU hospitalization found that 50% of them had signs of periodontal bone loss and severe periodontitis [27•]. Another record-based case–control study ($N = 568$) found an association between periodontitis and COVID-19 complication including death (OR = 8.81, 95% CI 1.00–77.7), ICU admission (OR = 3.54, 95% CI 1.39–9.05), and need for assisted ventilation (OR = 4.57, 95% CI 1.19–17.4) [28••]. A retrospective cohort study on radiographic data ($N = 188$) also found that patients with periodontitis were three times more likely to be associated with COVID-19 complications ($P = 0.025$) [29•].

A record-based case–control study ($N = 1325$) comparing COVID-19 patients who suffered complications (death, ICU admissions, and/or mechanical ventilation) to those who recovered without major complications also found that radiographic signs of periodontitis were associated with higher risk of COVID-19 complications (i.e., need for mechanical ventilation [adjusted odds ratio [AOR] = 3.32, 95% CI 1.10–10.08, $P = 0.034$]) [30•].

Few studies used clinical periodontal examinations to investigate the association between COVID-19 and periodontitis, and they have also found similar results as the studies based on self-reported questionnaires and dental radiographic assessments. For instance, Kalsi et al. [31•] found that pre-COVID-19 levels of CRP, probing depth, and clinical attachment loss were all higher among patients ($N = 44$) who ended up suffering from moderate-to-severe COVID-19 as compared to those who were not infected or only suffered from mild COVID-19. Furthermore, a study designed to assess links between periodontitis and COVID-19 severity found an odds ratio for death of 14.48 in those with active periodontitis on the basis of clinical examination [32]. In summary, the results of the above studies provide evidence of a strong association between periodontitis and COVID-19 severity.

Mechanisms Behind the Association Between Periodontitis and COVID-19

Five main possible hypotheses have been proposed as possible mechanisms associating COVID-19 severity with periodontitis. Potential direct mechanisms could relate to the effect of periodontal pathogens on the respiratory system or direct translocation of SARS-CoV-2 from the mouth via the blood stream. Indirect mechanisms involve the effect of periodontitis on systemic inflammation and coagulation. Moreover, there is also evidence suggesting that genetic variants could also play a role in both COVID-19 and periodontitis. Below we discuss the evidence for each one of these possible hypotheses while acknowledging that a combination of these processes may be in action.

Inflammatory Hypothesis

Several studies have provided clinical evidence of potential inflammatory pathways involved in the association between periodontitis and COVID-19 severity. For instance, blood levels of CRP, a key inflammatory biomarker associated to the COVID-19 inflammatory response, have been found to be significantly higher in COVID-19 patients with radiographic signs of periodontal bone loss in a retrospective study ($N = 568$) [28••], and with increased probing depths and clinical attachment loss in a prospective study ($N = 82$) [33••]. In the same study, serum levels of ferritin and HbA1c in COVID-19 patients were also significantly associated with probing depth [33••]. This increase in ferritin could be related to increased levels of hepcidin, an iron-regulating hormone that is upregulated in both periodontitis and COVID-19 [32]. Blood levels of white blood cells were also higher in COVID-19 patients with signs of periodontitis [28••].

These associations between periodontitis and COVID-19 inflammatory biomarkers could be due to the fact that both diseases share common immune pathways. For example, the nuclear factor kappa B (NF-κB) pathway, which is excessively activated in periodontitis [34], is also activated by SARS-CoV-2 [35] inducing a wide spectrum of pro-inflammatory cytokines. This pathway activates T cells (TH1 and T TH17 cells) and can result in the production of numerous acute-phase proteins and adhesion molecules that can cause a vascular leak syndrome and eventually pulmonary inflammation and edema [36]. Other inflammatory pathways shared by both periodontitis and COVID-19 include the NLRP3/IL-1β and the IL-6 signaling pathways, which can shift the systemic inflammation towards a more destructive response [37].

