

Periodontitis and coronavirus disease 2019

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Funding information

The authors acknowledge support from the Hamad Medical Corporation Business Intelligence Center.

1 | INTRODUCTION

Coronavirus disease 2019 (commonly referred to as COVID-19) is caused by a virus from the *Coronaviridae* family called severe acute respiratory syndrome coronavirus 2, which can infect patients of all ages, mainly through airborne droplets and aerosols.¹⁻⁵ Coronavirus disease 2019 was first identified in the city of Wuhan in China in 2019, and within a very short period it caused the worst global pandemic in recent history with more than 160 million confirmed cases and almost 3.5 million deaths, as of May 25, 2021 (<https://coronavirus.jhu.edu/map.html>).³ This public health emergency has threatened the well-being of individuals, ruined economies, and imposed a tremendous burden on health care systems worldwide.^{4,5}

Although most coronavirus disease 2019 patients are asymptomatic or only suffer a mild disease, a significant group can present signs and symptoms of severe disease, frequently causing serious complications and even death. Indeed, about 14% of coronavirus disease 2019 cases may require hospitalization and oxygen support, about 5% need admission to intensive care units, and about 1% would end up dying from the disease.^{3,6}

Coronavirus disease 2019 symptoms vary depending on the severity of the disease. Most patients present mild symptoms, such as low-grade fever, sore throat, fatigue, dry cough, diarrhea, and other nonspecific symptoms that usually get resolved without any major complication.⁷⁻¹⁰ However, in some cases the disease can progress into a serious and life-threatening condition. Severe symptoms include signs of pneumonia, dyspnea at rest, increased respiratory (above 20 breaths per minute) and heart rates (above 100 beats per minute), loss of appetite, confusion, tightness or pressure in the chest, cyanosis, hypoxia (eg, 93%), and high fever (greater than 38°C).⁷⁻¹¹

Upon entering the body, the virus causes viremia, leading to an early phase of the disease that involves an incubation period of

1-14 days (mostly 3-7 days).⁷⁻¹¹ Afterwards, the disease may enter a second phase in which the virus spreads to the bloodstream, targeting a wide range of tissues and organs.⁸⁻¹² This results in a deterioration of the patient's condition due to damage to vital organs, such as the lungs, heart, nervous system, gastrointestinal tract, and kidneys, as well as an aberrant inflammatory response termed the "cytokine storm" that contributes to coronavirus disease 2019 mortality.^{13,14} This "cytokine storm" features a hyperactive immune response characterized by increased blood levels of inflammatory mediators such as interferons, interleukins, tumor-necrosis factors, and chemokines, as well as lymphopenia (decrease of cluster of differentiation 3⁺, cluster of differentiation 4⁺, and cluster of differentiation 8⁺ T lymphocytes), neutrophilia, alterations of the coagulation cascade (eg, prolonged prothrombin time, thrombocytopenia, elevated D-dimer, low fibrinogen), increased levels of markers for organ damage (aspartate aminotransferase, creatinine, procalcitonin, lactate dehydrogenase, high-sensitivity cardiac troponin), and increased inflammatory markers (eg, erythrocyte sedimentation rate, C-reactive protein, ferritin).^{6,15-18} The release of inflammatory mediators involved in the innate immune response is usually essential for the clearance of infectious agents; however, at excessively high levels, such as those seen in the "cytokine storm," these mediators can be harmful and cause severe complications.¹⁵

The infectivity of severe acute respiratory syndrome coronavirus 2 is mainly mediated by a protein spike on its surface that is able to bind to the angiotensin-converting enzyme 2, an enzyme found on the membrane of many cells of the human body.¹⁹⁻²¹ Angiotensin-converting enzyme 2 is a counter-regulatory enzyme involved in the breakdown of angiotensin II, thus antagonizing the activation of the classical renin-angiotensin-aldosterone system.¹⁹⁻²¹ Thus, angiotensin-converting enzyme 2 activity is protective against hypertension, diabetes, cardiovascular disease, and damage to the lungs.¹⁹⁻²¹ In fact, angiotensin-converting enzyme 2 is highly

