

Periodontal disease and clinical association with COVID-19 infection

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SARS-CoV-2 infection can cause long-standing damage to the immune system characterized by increased inflammatory cytokine activation. Maintaining periodontal health may reduce host susceptibility to COVID-19 and prevent COVID-19 aggravation in infected patients. There is sufficient evidence in the literature to warrant an association between the presence of PDs and the development and course of respiratory illnesses. Optimum oral health, maintaining good systemic health, and elimination of smoking habits may be beneficial for the prevention and management of COVID-19 infections. Future studies on the periodontal status of patients with COVID-19, including from mild to severe forms, could allow the opportune identification of people at risk of severe illness and generate relevant recommendations. The connection, if any, between the oral microbiome and COVID-19 complications is urgently required to establish the importance of oral hygiene and pre-existing oral disease in the severity and mortality risk of COVID-19.

Key words: COVID-19; periodontitis; pneumonia; respiratory diseases; periodontal disease; brain; spine; coronavirus

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COVID-19 is a disease caused by the recent coronavirus named SARS-CoV-2 that triggers damage to the lungs and other organs. Most COVID-19 patients present mild symptoms; however, other patients could develop severe illnesses having pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndromes, or even die (1-5). Additionally, patients with COVID-19 can present neurologic manifestations, such as headache, loss of sense of smell, stroke and seizures, suggesting that SARS-CoV-2, like MERS-CoV and SARS-CoV-1, displays neurotropism and enters the central nervous system (6,7). Many neurological disorders and conditions affect individuals' functioning, result in disabilities, limit activities, and restrict participation, representing an important global public health (8-22).

SARS-CoV-2 infection can cause long-standing damage to the immune system characterized by increased inflammatory cytokine activation (23-27). Vaccines provide a significant reduction in breakthrough infections with COVID-19 (23). While 80% of patients with COVID-19 infections have mild symptoms, 20% have a severe form of infection associated with higher inflammatory markers (IL-2, IL-6, IL-10), bacteria neutrophil-to-lymphocyte count (28). Optimal oral hygiene and treatment of periodontal diseases (PDs) can reduce ACE2 expression, inflammatory cytokines, and aspiration pneumonia (29-33). Maintaining periodontal health may reduce host susceptibility to COVID-19 and prevent COVID-19 aggravation in infected patients (34). PD therapy also improves systemic diseases such as COPD and diabetes (3,16,35-39). Pitones-Rubio et al. (40) proposed that although some of the known risk factors have not been strongly associated with PDs or their causal relationships are not completely established, it is convincing to propose an association between PDs and COVID-19, where the latter could be affected by the intervention of periodontopathogenic bacteria outside its ecological niche and cause chronic inflammation. Additionally, the association between PDs and severe COVID-19 illness could be non-causal, suggesting that prevention or treatment of PDs does not prevent a worse progression and outcome of COVID-19 (40).

Periodontitis is a chronic inflammatory disease

that progressively affects the integrity of the tissues supporting the teeth and is associated epidemiologically with several chronic disorders, such as cardiovascular disease, type 2 diabetes mellitus, rheumatoid arthritis and spine, inflammatory bowel disease, Alzheimer's disease and certain cancers (41-63). PD comprises a group of diseases involving inflammatory aspects of the host and dysbiotic events that affect periodontal tissues and could have systemic implications (40). Diverse factors and comorbidities have been closely associated with PDs, such as diabetes, obesity, ageing, hypertension and brain disease (40).

This oral disease remains a major public health and socioeconomic burden and affects, in its severe form, about 10% of adults (53). PDs are among the most common diseases that affect adults. It is estimated that about 42% of those above 30 years-of-age and 60% of those above 65 years-of-age have periodontitis (64-67). Severe stages of periodontitis are the sixth most common disease in older adults, affecting about 11% of the global adult population (23,64). PD should also be considered a pandemic, with the reported case load exceeding COVID-19 (5,65-69). Among other chronic inflammatory diseases and conditions, periodontal inflammation may influence COVID-19 susceptibility and pathogenesis (70,71-80).

