The Journal of the Michigan Dental Association

Volume 104 | Number 5 Article 8

5-1-2022

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-chain RNA virus with spike-shaped proteins (S-proteins) binding to angiotensin-converting enzyme 2 (ACE2), is the cause of a novel coronavirus disease known as COVID-19.[1–3] Being highly transmissible, COVID-19 poses an extraordinary threat to human health and public safety, and the emergence of SARS-CoV-2 variants of concern (VOCs) has exacerbated the COVID-19 pandemic. Patients may present mild symptoms (e.g., fever, fatigue, and dry cough) to severe respiratory and other organ failures.[4] The rapid replication of virus may trigger a strong immune response.

Considered the main cause of death in patients infected with SARS-CoV-2, hyperinflammation as a cytokine storm may result in acute respiratory distress syndrome (ARDS) and even respiratory failure.[5] In addition, respiratory viral infections predispose patients to co-infections, leading to increased disease severity and mortality.[6] According to the World Health Organization's March 6, 2022, statement, more than 433 million people had been confirmed with infection, with 5.9 million deaths worldwide.[7]

Abstract

As the gateway to the respiratory system, the oral cavity can play an essential role in SARS-CoV-2 invasion and transmission. Besides expressing high levels of angiotensin-converting enzyme 2 (ACE2), the oral cavity can harbor viral particles in saliva, gingival crevicular fluid, and the periodontal pocket. Microbial and inflammatory associations closely link periodontitis and COVID-19.

In this review, we summarize the reported oral manifestations of COVID-19, its association with periodontal diseases, the plausible underlying mechanisms of microbial and inflammatory crosstalk between COVID-19 and periodontal diseases, long COVID-19, and mitigation protocols during periodontal treatment.

Keywords: Covid-19, SARS-CoV-2, inflammation, periodontal disease, infection control, evidence-based dentistry.

Relationship between SARS-CoV-2 and oral cavity

In confluence with the upper respiratory tract, the oral cavity is one of the first places where the SARS-CoV-2 interacts with the host. The oral mucosa and salivary glands express high levels of the viral receptor ACE2, which may predict potential SARS-CoV-2 infection routes and predispose the oral cavity to infection and subsequent tissue damage.[8,9] Moreover, cell proteins related to coronavirus invasion, e.g., transmembrane protease serine 2 (TMPRSS2), cathepsin, furin, are found in the oral epithelium.[8]

The oral cavity harbors viral particles in saliva, gingival crevicular fluid (GCF), and periodontal pockets. SARS-CoV-2 can enter the saliva by three routes: secretions from upper and lower respiratory tracts, salivary glands, and gingival crevicular fluid (GCF).[10,11] Early detection of asymptomatic patients can contribute to the prevention of virus transmission. A salivary diagnostic test has been used for the early detection of SARS-CoV-2 that can be self-collected without involving specialized health care personnel. When compared to nasal swabs, it has significantly contributed to the prevention of virus transmission by delivering faster test results with earlier detection of asymptomatic patients.[12,13]

GCF is an inflammatory exudate consisting of serum, inflammatory mediators, immunoglobulins, and materials formed from tissue breakdown. GCF could be a possible mode of transmission of SARS-CoV-2. It has been reported that the detection sensitivity of SARS-CoV-2 in GCF and saliva are comparable.[11] Within the periodontal environment, previous studies have shown that oral epithelial cells express not only ACE-2, but also CD-147, which has been suggested as a novel SARS-CoV-2 infection route.[14] Furthermore, the expression of CD-147 in gingival epithelium has been found to be higher in cells harvested from patients with periodontitis.[15] SARS-CoV-2 RNA has also been detected in dental biofilms from symptomatic COVID-19 patients; hence, dental biofilms might be a potential reservoir in SARS-CoV-2 transmission.[16]

Oral manifestations of COVID-19

In COVID-19 infection, besides respiratory symptoms,

it has been reported that patients could present with a wide variety of oral manifestations.[17–19]