expressed in the lower respiratory track, mainly on type II alveolar pneumocytes, which is one of the main reasons why severe acute respiratory syndrome coronavirus 2 infection can harm the lungs and cause an acute respiratory distress syndrome, a highly lethal clinical condition.¹⁹ Type II alveolar pneumocytes act as epithelial immune cells that are able to produce several cytokines such as tumor necrosis factor- α , interleukin-6 (IL-6), interleukin-1 β , monocyte chemoattractant protein-1, and granulocyte-macrophage colony-stimulating factor.²² Thus, severe acute respiratory syndrome coronavirus 2 infection of these cells could trigger a strong immune reaction mediated by T helper 1 cells and activated intermediate cluster of differentiation 14⁺ cluster of differentiation 16⁺ monocytes through membrane-bound immune receptors and downstream signaling pathways. This reaction results in increased production of inflammatory cytokine and reduced interferon response, as well as inflammation of the lungs, with predominant infiltration of macrophages, T helper 17 cells and neutrophils.¹⁹⁻²³ Besides the lungs, angiotensin-converting enzyme 2 activity is also widely expressed in several other tissues including the kidneys, the male testis, the female breast, the liver, and the cardiovascular and gastrointestinal systems. Therefore, severe acute respiratory syndrome coronavirus 2 not only affects the lungs, as it was initially believed, but could also affect multiple organs in the body, thus becoming a multisystemic disease.²⁴⁻²⁶

Several risk factors have been associated with severe coronavirus disease 2019. These include factors such as advanced age and sex (male) and comorbidities such as obesity and the presence of underlying diseases (eg, hypertension, cardiovascular disease, cerebrovascular disease, chronic kidney disease, and diabetes).^{7,14,19,27} These predisposing conditions share several standard features that could explain why they are associated with worse disease outcomes. Some of the conditions are known to alter angiotensin-converting enzyme 2 expression in the body, cause endothelial dysfunction, a proinflammatory state, and alterations in the innate immune and inflammatory response.^{21,28,29} The latter may suggest that a chronic inflammatory condition, such as periodontitis, could play a role in the course of coronavirus disease 2019.

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic dental plaque biofilms, characterized by progressive destruction of the tooth-supporting apparatus.³⁰ This disease is one of the most common chronic inflammatory noncommunicable diseases and the sixth-most prevalent condition in the world, affecting about 50% of adults. In its more severe form, periodontitis affects about 11% of the population.^{30,31} Owing to its high prevalence and its consequences, periodontitis is a significant public health and socioeconomic problem. Periodontitis not only leads to tooth loss and disability, with the consequent impairment of the patient's quality of life, but it also affects general health.³²⁻³⁵ Severe periodontitis has been associated with a range of systemic diseases, including diabetes, cardiovascular diseases, and increased mortality.^{34,35}

Owing to this increased systemic risk, various investigations have suggested a possible link between periodontitis and increased severity of coronavirus disease 2019 disease.^{1,2} It was, therefore, the main objective of this review to evaluate the scientific evidence studying these links and the possible mechanisms behind this association.^{1,2}

2 | CORONAVIRUS DISEASE 2019 INFECTION AND THE ORAL CAVITY

The oral cavity seems to play an important role in coronavirus disease 2019 pathogenicity.³⁶⁻⁴³ The membrane proteins used by severe acute respiratory syndrome coronavirus 2 to infect cells (angiotensin-converting enzyme 2 and transmembrane protease serine 2)²⁵ are highly expressed in the oral cavity.³⁹⁻⁴³ They have been found on the epithelial cells of the tongue, oral mucosa, salivary glands, gingiva, and periodontal pockets at levels comparable to those in the lungs and tonsils. In addition, severe acute respiratory syndrome coronavirus 2 can be identified in oral fluids and saliva, and its oral viral load has been associated with disease severity.³⁷⁻⁴⁰

Some unspecific oral lesions have been associated with coronavirus disease 2019. These include dry mouth, oral vesicobullous or pustulous lesions, lip necrosis, fissured or depapillated tongue, or erythematous or hemorrhagic mucosal lesions.³⁹⁻⁴¹ Such lesions are mostly found among patients with systemic conditions that involve some degree of immunosuppression.⁴³

3 | PERIODONTITIS AND CORONAVIRUS DISEASE 2019 INFECTION SEVERITY

Relevant risk factors associated with coronavirus disease 2019 severity, including smoking, increased age, obesity, diabetes, hypertension, and cardiovascular disease,^{26,27,29} are also significantly associated with periodontitis.^{31,34} Hence, it is uncertain whether these factors could just behave as comorbidities or whether there are specific mechanisms and pathological pathways linking periodontitis and increased coronavirus disease 2019 severity.^{46,47}

