Periodontal disease and COVID-19: Prognosis and potential pathways of association in their pathogenesis

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PRACTICAL IMPLICATIONS OF THIS RESEARCH

- COVID-19 is a new factor of concern for dental and dental hygiene practice, since in the presence of periodontitis, systemic health may be compromised.
- Knowing the impact of periodontal disease and COVID-19 on clients' health allows oral health professionals to pay more attention to the diagnosis and treatment of periodontal diseases.

ABSTRACT

Objective: The objective of this narrative review is to determine if periodontal disease is a factor in the development of a poor prognosis for COVID-19. **Method:** A bibliographic search was conducted in PubMed, Virtual Health Library, Google Scholar, and in the databases of Science Direct, Scopus, Lilacs, Bireme, Scielo, and Web of Science, using the following keywords: "COVID-19," "SARS-CoV-2," and "periodontal diseases." **Results:** Fifty-six records were retrieved from the database searches. After screening, 39 articles were selected for study: 13 reviews, 2 case–control studies, 1 systematic review, 8 letters to the editor, 2 cohort studies, 1 thesis, 7 hypotheses, 1 short communication, 3 commentaries, and 1 scoping review. **Discussion:** Both periodontal disease and COVID-19 produce an inflammatory response. This immune response generates an over-production of inflammatory cytokines that can harm overall health. **Conclusion:** The mouth serves as the entryway for many microorganisms that can harm health in general, among them SARS-CoV-2. It is important to maintain good oral health to lower the inflammatory load present in periodontal disease, lessening the possibility of complications from COVID-19.

RÉSUMÉ

Objectif : L'objectif de cette revue narrative est de déterminer si la maladie parodontale est un facteur dans le développement d'un mauvais pronostic de la COVID-19. **Méthodologie :** Une recherche bibliographique a été effectuée dans PubMed, la bibliothèque virtuelle de la santé, Google Scholar, et dans les bases de données de Science Direct, Scopus, Lilacs, Bireme, Scielo, et Web of Science, en utilisant les mots-clés suivants : « COVID-19 », « SRAS-CoV-2 » et « maladie parodontale » (en anglais). **Résultats :** Cinquante-six dossiers ont été extraits à partir des recherches dans les bases de données. Après la sélection, 39 articles ont été choisis pour l'étude : 13 revues, 2 études cas-témoins, 1 revue systématique, 8 lettres à l'éditeur, 2 études de cohorte, 1 thèse, 7 hypothèses, 1 courte communication, 3 commentaires et 1 examen de la portée. **Discussion :** La maladie parodontale et la COVID-19 produisent toutes deux une réponse inflammatoire. Cette réponse immunitaire produit une surproduction de cytokines inflammatoires qui peuvent nuire à la santé globale. **Conclusion :** La bouche sert de voie d'entrée à de nombreux micro-organismes qui peuvent nuire à la santé en général, parmi lesquels le SRAS-CoV-2. Il est important de préserver une bonne santé buccodentaire pour diminuer la charge inflammatoire présente dans la maladie parodontale, réduisant ainsi la possibilité de complications de la COVID-19.

Keywords: COVID-19; periodontal diseases; periodontal pocket; periodontitis; risk factors; SARS-CoV-2
CDHA Research Agenda category: risk assessment and management

INTRODUCTION

As of December 2019, 6 coronaviruses known to cause respiratory diseases had been identified: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoVHKU1, SARS-CoV, and MERS-CoV, the last 2 being the most pathogenic.[1-5] In early 2020, a novel coronavirus, SARS-CoV-2, was identified in Wuhan, China. It quickly spread throughout the world, creating the fifth influenza pandemic since 1918. The World Health Organization (WHO) labelled the disease COVID-19.[1-9]

Being an inflammatory infection, periodontal disease can lead to a general inflammation of the body, acting as a factor that can modify systemic health.[10,11] Periodontitis is an inflammatory condition of the tissues that support the teeth, including the gums, bone, and periodontal ligament. Its pathogenesis involves complex relationships between microorganisms present in dental biofilm and the host's immune response, which can be affected by genetic and environmental factors or acquired conditions, such as smoking and systemic diseases.[10,11]