Taste disorders. Taste disorders are commonly reported among patients infected with COVID-19. They present at a higher prevalence in the North American (53%) and European populations (50%) than with Asians (27%). Taste disorders show a significant association with female patients and those with mild/moderate COVID-19 infections.[17] The exact mechanisms remain unclear, but one theory is that viruses are able to invade cells on the dorsal surface of the tongue, which express high levels of ACE2. Subsequent inflammation may result in the loss of function of taste buds and dysfunction of supporting non-neuronal cells in the mucosa.[20]

Oral mucosal lesions. Oral mucosa lesions associated with COVID-19 include blisters, ulcers, desquamative gingivitis, petechiae, and candidiasis.[17] However, it remains uncertain whether these lesions are the direct result of virus infection or secondary manifestations, considering the possibility of coinfections, a weakened immune system, and adverse reactions of medical treatment.[6]

Periodontal manifestations. Regarding periodontal manifestations of COVID-19, in a cross-sectional study including 33 COVID-19 positive patients (20 asymptomatic and 13 with mild symptoms), 17 out of 19 patients presented with periodontal disease.[11] However, it is unclear whether COVID-19 causes or exacerbates periodontal disease. It should be noted that Patel and Woolley[21] published a case report of necrotizing gingivitis in a SARS-CoV-2-infected patient. Without any other relevant medical history, this 35-year-old patient presented with bilateral submandibular lymphadenopathy, severe halitosis, generalized erythema and edema, necrotic interdental papillae, and spontaneous gingival bleeding. The patient had a fever starting three days prior to any oral symptoms and was suspected of COVID-19 infection.

Figure 1 — (a) Initial oral presentation and (b) Five weeks re-eval after Phase I periodontal therapy.

Similar to this case, a 29-year-old female patient visited our clinic (Graduate Periodontics Clinic, University of Michigan School of Dentistry) after her quarantine and reported that she had halitosis, bilateral submandibular lymphadenopathy, and severe gingival swelling, pain, and bleeding starting two days before her diagnosis as COVID-19 positive (with a mild symptom of fatigue and shortness of breath). An oral exam (15 days post-symptom onset) revealed the signs of

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necrotizing periodontal disease and multiple periodontal abscess formation (Figure 1a, see Page 47). In this case, resolution of acute periodontal lesions (Figure 1b, see Page 47) was achieved following mechanical debridement and antibiotic regimen.

Acute periodontal lesions, such as periodontal abscesses and necrotizing periodontal diseases (NPD), often develop in patients with impaired host immune defense.[22] Given that the patients with COVID-19 exhibit dysregulated immune response and a higher quantity of *Prevotella intermedia* and *Fusobacterium* (bacteria that are highly associated with acute periodontal lesions), it is suspected that the etiology of these periodontal conditions may be associated with bacterial co-infections in COVID-19 patients.[23,24] In addition, psychological stress, insufficient sleep, isolation, and inadequate oral hygiene, as relevant predisposing factors for NPD, are commonly found in the COVID-19 pandemic and could have an impact on or could solely explain these periodontal manifestations.

Association between COVID-19 and periodontal diseases

Periodontal diseases increase COVID-19 severity. Given the impact of periodontal diseases on systemic conditions, such as diabetes, cardiovascular diseases, preterm low-weight birth, Alzheimer's disease, and cancer, it is reasonable to assume a possible link between periodontal diseases and COVID-19. The potential relationship between periodontal disease and COVID-19 has become of major interest.[18,20,25,26] Recent case-control studies[27,28] demonstrated a significant association between periodontal disease and COVID-19. Compared to the patients without COVID-19, the population of patients with COVID-19 have been found to have a higher proportion of individuals with a mean plaque score ≥1 (odds ratio: 7.01), gingivitis (OR: 17.65), mean clinical attachment loss ≥ 2 mm (OR: 8.46), and severe periodontitis (OR: 11.75).[27]