A recent case-control study in Qatar on 568 patients investigated the association between coronavirus disease 2019 complications and the presence of periodontitis.⁴⁸ The study used dental panoramic radiographs for the assessment of periodontal health. The results of this study showed that, after adjusting for potential confounders (ie, age, gender, smoking, body-mass index, other chronic diseases, among other factors), moderate to severe periodontitis (stage 2-4) was significantly associated with a higher risk of coronavirus disease 2019 complications, including death (odds ratio 8.81, 95% confidence interval 1.00-77.7), intensive care unit admissions (odds ratio 3.54, 95% confidence interval 1.39-9.05), and need for assisted ventilation (odds ratio 4.57, 95% confidence interval 1.19-17.4).⁴⁸ Similarly, another study on 137 coronavirus disease 2019 patients (20-65 years) based on oral examination records and panoramic X-rays concluded that patients with signs of oral disease (apical periodontitis, radiographic alveolar bone loss, and dental caries) were significantly more likely to suffer from coronavirus disease 2019 complications, such as positive symptomatology, hospitalizations, and death, than individuals free of oral disease were.⁴⁹ However, a positive specific association with periodontitis could not be assessed in this study.⁴⁹

Another study used periodontal health data from a telephone survey that was conducted before the pandemic onset and combined it with more recent data on infection and complications caused by coronavirus disease 2019.⁵⁰ This study also reported an association between periodontitis and increased coronavirus disease 2019 infection and risk of death.⁵⁰ Coronavirus disease 2019–positive participants who had initially reported painful or bleeding gums had a higher risk of mortality from coronavirus disease 2019 (odds ratio 1.71, 95% confidence interval 1.05–2.72), although having loose teeth did not demonstrate a significant association.⁵⁰

The association between coronavirus disease 2019 infection and periodontitis has also been investigated in two retrospective studies. One of them used the patient's registry platform of the University of Florida Health Center and reported that oral diseases were associated with increased odds for having coronavirus disease 2019. Those with periodontitis were 4.7 times more likely to have coronavirus disease 2019 after adjustment for smoking.⁵¹ However, another retrospective study based on self-reported oral health indicators reported that there was not a significant increase in the risk of coronavirus disease 2019 infection among periodontitis patients.⁵⁰

Other studies have also suggested a possible effect of coronavirus disease 2019 infection on periodontal health. It has been predicted that an increased prevalence of acute periodontal lesions, particularly necrotizing periodontal disease, could arise in association with coronavirus disease 2019–confirmed cases.⁵² However, this hypothesis is yet to be confirmed.

It is well established that translocation of periodontal pathogens to blood (eg, bacteremia) and the associated systemic inflammation are mechanisms contributing to the links between periodontitis and systemic diseases, such as diabetes, cardiovascular diseases, and rheumatoid arthritis.^{46,53} However, these mechanisms have not been clearly demonstrated in the association between periodontitis and increased coronavirus disease 2019 severity.

4 | MECHANISMS LINKING PERIODONTITIS WITH CORONAVIRUS DISEASE 2019 PATHOGENESIS

4.1 | Severe acute respiratory syndrome coronavirus 2 in the periodontal pockets

A study on cadaver biopsies from coronavirus disease 2019–positive patients has reported the presence of the severe acute respiratory syndrome coronavirus 2 within their periodontal tissues.⁵⁴ This has led to the hypothesis that periodontal pockets may serve as reservoirs for severe acute respiratory syndrome coronavirus 2.⁵⁴ It is well established that periodontal pockets present an ideal environment for harboring biofilms rich in bacterial and viral species that may invade the tissues through the frequently ulcerated pocket epithelium.^{55,56} This pathogenic environment could facilitate the entrance of the severe acute respiratory syndrome coronavirus 2, either directly through this damaged epithelia or indirectly by the upregulation

in the expression of angiotensin-converting enzyme 2 receptors induced by some periodontal pathogens, such as *Fusobacterium nucleatum*.^{56,57} Indeed, periodontitis can increase in the oral cavity the expression micro-ribonucleic acids (eg, micro-ribonucleic acids 146a and 155) involved in the regulation of angiotensin-converting enzyme 2, especially among diabetic patients.⁵⁷