There is sufficient evidence in the literature to warrant an association between the presence of PDs and the development and course of respiratory illnesses (81). These mechanistic links range from a direct aspiration of these pathogens into the lungs to more indirect mechanisms wherein virulence factors and enzymes released by periodontopathogens may modify mucosal surfaces to make them more amenable to colonization, destroy bacterial salivary pellicle to inhibit their subsequent clearance or modify the respiratory epithelium via cytokines to promote infection (28,82-86). COVID-19 patients with PD have a higher mortality risk than patients without periodontitis (88). In addition, the immune cellular release of cytokines, including IL-1 and TNF in periodontitis, may exacerbate the recognized "cytokine storms" associated with COVID-19 infections (71).

Marouf et al. (89) found a significant association between PDs and COVID-19-related outcomes.

However, no clinical assessment of their periodontal status at the time of suffering from the COVID-19 infection was made and hence patients with previous bone loss but no active disease at the time of the study might have been grouped along with those experiencing an active disease. On the other hand, Gupta et al. (5) did not conduct a real-time clinical examination of all the patients involved and made the important distinction of assessing active PDs and their relation to COVID-19-related outcomes.

Sampson et al. (28) reported that the four main comorbidities associated with an increased risk of complications and death from COVID-19 are also associated with altered oral biofilms and PDs, hence the link between poor oral health and COVID-19 complications is suggested. Periodontopathic bacteria are implicated in systemic inflammation, bacteremia, pneumonia, and death. Epigenetic mechanisms contribute to many aspects of the SARS-CoV-2 replication cycle, including expression levels of viral receptor ACE2, cytokine genes as part of the host immune response and the implication of various histone modifications in several aspects of COVID-19 (90). SARS-CoV-2 proteins physically associate with many different host proteins throughout infection, and notably, there are several interactions between viral proteins and epigenetic enzymes such as HDACs and bromodomain-containing proteins, as shown by correlation-based studies (90).

Several studies give credence to the association between the COVID-19 and PDs since the beginning of the pandemic. For example, a recent publication has reported that the patients with COVID-19 have higher dental plaque scores and gingival oedema than their matched SARS-CoV-2 negative controls (85). In addition, Larvin et al. (87) analyzed the data on surrogates of periodontitis from 13,253 participants in the United Kingdom Biobank, which included 1,616 COVID-19 positive cases, observing significantly higher mortality in the patients with COVID-19 with periodontitis.

In another retrospective study, Sirin and Ozcelik (91) analyzed the dental records and panoramic radiographs of 137 patients with COVID-19 and found a remarkable connection between dental damage and the prognosis of viral disease. Also,

Marouf et al. (88) conducted a case-control study by collecting the electronic health records, medical as well as dental, of the patients with COVID-19 and analyzed them for the associations between the presence of periodontitis and the severity of COVID-19 infections, reporting a significant association was observed between the presence of periodontitis and COVID-19 complications, such as death, ICU admission, or need for assisted ventilation. However, as PD is both reflective and deterministic of systemic health, it might also play an indirect role in worsening the status of comorbidities more directly associated with a poorer prognosis of COVID-19-related adverse outcomes (5). The use of telemedicine can be an essential tool to avoid unnecessary travel to hospitals and clinics, reducing the potential risk of COVID-19 infection and continuous observation and daily clinical practice by physicians and surgeons, continuous scientific research and new technologies can improve long-term patient outcomes and provide further insights and discoveries (92-105).

Survival against SARS-CoV-2 infection may partially depend on periodontal health, good oral hygiene and access to dental care. Optimum oral health, maintaining good systemic health, and elimination of smoking habits may be beneficial for the prevention and management of COVID-19 infections (71). Future studies on the periodontal status of patients with COVID-19, including from mild to severe forms, could allow the opportune identification of people at risk of severe illness and generate relevant recommendations (106-153). The connection, if any, between the oral microbiome and COVID-19 complications is urgently required to establish the importance of oral hygiene and pre-existing oral disease in the severity and mortality risk of COVID-19.

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