The new definition of periodontitis, based on the Consensus Report of Working Group 2 of the 2017 Classification of Periodontal and Peri-Implant Diseases and Conditions, reads as follows: "Periodontitis is a chronic multifactorial inflammatory disease associated with

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Manuscript submitted 11 March 2022; revised 22 June, 12 August, and 23 September 2022; accepted 30 September 2022

dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus".[12] To establish a case of periodontitis, a detectable interdental loss in ≥2 non-adjacent teeth, or an oral clinical attachment loss (CAL) of ≥3 mm with pockets ≥3 mm detectable in ≥2 teeth, is necessary.[12] The destruction of periodontal tissue seen in advanced periodontitis can have clinical consequences, such as dental mobility and tooth loss, affecting both masticatory function and aesthetics.[12] These consequences can affect the client's physiological state, as well as psychological and social aspects of their life, thus reducing their overall quality of life.[12] Other consequences that may occur due to the local inflammatory response, where inflammatory mediators are released into the bloodstream, are systemic. Research has confirmed an association between periodontal disease and systemic conditions such as cardiovascular disease and diabetes.[12]

Plaque-induced gingivitis is an inflammatory lesion resulting from interactions between the dental plaque biofilm and the host's immunoinflammatory response. It remains contained within the gingiva and can be reversed through a reduction in plaque levels.[10,13,14] In contrast, periodontitis develops due to the accumulation of microbial plaque (bacterial dysbiosis). It creates periodontal pockets and causes attachment loss, which leads to a loss of the supporting tissues of the tooth. Tissue destruction depends on environmental and host risk factors, which may be modifiable in some cases (e.g., smoking) or not (e.g., genetic susceptibility).[15-18] Unlike gingivitis, periodontitis cannot be reversed. Treatment only delays the progression of the disease and reduces inflammation; tissue loss and destruction are permanent.[10,19]

Since it has been shown that individuals with periodontal disease release inflammatory cytokines as an immune response to pathogen colonization, it is plausible that individuals with periodontal disease who are infected with SARS-CoV-2 may have a worse prognosis than those without periodontal disease. It is also plausible that periodontally induced cytokines may alter the nature and strength of the cytokine storm that ensues during COVID-19. Currently, scientific evidence on the association between these 2 inflammatory diseases is scarce.[20,21] Therefore, the aim of this narrative review is to examine the literature to determine if periodontal disease may be a factor in developing a poor prognosis for COVID-19.

METHODS

The search for scientific articles was carried out in PubMed, Virtual Health Library, Google Scholar, and in the databases of Science Direct, Scopus, Lilacs, Bireme, Scielo, and Web of Science, using the following keywords: "COVID-19," "SARS-CoV-2," and "periodontal diseases". The inclusion criteria for selecting articles were as follows: primary articles, secondary articles, letters to the editor, and commentaries related to COVID-19/SARS-CoV-2 and periodontal disease, research on humans, and written in English and Spanish. Articles that did not mention the relationship between periodontal disease and COVID-19 were excluded. Duplicate articles were excluded, and the first review was carried out by reading the title, abstract, objectives, methods, and conclusions. Then the full text of selected articles was analyzed.

RESULTS

There were 56 articles found, among them 7 duplicates, 16 reviews, 2 case–control studies, 1 systematic review, 9 letters to the editor, 6 cohort studies, 1 thesis, 7 hypotheses, 1 short communication, 5 commentaries, and 1 scoping review. Following screening (Figure 1), 39 articles were selected for study: 13 reviews, 2 case-control studies, 1 systematic review, 8 letters to the editor, 2 cohort studies, 1 thesis, 7 hypotheses, 1 short communication, 3 commentaries, and 1 scoping review.

The main weakness of this study is that research conducted directly with COVID-19 patients remains limited. However, there is ample theoretical evidence for the possible association between periodontal disease and a poor COVID-19 prognosis.