4.2 | Periodontitis as a source of systemic inflammation

Persistent and uncontrolled inflammation is a key manifestation of several diseases, such as periodontitis, cardiovascular diseases, neurodegenerative diseases, diabetes, and coronavirus disease 2019 infection (Table 1).^{58–62} Systemic inflammation in periodontitis is characterized by high levels of C-reactive protein and proinflammatory cytokines (interleukin-1 and IL-6) that have been associated with initiating or aggravating diseases, such as diabetes and cardiovascular diseases.^{32,34} Also, periodontitis can prime the immune system toward an exacerbated innate response through the synergistic activation of peripheral polymorphonuclear leukocytes to local and remote inflammatory triggers.⁶¹ Periodontitis has also been implicated with the release of neutrophil extracellular traps, an alternative form of cell death secondary to increased levels of mediators, such as interferon-alpha.^{61,62}

The adverse outcomes of coronavirus disease 2019 infections have also been associated with an uncontrolled hyperinflammatory reaction known as the “cytokine storm.” This condition involves increased serum levels of interleukin-2, 6, 7, 8, and 10, tumor necrosis factor-alpha, granulocyte colony-stimulating factor, interferon-gamma inducible protein 10 (IP-10), monocyte chemoattractant protein 1, macrophage inflammatory protein 1-alpha, galectin-3, and C-reactive protein, with concomitant significantly lower numbers of T-lymphocytes (cluster of differentiation 4⁺ T cells; cluster of differentiation 8⁺ T cells).^{12,63–66} Furthermore, circulating neutrophils in coronavirus disease 2019 patients exhibit an activated phenotype with an increased oxidative burst, release of neutrophil extracellular traps, and phagocytosis, thus contributing to the acute respiratory distress syndrome, a primary cause of morbidity and mortality.⁶⁶

Another possible link between systemic inflammation, periodontitis, and coronavirus disease 2019 is through the NOD-like receptor family pyrin domain-containing 3. The orf8b protein of the severe acute respiratory syndrome coronavirus-1, an analog of severe acute respiratory syndrome coronavirus 2, can trigger the NOD-like receptor family pyrin domain-containing 3 inflammasome in macrophages. This inflammasome, which has been shown to increase the serum and salivary of periodontitis patients,⁵⁸ may play a significant role in the coronavirus disease 2019 cytokine storm and has been shown to aggregate in the lungs, resulting in fatal pneumonia.⁶⁷

The hypothesis linking periodontitis and increased severity of coronavirus disease 2019 infection based on this inflammatory upregulation^{41,68,69} has recently been confirmed in a retrospective

TABLE 1 Common features of patients with periodontitis and patients with severe COVID-19

Severe coronavirus disease 2019	References	Periodontitis	References
Associated comorbidities			
Hypertension, obesity, age, sex, diabetes, cardiovascular diseases, smoking, chronic pulmonary disease, coronary artery disease, chronic renal disease, cancer, atherosclerotic diseases	[7,14,19,27,29,83]	Hypertension, obesity, age, diabetes, cerebrovascular disease, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, hypertension, atherosclerotic disease	[31-35,46,53,84,85]
Elevated inflammatory biomarkers			
Interleukin-1, 1beta, 1RA, 2, 6, 7, 8, 9, 10, C-reactive protein, galectin-3 prostaglandin E2, interferon-gamma inducible protein 10, monocyte chemotactic protein-1, macrophage inflammatory protein-1alpha, fibroblast growth factor-2, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, interferon-gamma, tumor necrosis factor-alpha, C3 and C5, and NOD-like receptor family pyrin domain-containing 3 inflammasome, ferritin	[6,13,15-18,27,29,36,37,45,48,65-67,72]	Interleukin-1, 1beta, 1RA, 2, 6, 7, 8, 9, 10, C-reactive protein, galectin-3, prostaglandin E2, interferon-gamma inducible protein 10, monocyte chemotactic protein-1, macrophage inflammatory protein-1alpha, fibroblast growth factor-2, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon-gamma, tumor necrosis factor-alpha, C3, C5, NOD-like receptor family pyrin domain-containing 3 inflammasome, ferritin	[37,46,86]
Coagulation biomarkers			
D-dimer (elevated)	[6,16,21,23,36,48]	D-dimer (elevated)	[34,61,86,87]
Fibrinogen (decreased)		Fibrinogen (increased)	
Prothrombin time (prolonged)		Prothrombin time (prolonged)	
Platelet counts (decreased)		Platelet counts (increased)	
Plasminogen activator inhibitor (increased)		Plasminogen activator inhibitor (increased)	
Immune cell activity			
Neutrophils (increased)	[6,12,13,15,18,23,36,48,63-67,69]	Neutrophils (increased)	[34,46,61,62,69,86]
Release of neutrophil extracellular traps (increased)		Release of neutrophil extracellular traps (increased)	
Monocytes/macrophage (increased)		Monocytes/macrophages (increased)	
T cells (cluster of differentiation 3 ⁺ , cluster of differentiation 4 ⁺ , cluster of differentiation 8 ⁺) (decreased)		T cells (cluster of differentiation 4 ⁺) (increased)	
B cells (cluster of differentiation 19 ⁺) (decreased)		T helper 17 cells (increased)	
Natural killer cells (cluster of differentiation 16 ⁺ 56) (decreased)			
T helper 17 cells (increased)			
Elevated tissue-damage biomarkers			
Matrix metalloproteinases	[6,23,36]	Matrix metalloproteinases	[46,88-90]
Lactate dehydrogenase		Lactate dehydrogenase	
Alanine aminotransferase		Alanine aminotransferase	
Troponin I		Troponin I	
Procalcitonin		Procalcitonin	
Aspartate aminotransferase		Aspartate aminotransferase	