A higher rate of intensive care unit (ICU) admission, increased need for assisted ventilation, higher mortality, and greater levels of biomarkers linked to worse COVID-19 outcomes such as D-dimer, white blood cells, and C-reactive protein, have been reported in COVID-19 patients with periodontitis (Stage II-IV) than periodontally healthy or initial periodontitis (Stage I).[28] A cross-sectional study investigated UK Biobank participants (n=13,253), and showed that patients with painful or bleeding gum have a higher risk of mortality following COVID-19 infection.[29]

Possible mechanisms and patient management. Hypotheses for possible mechanisms explaining the association of periodontal disease with COVID-19 risk and severity have been proposed, including shared risk factors (e.g., smoking and diabetes) between these two diseases, "refraining from dental visits" during the pandemic, and microbial and inflammatory associations.[26] As a niche for microbial infection, the periodontal pocket may harbor both active and latent (inactive or dormant) SARS-CoV-2 forms,[30,31] and the presence of periodontal pathogens may increase the cellular entry of SARS-CoV-2 by facilitating the degradation of S-protein.[25,26] In addition, ulceration of the gingival epithelium caused by periodontitis reduces the protection and increases the risk of virus invasion.[30]

Following replication in the periodontium, the virus may transmit into the oral cavity and saliva or enter the periodontium blood vessels to reach distant organs.[31] Cytokines released in response to periodontitis could enhance the cytokine storm in severe forms of COVID-19.[32] As such, maintaining adequate oral hygiene and periodontal health may be an important measure for the prevention of COVID-19 and its complications. Given that periodontal therapy has been shown to reduce bacterial burden and serum inflammatory biomarkers, it may have a therapeutic effect on both periodontitis and COVID-19 severity.

Another hypothesized mechanism is related to the aspiration of periodontal pathogens, mainly occurring in elderly patients.[25] Aspirated periodontopathic bacteria and other oral bacteria may increase ACE2 expression on the respiratory epithelium,[33] stimulate the production of proinflammatory cytokines and exacerbate lung inflammation,[34] and promote decreased respiratory function and alveoli/bronchi epithelial barrier destruction by overproduction of mucin.[35] In this regard, hospitalized patients are more likely to require more meticulous oral health management. The oral examination in patients with COVID-19, especially those in the ICU, should not be neglected.

Long COVID-19. Post-acute sequelae of COVID-19 (PASC; aka Long COVID) is characterized by long-term symptoms and/or complications after the onset of COVID-19.[36] Little is known regarding the association of PASC with periodontal disease. However, as studies link periodontal disease with severity of COVID-19 and severity of COVID-19 links with PASC, further investigation is of interest.[15,28,33,37] Microbial findings from studies of the gut point to the potential for microbial dysbiosis in PASC, raising the question of what the microbial perturbations are in the oral cavity and whether the periodontal microbiome associates with PASC.[38]

In a hospital-based study, the administration of bacteriotherapy/probiotics significantly reduced symptoms of fatigue associated with PASC.[39] An elegant recent study utilized a deep multi-omic longitudinal investigation of COVID-19 patients to identify four PASC risk factors, which included type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and particular autoantibod-

ies.[40] They did not associate PASC with oral findings, but Epstein-Barr virus has been shown to be associated with periodontitis,[41] as is type 2 diabetes, rendering it plausible that periodontitis may also predispose individuals to PASC. This is an open question that future studies will need to clarify. In the meantime, clinicians need to be aware of the wide variety of symptoms associated with PASC, including fatigue, shortness of breath, chest pain, risk of thromboembolism, and neurologic and psychiatric complications, and be prepared to treat these individuals safely and with compassion in a clinical setting.[42]

Mitigation protocols during periodontal treatment. The SARS-Cov-2 virus has a predominantly respiratory transmission through aerosol and droplets.[43] The importance of infection control, such as patient screening and triage, hand hygiene, preprocedural application of mouth rinses, personal protective equipment (PPE), limitation of aerosol-producing procedures, and cleaning of potentially contaminated surfaces, is therefore crucial in minimizing viral diffusion.[44,45] Testing is becoming more straightforward and has value beyond the presence or absence of disease.[46] Given the high probability of transmission from asymptomatic patients,[47] it is necessary for us to pay close attention to the aforementioned oral manifestations in patients during dental visits to prevent nosocomial infections.

