Abstract: Coronavirus infectious disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic in March 2020 by the World Health Organization. Periodontitis, one of the most prevalent diseases worldwide, leads to alveolar bone destruction and subsequent tooth loss, and develops due to pro-inflammatory cytokine production induced by periodontopathic bacteria. Periodontopathic bacteria are involved in respiratory diseases, including aspiration pneumonia and chronic obstructive pulmonary disease (COPD), and other systemic diseases, such as diabetes and cardiovascular disease. Patients with these diseases have an increased COVID-19 aggravation rate and mortality. Because aspiration of periodontopathic bacteria induces the expression of angiotensin-converting enzyme 2, a receptor for SARS-CoV-2, and production of inflammatory cytokines in the lower respiratory tract, poor oral hygiene can lead to COVID-19 aggravation.

Conversely, oral care, including periodontal treatment, can prevent the onset and aggravation of aspiration pneumonia, COPD, and influenza [13-15]. Periodontal treatment is also effective in improvement of diabetes [16,17].

Therefore, it can be speculated that an increase in periodontopathic bacteria owing to poor oral hygiene aggravates COVID-19 in relation to the mechanisms shown below:

- Periodontopathic bacteria promote SARS-CoV-2 infection by increasing the expression of ACE2.
- Promoted secretion of pro-inflammatory cytokines in the lower respiratory tract by stimulation with aspirated periodontopathic bacteria lead to COVID-19 aggravation.
- The protease of periodontopathic bacteria promotes SARS-CoV-2 infection by degrading the S protein of SARS-CoV-2.

Therefore, it can be argued that the management of good oral hygiene can potentially prevent COVID-19 aggravation.

Induction of receptor for respiratory pathogens by periodontopathic bacteria

Binding of the virus or bacterium to a host cellular receptor is important for infection. The expression of ACE2 is enhanced by stimulations such as smoking [18]. When periodontopathic bacteria are aspirated, ACE2 expression may increase in the lungs and bronchus due to the stimulation by periodontopathic bacterial cells and their pathogenic factors, such as endotoxins. In fact, periodontopathic bacteria can enhance the expression of platelet-activating factor receptor, the receptor for etiological bacteria of pneumonia, such as Streptococcus pneumoniae (S. pneumoniae) and Pseudomonas aeruginosa (P. aeruginosa) [19]. The protease produced by P. gingivalis enhances the expression of influenza virus receptor by degrading the surface protein of the airway mucosa [20]. Therefore, aspiration of periodontopathic bacteria potentially contributes to promote infection of SARS-CoV-2 by increasing ACE2 expression (Fig. 1). In fact, some periodontopathic bacteria can induce in vitro expression of ACE2 in human respiratory cells (data not shown).

COVID-19 is more likely to be severe in elderly and medically compromised patients [21,22], who have a higher risk of aspiration due to decreased swallowing function [23]; therefore, management of oral hygiene to reduce the amount of aspirated oral bacteria is essential in these patients. Furthermore, as ACE2 is highly expressed in the oral cavity, particularly in the tongue and gingiva, it thereby promotes infection of SARS-CoV-2 in the oral cavity [24]. In fact, a large amount of SARS-CoV-2 is present in the saliva of infected individuals and is transmitted through droplets and aerosol [25,26]. An increase in the expression of ACE2 in the oral cavity, promoted by periodontopathic bacteria, may increase SARS-CoV-2 infection rate in the oral cavity as an important reservoir of SARS-CoV-2.

Keywords: ACE2, COVID-19, oral hygiene, periodontitis, periodontopathic bacteria, SARS-CoV-2
Mechanism of COVID-19 aggravation induced by the production of inflammatory cytokines from the lower respiratory tract by stimulation with periodontopathic bacteria

Although severe respiratory disorders, such as acute respiratory distress syndrome (ARDS), are the leading cause of death in patients with COVID-19, cytokine storm is the major cause of ARDS rather than direct lung injury by SARS-CoV-2 [27]. In particular, elevated interleukin (IL)-6 is associated with excess inflammation which contributes to increased mortality in patients with COVID-19 [27,28]. Therefore, in addition to antiviral drugs such as remdesivir, drugs that suppress host inflammation are of interest as therapeutic agents for COVID-19 [34,35]. Similarly, the involvement of secondary bacterial infection has been observed in the BALF and sputum of patients with severe COVID-19 [35], studies on oral bacteria have not yet been realized. However, it is clear that aspirated periodontopathic bacteria cause respiratory inflammation. Thus, there is an increased risk of inflammation of the lower respiratory tract due to the aspiration of periodontopathic bacteria, because of the reduced chance of receiving professional oral care due to long-term hospitalization of patients with COVID-19 and the spread of SARS-CoV-2 over a long period of time.

The protease of periodontopathic bacteria may promote infectivity of SARS-CoV-2 by degrading the S protein of SARS-CoV-2.

When the influenza virus infects the cells, degradation of hemagglutinin (HA) into HA1 and HA2 is essential [36]. This degradation also occurs by bacterial proteases [36,37]. During infection with SARS-CoV-2, it is important that the S protein of SARS-CoV-2 is cleaved by proteases, such as TMRPRSS2 and furin for adsorption and fusion with the host cells [2,3,38]. Although ACE2, TMRPRSS2, and furin are expressed in the oral cavity [39,40], S protein may also be cleaved by the proteases produced by periodontopathic bacteria. Therefore, periodontopathic bacteria may increase the infectivity of SARS-CoV-2.

Prevention of respiratory diseases by management of oral hygiene

Several reports suggest that treatment of periodontitis improves systemic medical conditions such as COPD and diabetes [14,16,17]. Moreover, professional oral care suppresses mortality due to pneumonia and prevents morbidity of influenza [13,15]. Management of oral hygiene may prevent elevated ACE2 expression and increased inflammatory cytokine production. In addition, preventing the onset and exacerbation of aspiration pneumonia and COPD by the management of oral hygiene may lead to low host susceptibility to COVID-19. Therefore, despite being infected with SARS-CoV-2, it may lead to prevention of COVID-19 aggravation in infected patients when good oral condition is maintained.

Discussion

The severity and mortality of COVID-19 are higher in the SARS-CoV-2-infected individuals with comorbidities, such as COPD, pneumonia,
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diabetes, and cardiovascular disease [21,22]. All diseases are closely related to periodontitis and periodontopathic bacteria. Therefore, periodontopathic bacteria can considerably influence the aggravation of COVID-19 through the mechanisms described above. In addition, SARS-CoV-2 can easily invade the periodontal tissue of a patient with periodontal lesions that bleed. Entry of periodontopathic bacteria and endotoxins into the blood vessels can lead to bacteremia and endotoxemia, thereby increasing the severity of COVID-19 in mildly SARS-CoV-2-infected individuals. Although the periodontopathic bacteria induced the expression of ACE2 receptor in the respiratory tract. Dev Cell 53, 514-529, e3. 
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Conflict of interest

The authors declare that there is no conflict of interest in regard to this study.

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