study using the hospital records of coronavirus disease 2019 patients. In this study, coronavirus disease 2019 patients with periodontitis had significantly higher blood levels of inflammatory markers, such as C-reactive protein, than coronavirus disease 2019 patients without periodontitis did.⁴⁸ Moreover, blood analyses before patient discharge revealed significantly higher concentrations of neutrophils and higher levels of C-reactive protein than in periodontitis-free patients.⁴⁸

Systemic inflammation has also been related to alterations in the sleep-wake cycles of the body (i.e., the circadian rhythm) through the action of the so-called clock genes. These circadian regulatory genes are expressed in most cells and tissues, and their disruption has been associated with inflammatory conditions such as periodontitis and viral infections. For example, the brain and muscle ARNT-like protein-1, an essential circadian regulatory gene, is decreased in periodontitis and viral infections, which suggests common pathogenesis,

probably through the nuclear factor- κ B pathway.⁷⁰ Considering the importance of the dysregulation of the inflammatory response in coronavirus disease 2019 complications, modulation of the immune system has been explored as a therapeutic approach to prevent the cytokine storm. One strategy could be the use of inhibitors of galectin-3 (which have been shown to reduce IL-6 and tumor necrosis factor- α levels in vitro) as anti-inflammatory agents in clinical situations of increased cytokine release associated with severe acute respiratory syndrome coronavirus 2 patients.^{47,59} Similarly, the use of specialized pro-resolving mediators, which have been tested to improve inflammatory lung conditions such as acute respiratory distress syndrome and chronic obstructive pulmonary disease,⁷¹ may be used in promoting the resolution of inflammation in severe acute respiratory syndrome coronavirus 2 patients. Furthermore, the use of immunomodulators with pleiotropic effects, such as melatonin, could help suppress the likely synergistic association between coronavirus disease 2019 and periodontitis.³⁷ Another promising strategy is to target the complement system. C3 and C5 inhibitors can achieve substantial anti-inflammatory effects and have shown promising results in coronavirus disease 2019 patients.⁷² These types of drugs can reduce the levels of C-reactive protein and IL-6 levels, improve lung function, and resolve acute respiratory distress syndrome in coronavirus disease 2019 patients.⁷²

4.3 | Periodontitis as a source of direct aspiration of bacterial pathogens to the lungs in coronavirus disease 2019 patients