DISCUSSION

Is periodontitis a factor associated with COVID-19 infection?

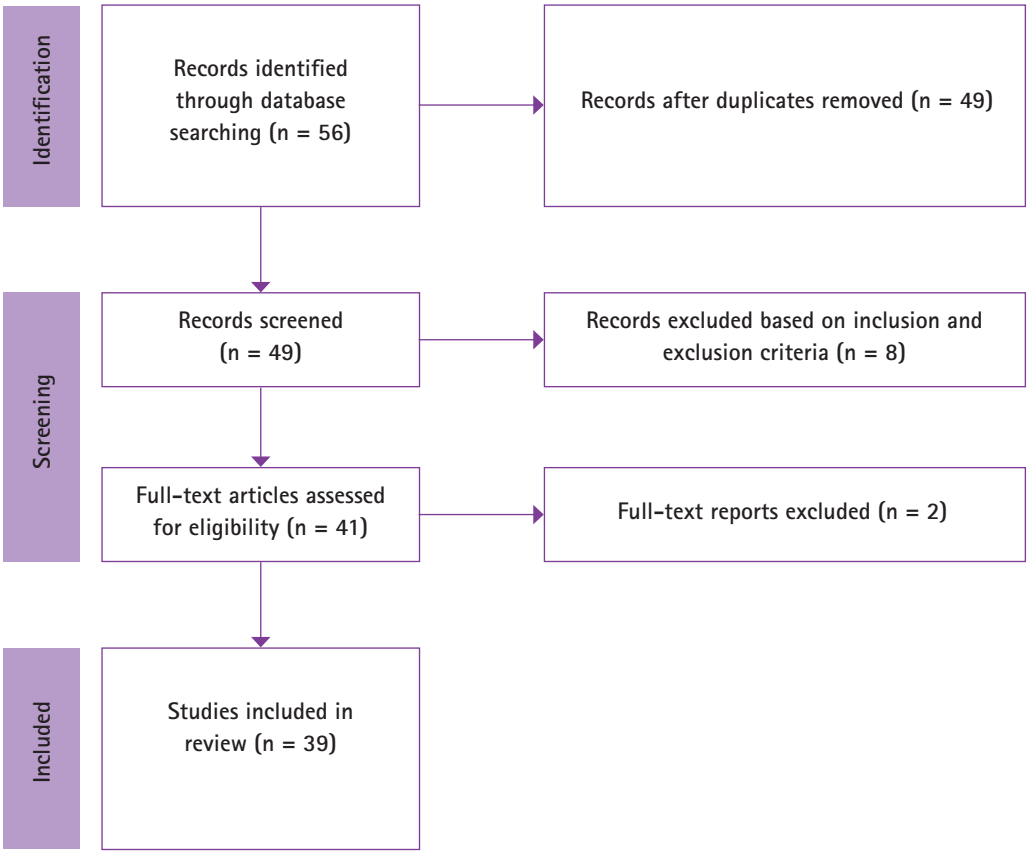
Elevated levels of osteopontin and cathepsin L protease have been found at sites of periodontal destruction in clients with chronic periodontitis. Osteopontin in turn elevates the level of protease furin, and these proteases allow infection of host cells by SARS-CoV-2 to occur because they cleave the S-glycoprotein of the virus into S1 and S2, giving way to the binding of S1 and angiotensin-converting enzyme 2 (ACE-2).[22-25] The risk of becoming infected by the virus is also increased in cases of hyposalivation as a consequence of periodontal disease, since the surface of the oral mucosa can be infected and ulceration of the gingival epithelium no longer allows it to act as a physical barrier, i.e., it no longer has protection capacity, allowing greater adhesion and colonization of the virus. In addition, the secretion of antiviral peptides is affected.[22,25-31]