Microbiological Hypothesis

Some studies have suggested that periodontal pathogens could also play a direct role in COVID-19. One study showed dysbiosis of the oral microbiome in COVID-19 patients ($N=75$). However, this study did not clarify if this was a cause or a consequence of SARS-CoV-2 infection [38•]. Another in vitro study found that the supernatant of the culture medium of *Fusobacterium nucleatum*, a key periodontopathogenic bacterium, upregulates the expression ACE2 in alveolar epithelial cells, and increases the production of IL-6 and IL-8 by alveolar, bronchial, and pharyngeal epithelial cells [39]. These findings would suggest that the presence of *Fusobacterium nucleatum* could play a role in increasing the risk of SARS-CoV-2 infection and inflammatory complications observed in patients with periodontitis.

Moreover, a study on 110 COVID-19 patients that underwent bacterial culture from respiratory sites (i.e., lungs) found nine cases of positive cultures, five of whom were in periodontitis subjects [30•], and four of the identified pathogens are known to be associated with periodontitis (*Staphylococcus epidermidis* and *Klebsiella pneumonia*). Even though these numbers were small, they presented an extremely high mortality (four out of the nine patients with positive cultures died). These findings suggest that the oral microbiome might be playing a direct role in SARS-CoV-2 infection and complications, although further research is needed to confirm this hypothesis.

Hypercoagulable State

COVID-19 can cause coagulation disorders that are behind many of the severe complications associated with the disease. Interestingly, biomarkers of coagulation associated with COVID-19 complications, such as D-dimer, are also present in patients with periodontitis. Two independent studies found an association between these coagulation biomarkers and the presence of periodontitis in COVID-19 patients. In the case–control study of Said KN et al. [30•], blood samples from COVID-19 patients with periodontitis ($N=1325$) revealed significantly lower levels of D-dimer in treated periodontitis patients than in non-treated periodontitis patients. In another prospective study in which the periodontal conditions of COVID-19 patients were assessed clinically ($N=82$), it was found that increased D-dimer levels were associated with gingival recession, number of teeth lost due to periodontitis, and probing depth, and it was positively correlated with the severity of periodontitis [33••]. The same study also observed an association between increased levels of heart damage biomarkers, such as troponin and pro-BNP, and higher levels of clinical attachment loss, as well as periodontitis severity.

The release of D-dimer into the bloodstream is caused by fibrin degradation within the blood clot, which is regulated by the plasmin/plasminogen pathways. Plasmin is also present in the oral cavity, and plays a role in bacterial and viral invasions, as it is important for the cleavage process that takes place during the SARS-CoV-2 virus binding to the receptors on the infected cells [40]. Thus, plasmin depletion via this intra-oral process may inhibit thrombolysis functions, thus limiting breakdown of thrombus systemically. Another mechanism that could be linking the hypercoagulation state observed in severe COVID-19 with periodontitis could be endothelial dysfunction. This systemic pathological condition of the endothelium of blood vessels is known to promote coagulation, and there are extensive evidences associating it with periodontitis [41]. Moreover, SARS-CoV-2 infection is also known to cause endothelial dysfunction, and this could play a key role in hypercoagulation, thrombosis, and multi-organ injury associated with severe COVID-19 [42].

Genetics

Several genes have been linked to the association between periodontitis and SARS-CoV-2 infection and severity. For example, periodontitis is known to cause the overexpression of genes involved in SARS-CoV-2 infection (i.e., ACE2, TMPRSS2, FURIN, CD147), and the under-expression of genes involved in the protection against SARS-CoV-2 infection (i.e., BMAL1) [43–45]. Moreover, a study using ChIP-Atlas and GEO datasets ($N=247$) found that estrogen receptor 1 (ESR1), a gene highly expressed in gingiva with periodontitis, correlates with the expression of TMPRSS2 in gingival tissues [21•]. Also, an ESR1 ligand has been found to induce TMPRSS2 expression in cultured keratinocytes [21•].