Another possible association between periodontitis and coronavirus disease 2019 severity may involve the well-established connection between the oral microbiome and respiratory diseases.^{44,73} The oral cavity is a reservoir for respiratory pathogens,⁷⁴ especially among patients with poor oral hygiene and periodontitis, and dysregulated inflammatory and immune response.¹ In fact, periodontal pockets in the elderly have been associated with increased risk of mortality from pneumonia, and periodontitis patients are more likely to develop hospital-acquired pneumonia than healthy ones are.^{74,75} In these patients, oral and respiratory bacteria can disseminate into the lower respiratory tract through aspiration or by inoculation during invasive mechanical ventilation procedures.^{76,77} Thus, it has been hypothesized that patients suffering from the aforementioned respiratory diseases linked to periodontitis may have an increased coronavirus disease 2019 aggravation rate and mortality.⁷⁷ This fact can be explained by the capability of certain periodontopathic bacteria to upregulate the expression of angiotensin-converting enzyme 2, the primary receptor for severe acute respiratory syndrome coronavirus 2, and the production of inflammatory cytokines in the lower respiratory tract.^{44,73}

Oral opportunistic pathogens, such as *Capnocytophaga* and *Veillonella*, have been found in the bronchoalveolar fluid of coronavirus disease 2019 patients.¹ These anaerobes originating from the oral microbiota could be further favored by the lung hypoxia observed in coronavirus disease 2019 patients.¹ In addition, it has also been hypothesized that the translocated gram-negative periodontal

bacteria may cause lipopolysaccharide-induced senescence and facilitate severe acute respiratory syndrome coronavirus 2 replication in lung cells.⁷⁶ These possible links between life-threatening coronavirus disease 2019 lung infection and periodontal pathogens highlight the need to diagnose and treat oral infections in patients suffering from severe respiratory viral infections.⁵²

5 | HEALTH IMPLICATIONS OF THE ASSOCIATION BETWEEN CORONAVIRUS VIRUS DISEASE 2019 AND PERIODONTITIS

Given the potential associations between periodontitis and coronavirus disease 2019 severity, it has been hypothesized that periodontal care may play a role in preventing and managing coronavirus disease 2019 complications.⁷⁸ Prevention of periodontitis is achieved by daily self-performed oral hygiene and quarterly or bi-annual professional removal of the microbial biofilm.⁷⁹ This reduces the risk of pneumonia and other systemic diseases^{80,81} and results in a well-functioning gingival epithelial barrier that helps prevent oral pathogenic viruses and bacteria from entering the bloodstream. Thus, it could be hypothesized that periodontal care could potentially reduce the systemic consequences of a severe acute respiratory syndrome coronavirus 2 infections.

Periodontal care could also help prevent coronavirus disease 2019 complications indirectly by managing associated comorbidities, such as diabetes and systemic inflammation. Controlling the hyperinflammation and hyperglycemia observed in severe coronavirus disease 2019 patients are very important strategies in the prevention of coronavirus disease 2019 mortality.^{82,83} Thus, given the ability of periodontal therapy in reducing systemic inflammation and improving glycemic control in type 2 diabetic subjects,⁷⁹⁻⁸¹ it has been hypothesized that periodontal care could help prevent coronavirus disease 2019 complications, although future research would be needed to test this possibility.

Oral hygiene has a well-established relationship with infectious respiratory diseases; oral care, particularly periodontal treatments, can help prevent the onset of pneumonia and influenza and the exacerbation of chronic obstructive pulmonary disease.⁷⁷ Thus, good oral hygiene could potentially contribute to the prevention of coronavirus disease 2019 complications by reducing the risk of aspiration pneumonia.^{1,77,84} Indeed, there are suggestions that periodontal care could help in prevention of coronavirus disease 2019 complications, but currently there is no evidence on the possible impact of periodontal treatment in coronavirus disease 2019 complications.

6 | CONCLUSIONS

Periodontitis shares several common features with coronavirus disease 2019 including similarities in comorbidities and effects on systemic inflammation. Indeed, some early studies have identified a possible association between the presence of periodontitis and the

risk of coronavirus disease 2019 infection and complications. These associations could stem from a priming effect on systemic inflammation, although the presence of periodontal bacterial in the lungs could also be playing a role. In this context, preventive oral hygiene measurements and periodontal care could play a role in preventing coronavirus disease 2019 infections and complications. However, further research would be needed to confirm these hypotheses.

ACKNOWLEDGMENTS

The authors acknowledge support from the Hamad Medical Corporation Business Intelligence Center.

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How to cite this article: Tamimi F, Altigani S, Sanz M. Periodontitis and coronavirus disease 2019. *Periodontol 2000*. 2022;89:207-214. doi:[10.1111/prd.12434](https://doi.org/10.1111/prd.12434)