Cytokine storm, periodontal disease, and COVID-19

In periodontal disease, a chronic inflammatory response is produced by the presence of bacteria in the subgingival biofilm. Inflammatory cells try to dislodge the bacteria that are generating the infection through the secretion of inflammatory cytokines. However, an overproduction of cytokines, known as a cytokine storm, can occur, producing unfavourable results.[32-37] This overproduction is related to periodontal degradation, including alveolar bone resorption, collagen destruction, periodontal junction loss, expression of multiple viral receptors, bacterial superinfection, and aspiration of periodontal pathogens.[33,38]

COVID-19 also has the capacity to unleash a cytokine storm, causing tissue damage, especially to the connective tissue of the lungs. Some of these cytokines

Figure 1. PRISMA flow diagram of record processing and elimination



are also released in periodontitis, such as IL-6 and IL-17. Overproduction of IL-6 can lead to interstitial pneumonia, multi-organ damage, and risk of death, and IL-17 increases lung inflammation. This cytokine may be a biomarker of the severity of COVID-19.[30,31,33,39-44] The cytokine storm may lead to adverse outcomes such as multiple organ failure and acute respiratory illness. Through this immune response, COVID-19 may be related to periodontitis.

An individual with periodontitis is more vulnerable to the development of a poor COVID-19 prognosis given that, before becoming infected with SARS-CoV-2, there was already an inflammatory state that could worsen the cytokine storm produced by COVID-19.[25,30,32,33,35-42,44] Individuals with periodontitis have much higher levels of white blood cells and C-reactive protein (CRP) than those without periodontitis, so it may be concluded that an association between periodontal disease and COVID-19 complications exists through the systemic inflammatory state.[45] Epithelial sensitization and hematogenous dissemination of proinflammatory mediators present in the inflamed periodontal tissue may increase the systemic inflammatory state and reduce airflow; the liver can aggravate the situation due to its need to produce acute-phase proteins, among them IL-6, to enhance the inflammatory response in the lungs. The same situation occurs in severe cases of COVID-19, where a systemic inflammatory state is triggered and high levels of IL-6, IL-2, IL-10, TNF-alpha and CRP are present.[30,46] In clients with both COVID-19 and periodontitis, much higher levels of serum markers of systemic inflammation have been found.[30,40,46]

Neutrophil extracellular traps (NET) are another mechanism that occurs during periodontitis and may be associated with COVID-19. NET cause cell death at the tissue level, directly or indirectly through immune mechanisms, developing a state of severe inflammation.[22,27,42,47] Both periodontitis and SARS-CoV-2 can trigger NET production. In advanced stages of COVID-19, NET production can be exacerbated, which may be related to the cytokine storm. Thus, it is possible that clients with periodontitis are at higher risk of experiencing adverse outcomes during COVID-19, since a high number of neutrophils would be present. These neutrophils could increase the destruction of compromised tissues and consequently raise the mortality risk.[22,27,42,48]

The periodontal pocket as a reservoir for SARS-CoV-2

The main receptors allowing SARS-CoV-2 to enter host target cells are the angiotensin-converting enzyme 2 (ACE-2) together with the transmembrane serine protease 2 (TMPRSS2), which are expressed in the oral mucosa, gingiva, periodontal pocket, and dorsum of the tongue.[34] In addition, the ACE-2 receptor is expressed in various cells, among them nasopharyngeal cells, lung cells, salivary gland cells and in fibroblasts of the periodontal ligament.[27,34,49,50]

Furthermore, another route of infection has been suggested, where SARS-CoV-2 infects the cells through its S protein, binding to CD147, which is expressed in the oral epithelial cells that form the buccal and subgingival component of periodontal pocket cells. Gingival epithelial expression of CD147 is also increased in individuals with periodontitis.[25,49]

The periodontal pocket is formed by 2 walls: the mucosal wall with the ulcerated epithelium, exposed connective tissue, and vascular ramifications, and the root wall of the tooth, where complex subgingival biofilms develop.[49] A relationship between periodontitis and COVID-19 has been established by way of periodontal pockets, as they act as reservoirs, providing a favourable environment for viral replication and predisposing the development of severe forms of COVID-19. In the areas affected by periodontal disease, the inflammatory response may bring in mononuclear cells infected by SARS-CoV-2.[24,30,31,42,45,49,51] The presence of the virus has been detected in gingival tissues, gingival crevicular fluid (GCF), and subgingival plaque; from those locations, it can migrate to the systemic circulation by means of GCF mixing with saliva or also through the periodontal capillary system.[24,30,38,49]

Are periodontal pathogenic bacteria involved in the systemic inflammatory state?