Infection protection and control strategies for aerosol mitigation have been extensively reviewed before.[48] The most effective strategy is elimination and substitution (e.g., symptom screening, preprocedural testing, preprocedural mouth rinses, line microbiota decontamination, high volume evacuation), followed by engineering controls (air cleaning systems, surface decontamination, negative pressure room), and administrative controls and personal pro-

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Purnima S. Kumar, BDS, MS, PhD, served as tenured professor of periodontology and chair of the Oral Biology Graduate Program at The Ohio State University. She became the chair of the Department of Periodontics and Oral Medicine at the University of Michigan School of Dentistry on May 1, 2022. She is a Diplomate of the American Board of Periodontology and a Fellow of The Hedwig van Ameringen Executive Leadership in Academic Medicine program. She is the Principal Investigator of the Oral Microbial Ecology Laboratory at OSU, funded through the NIH, NCI, and oral health care industry. She currently serves as chair of the Continuing Education Oversight Committee for the American Association of Periodontology (AAP) and is a member of the AAP's Taskforce for Women in Periodontics and the Taskforce for Future Science Strategies. Her research focuses on the oral microbiome and its interactions with the host to promote health or cause disease and the role of human behaviors in shaping this ecosystem.

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tective equipment (PPE).[49] Given that the infection rates among dental health care workers remain extremely lower than those in the general public,[50] this may reflect the pre-existing blood-borne pathogens precautions in dental environments and effective strategies adopted in response to the current pandemic.

Regarding PPE, the current recommendation for aerosol-generating dental procedures (such as ultrasonic scaling, implant osteotomy, and restorative procedures) includes the use of an N95 or equivalent mask or a mask in combination with a face shield. A full-sleeved cuffed gown with a back closure is recommended to minimize risk to dental health care providers.[48]

As a primary source of microbial pathogens in aerosols, dental unit waterlines play a major role in infection control.[51,52] Reducing microbial contamination in waterlines is essential for lowering the aerosol microbial load and can be achieved by the use of filters, biocides (e.g., sodium hypochlorite, phenol), waterline flushing for a minimum of two minutes at the beginning of each day and at least 20 seconds between each patient, and emerging methods, such as nano-adsorbents, ionizing currents, and acoustic waves.[48]

Preprocedural mouth rinses with chlorhexidine gluconate (CHX) are effective approaches to reduce the bacteria load in aerosols.[53] A four-arm randomized clinical trial[54] investigated SARS-Cov-2 viral load in saliva after 60-second mouth rinses from symptomatic, asymptomatic, pre-symptomatic, and post-symptomatic patients with COVID-19. It showed that regardless of the types of mouth rinses (normal saline, 0.12% CHX, 1% hydrogen peroxide, or 0.5% povidone iodine), viral load was decreased by 61%-89% at 15 minutes and by 70%-97% at 45 minutes after rinsing.

During ultrasonic scaling, high-volume evacuation can reduce atmospheric aerosol by 80.7% to 94%. Air cleaning systems also contribute to the reduction of viral particles suspended in the atmospheric aerosol.[48] In all, when standard infection control practices are adopted, such as mouth rinses prior to the procedure and intraoral high-volume evacuation, the risk for transmission of SARS-CoV-2 from aerosolized saliva in dental treatment of asymptomatic patients is moderately low.[51]

Conclusions

The COVID-19 pandemic has continued for more than two years, and SARS-COV-2 and its long-term effects will likely coexist with us for a long time. Understanding the association between COVID-19 and periodontal diseases, the detection and management of the possible oral manifestations, and following strict clinical infection control is essential for providing dental care, both today and in a post-pandemic era. Assisting our patients in maintaining adequate oral hygiene and periodontal health may further contribute to the management and prevention of COVID-19. ●

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