Transcriptomic data analysis of blood samples obtained from patients with SARS-CoV-2 and periodontitis revealed that 56 genes, including five top hub genes (i.e., DDX56, GNAS, CA10, GRM5, CCL5), are significantly co-expressed in COVID-19 and periodontitis [46•]. These genes are enriched in the regulation of hormone secretion, cell secretion, protein phosphorylation, cell chemotaxis, actin filament bundle assembly, gap junction, phospholipase D signaling pathway, Rap1 signaling pathway, and rheumatoid arthritis. The intersected differentially expressed genes in periodontitis and COVID-19 share one gene in particular and that is MYOZ2 (myozenin 2). This gene was found to be down-regulated in both COVID-19 and periodontitis, and

it has been associated with elements of the immune system that are key in the fight against the infection such as activation of B cell, memory B cell, effector memory CD4 T cell, type 17 helper cell, T follicular helper cell, and type 2 helper cell [46•].

Oral-Vascular-Pulmonary Route

Lloyd-Jones et al. in 2021 proposed an oral-vascular-pulmonary route for SARS-CoV-2 infection according to which direct viral delivery from the oral cavity to pulmonary vessels occurs via the venous drainage of the mouth, jugular veins of the neck, and the superior vena cava, through the right side of the heart. The permeable nature of the junctional epithelium can facilitate viral invasion, and this is likely to worsen with poor oral hygiene and in the presence of periodontal diseases due to potential disruption of the pocket epithelium caused by the local inflammation [47, 48]. Accordingly, periodontitis could be enabling the SARS-CoV-2 virus in the oral cavity to enter the gingival capillaries, facilitating endovascular transmission directly to the pulmonary vessels [49].

Periodontal Therapy and Risk of COVID-19 Complications

Treatment of periodontitis reduces the microbial load and the levels of inflammatory cytokines, both locally and systemically. Accordingly, a case–control study was designed to investigate how periodontal treatments could influence COVID-19 complications ($N = 1325$) [30•]. Compared to patients with healthy periodontium, patients with non-treated periodontitis showed significantly increased risk of need for mechanical ventilation (AOR = 3.91; 95% CI 1.21–12.57, $P = 0.034$), while patients with treated periodontitis did not show significant risk of COVID-19 complications (AOR = 1.28; 95% CI 0.25–6.58, $P = 0.768$). Moreover, periodontal therapy seems to decrease the serum levels of ferritin and D-dimer in COVID-19 patients with signs of periodontitis. This would suggest that periodontal-related coagulopathies might be playing a key role in the association between periodontitis and COVID-19. These observations seem to indicate that among the five possible mechanisms that have been proposed linking periodontitis to COVID-19, the role of inflammation and coagulopathy seems to have more solid evidence at this point. However, further studies would be needed to provide more evidence on the role of genetic variants, the pulmonary invasion of periodontal pathogens, and the direct oral-vascular-pulmonary route of infection in the pathogenesis of COVID-19. It should also be acknowledged that a combination of the mechanisms discussed above is potentially responsible for the strong associations reported between periodontitis and COVID-19 severity.

Conclusion

Our review highlights that periodontitis has been associated both with an increased risk of initial infection with SARS-CoV-2 and with COVID-19 disease severity. The increased risk of infection could be because periodontitis increases the expression of the receptors responsible for entry of SARS-CoV-2 into host cells. The increased risk of COVID-19 severity in those with periodontitis could be due to a combination of mechanisms influenced by shared genetic phenotypes, the effect of periodontitis on systemic inflammation and coagulation, and susceptibility to direct disease progression via the respiratory tract or bloodstream.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent Not applicable.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance*
- •• Of major importance**

* Studies based on self reported surveys providing evidence on the association between COVID-19 and Oral health, or studies providing evidence on the mechanisms linking COVID-19 with oral health.

** Relatively large studies providing clinical evidence on the association between COVID-19 and oral health.

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