The periodontal pathogenic bacteria present in periodontitis can aggravate COVID-19, since they increase ACE-2 expression in the lungs and bronchi, so that infection of alveolar and bronchial epithelial cells occurs. Furthermore, SARS-CoV-2 infectivity increases in the oral mucosa because any contact with periodontal pathogenic bacteria promotes the expression of ACE-2 in the mucosal epithelia of both tongue and gingiva.[25,29,30,36,43-45,52] These bacteria also promote the secretion of inflammatory cytokines, which are responsible for acute respiratory distress syndrome (ARDS), which is the principal cause of death by COVID-19.

Periodontal diseases increase the inflammatory response, aggravating systemic symptoms and the clinical development of the disease.[36,37,44,52] It is known that the progression towards a severe infection is associated with elevated levels of inflammatory markers such as IL2, IL-6, IL-10, CRP, TNF, and bacteria.[46,53] Periodontal pathogenic bacteria have been shown to be involved in pneumonia, systemic inflammation, and bacteremia.[47,53] In patients severely infected with COVID-19, large quantities of *Fusobacterium, Prevotella, Veillonella, Treponema,* and *Staphylococcus* have been found, which include periodontopathic microbes such as *Treponema denticola, Porphyromonas gingivalis,* and *Tannerella forsythia*.[25,32,34,35,47,53,54] Even if the periodontal pathogenic bacteria are not infective, they can aggravate COVID-19 symptoms because they cause respiratory inflammation when aspirated, increasing the risk of inflammation in the lower respiratory tract.[25,30,33,35,43-45,52,55] Furthermore, the proteases of these bacteria can degrade the S protein of SARS-CoV-2, increasing its infectivity since it is necessary for this protein to cleave for adsorption and fusion with host cells to take place.[25,29,38,43-45,52] Finally, another mechanism by which periodontal pathogenic bacteria and endotoxins can aggravate the disease is through the blood vessels, since they can easily enter the periodontal tissue of bleeding periodontal lesions and cause bacteremia and endotoxemia.[36,52]

The impact of periodontal treatment on COVID-19 infection

Maintaining good oral health and treating periodontal diseases are important, as studies have linked complications and deaths from COVID-19 to periodontal diseases.[37,56] Poor oral hygiene and severe forms of periodontitis may play a role in the progression to a severe form of COVID-19.[37,56,57] A causal relationship between periodontal disease and the aggravation of COVID-19 has not been established. In other words, treatment and prevention of periodontal disease may not prevent an individual from developing a severe case of COVID-19.[32] However, it has been shown that IL-17 levels in the GCF can be decreased in the serum of clients with periodontal disease who receive non-surgical periodontal treatment (NSPT).[27,39,44] Thus, NSPT could be beneficial for patients with COVID-19, since it could decrease the pulmonary inflammatory response.[27] Moreover, another advantage of periodontal therapy is that it decreases serum markers of systemic inflammation, such as CRP and IL-6, and may serve to protect patients with COVID-19 from experiencing more serious disease outcomes.

However, performing periodontal therapy on individuals actively infected with COVID-19 may not be feasible due to mandatory quarantining of such individuals.[22,45] Given that periodontal pockets act as viral reservoirs, it might be beneficial to provide periodontal therapy to infected clients if a method could be devised to deliver this therapy safely and without risk to the oral health clinician.[22,25,44,45] Maintaining good hygiene in the oral cavity prevents the expression of ACE-2 and the liberation of proinflammatory cytokines, both in the mouth and lower respiratory tract. In this way, the susceptibility to infection from SARS-COV-2 may be decreased.[29]

Is there a correlation between NLRP3 and COVID-19 relating to the probability of tissue damage?

After virus replication occurs, ACE-2 decreases its activity, activating ACE-1, which leads to an increase in neutrophils, with an increase in the levels of reactive oxygen species, nuclear factor-kB (NF-kB), and the NLRP3 inflammasome. When activated, the NLRP3 inflammasome increases cytokine levels, generating caspase-mediated inflammatory cellular death (pyroptosis) and tissue loss. Both SARS-CoV-2 and periodontitis promote NLRP3 inflammasome expression, generating a cytokine response and pyroptosis. In contrast, it has been reported that melatonin treatment may reduce NLRP3 levels, i.e., melatonin prevents the cytokine cascade and pyroptosis. Unfortunately, lower levels of salivary melatonin have been observed in clients with gingivitis and periodontitis.[34]

Is there a 2-way relationship between COVID-19 and periodontal disease?

In patients with severe COVID-19, a dysbiosis of the microbiota in the oral cavity can occur, causing oral diseases including periodontal disease due to the appearance of periodontal pathogenic bacteria. This may occur because the patients' oral health has been adversely affected by the use of invasive mechanisms, such as intubation or drugs, along with the absence of oral hygiene.[22,32,35] The bacterial load in individuals with periodontal disease may affect their prognosis after COVID-19 infection.[56] ACE-2 and the TMPRSS are crucial for the virus to infect the host and, since these are found in the mouth, it is possible that the virus influences the inflammation of the periodontal tissues, as well as the lung tissue of infected patients, releasing proinflammatory cytokines necessary for the development of periodontal disease.[22,34,35]

In some cases, an increase in acute periodontal lesions has been observed, specifically necrotizing periodontal disease, which can occur due to bacterial co-infections in the oral cavity of infected patients.[22,54] In mild cases of COVID-19, it is possible that no oral manifestations are present. However, when the disease progresses in severity, the inflammatory response can also cause inflammation of the periodontal tissues, triggering a coagulation cascade and further degradation of fibrinogen.[22,51] Thus, it can be concluded that COVID-19 is capable of affecting periodontal tissues.[22,25,51]

In addition, COVID-19 is considered by many authors to be an endothelial disease that is produced by constant inflammation and invasion of the virus in endothelial cells.[41] These cells can express ACE-2, and when the virus binds to its receptor, an imbalance is generated in the receptor and together with the cytokine storm, endothelial dysfunction occurs.[41] In individuals with periodontitis, bacteria trigger a systemic inflammatory state and invade the endothelial cells, resulting in endothelial injury.[41] It has been suggested by Villegas et al.[41] that in clients with periodontitis there are more endothelial cells, so there may be a greater interaction of the virus with its receptor, which may lead to greater endothelial dysfunction and a greater possibility of thrombosis, the latter being one of the causes of multiorgan failure.[41] The endothelial dysfunction present in both COVID-19 and periodontal disease would be increased in individuals with both diseases, worsening their COVID-19 prognosis.[41]

Systemic diseases, periodontal disease, and severe COVID-19 outcome

Obesity, diabetes, and hypertension are considered the 3 main diseases related to unfavourable COVID-19 outcomes. These diseases are also associated with periodontitis.[22,25,29,31,33,56] In these cases, the seriousness increases significantly in infected patients, due to the production of cytokines in both periodontal and systemic diseases, which can trigger a cytokine storm leading to a collapse of the immune system.[25,51]

Obesity is associated with periodontitis, since adipose tissue is capable of secreting proinflammatory cytokines also involved in periodontitis, which can affect the function of T cells, in the same way adipokines such as leptin and adiponectin are secreted, which contribute to the development of periodontal disease by altering the response to bacteria in the gum tissue.[32,58] Furthermore, obesity increases the production of reactive oxygen species that generate oxidative stress; this is relevant because oxidative stress is increased in periodontal disease and could contribute to its progression.[32,58] In individuals who are obese, there is an increase in the local inflammatory response, the periodontal microbial composition is altered, and periodontal pathogens increase.[32,58]

Larvin et al.[59], in a study examining the impact of periodontal disease in obesity with respect to COVID-19 infection, concluded that obese patients with both periodontitis and COVID-19 were more likely to be hospitalized or die than obese patients without periodontal disease. They reported that hospitalization rates of patients with COVID-19 and periodontal disease were 3.9% for normal weight, 7.3% for overweight, and 10% for obese, and mortality rates were 0.8% for normal weight, 2.5% for overweight, and 3.6% for obese.[59]

The relationship between diabetes and periodontal disease is bidirectional. In individuals with diabetes, there is an increased expression of ACE-2 due to treatment with ACE inhibitors and angiotensin blockers. Upon binding of SARS-CoV-2 and ACE-2, angiotensin II levels are elevated, which is involved in the production of free-radicals, activation of protein kinases, recruitment of inflammatory cells, synthesis and release of cytokines and chemokines, which are related to inflammation, fibrosis and tissue damage.[32,35]

In addition, a relationship exists between hypertension, cardiovascular disease (CVD), and periodontal disease; the latter is a risk factor for the first 2 diseases.[32] Periodontal disease can predispose an individual to the development of systemic diseases. The oral microbiota causes inflammation

in the oral cavity and contributes directly to systemic inflammation through the liberation of toxins or microbial products into the bloodstream.[60]

An interesting study by Larvin and colleagues[56] sought to quantify the impact of periodontal disease on hospital admissions and mortality. Their results revealed no difference in the risk of infection by COVID-19 among patients with or without periodontal disease. However, in patients with painful or bleeding gums, there was a greater risk of mortality.[56]

Periodontal disease can aggravate COVID-19 by causing an overstimulation of the immune system, hypersensitivity of the host, bacterial superinfection, and bacterial dysbiosis in the oral cavity, the latter due to an increase of dental biofilm, which offers a suitable environment for the transport of respiratory pathogens.[37,38] Furthermore, Marouf et al.[45] found that, of the COVID-19 patients who had periodontitis, 82.5% presented complications, 92.9% died, 80.6% were admitted to the ICU, and 85% required assisted ventilation. This study demonstrated that there is a higher risk of COVID-19 complications in individuals with moderate to severe cases of periodontitis than in those with mild cases of periodontitis or without periodontitis.[45] Moreover, in a study by Gupta et al.,[61] COVID-19 patients who had bleeding on probing had 3.18 odds of requiring hospital admission, 4.14 odds of requiring assisted ventilation, and 3.63 odds of acquiring pneumonia from COVID-19. Additionally, patients with more serious forms of periodontitis had 36.52 odds of requiring hospital admission, 7.45 odds of requiring mechanical ventilation, 4.42 odds of acquiring pneumonia from COVID-19, and 14.58 odds of death.[61] The same authors also reported that patients who had died had significantly greater gingival recession, mean probing depth, and clinical attachment loss than the patients who survived.[61] Similarly, Shamsoddin and colleagues[36] conducted a study concluding that patients with periodontitis had a higher risk of developing COVID-19 complications, and estimated that a patient with periodontitis and COVID-19 is approximately 3 times more likely to develop complications and be admitted to the ICU, 4 times more likely to need assisted ventilation and 8 times more likely to die.[36] It was also observed that 12.8% of the patients with periodontitis had complications due to COVID-19, while only 2.2% of patients without periodontitis had complications.[36]

CONCLUSION

The mouth serves as an entry point for many microorganisms that can be detrimental to overall health, including SARS-CoV-2. Both periodontal disease and COVID-19 produce an inflammatory response. For this reason, it is important to maintain good oral health to reduce the inflammatory load, thus reducing the possibility of complications during COVID-19. It is also important that oral health professionals be trained to provide an adequate diagnosis and treatment options for periodontal disease.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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