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Review

Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19

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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, prevents the onset of pneumonia and influenza and the exacerbation of COPD. The reduced chance of receiving professional oral care owing to long-term hospitalization of patients with COVID-19 may increase the aggravation risk of infection in the lower respiratory tract. It can be hypothesized that periodontopathic bacteria are involved in the COVID-19 aggravation and therefore, the management of good oral hygiene potentially contributes to its prevention.

Keywords; ACE2, COVID-19, oral hygiene, periodontitis, periodontopathic bacteria, SARS-CoV-2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly discovered virus of the coronavirus family. Coronavirus infectious disease 2019 (COVID-19) caused by SARS-CoV-2 was deemed a worldwide pandemic by the World Health Organization in March 2020. The primary entry of SARS-CoV-2 is believed to be rendered by projected droplets leading to first contact and colonization of cells in the oral cavity, nose, or eyes [1]. The entry is induced by the binding of the viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2) as a host cellular receptor and is triggered by host cell proteases, such as transmembrane protease serine 2 (TMPRSS2) [2,3].

Periodontitis, one of the most prevalent diseases worldwide, is a polymicrobial infection and multifactorial disease and is characterized by chronic inflammation of the periodontium [4,5]. If left untreated, it can lead to alveolar bone destruction and subsequent tooth loss, during which major periodontopathic bacteria, such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum* (*F. nucleatum*), induce the production of pro-inflammatory cytokines [4,5]. Moreover, it may result in systemic complications, such as pneumonia, chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular diseases [4,5]. In fact, periodontopathic bacteria are observed in the bronchoalveolar lavage fluid (BALF) of patients with pneumonia [6], and the risk of onset of pneumonia and COPD is increased in patients with severe periodontal diseases [7-9]. In addition, it has been reported that periodontopathic bacteria can reactivate latent viruses, such as human immunodeficiency virus-1 and Epstein-Barr virus, and increase the infectivity of influenza virus [10-12]. 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.

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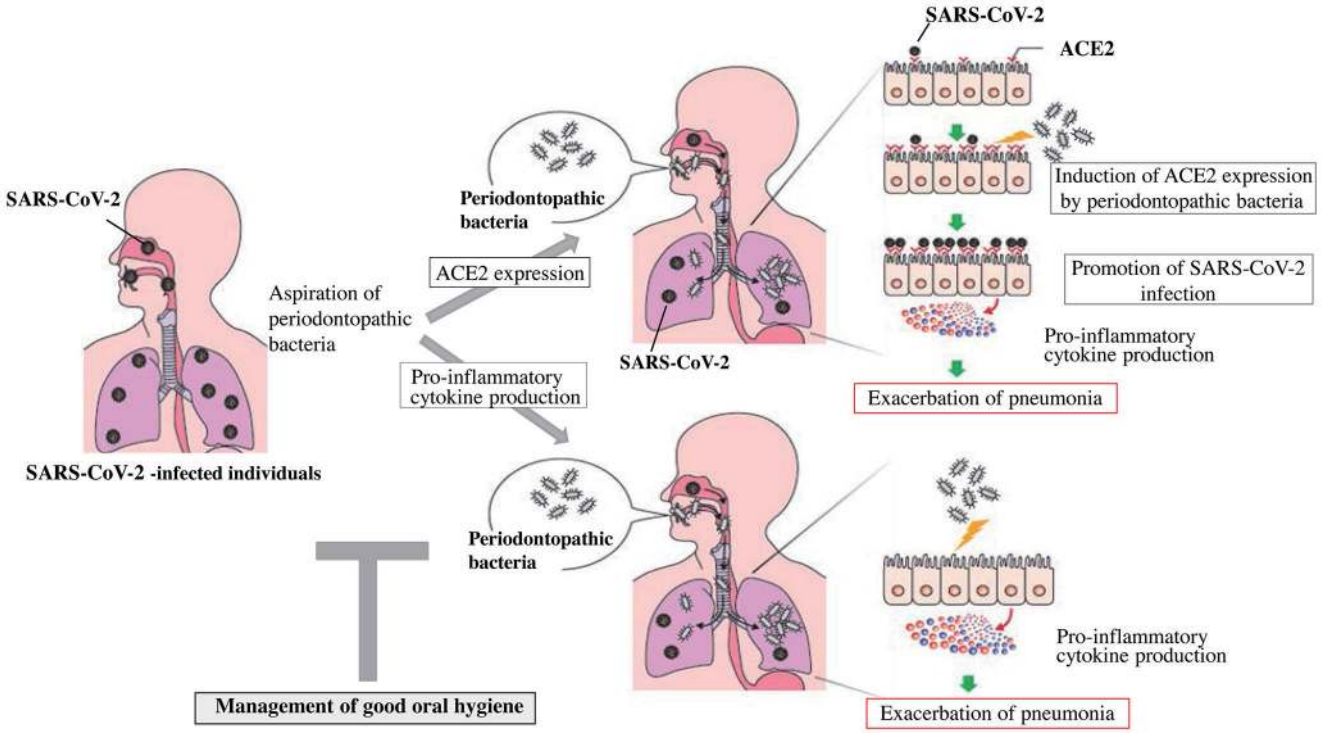

Fig. 1 Involvement of periodontopathic bacteria in the aggravation of COVID-19. Aspiration of periodontopathic bacteria in patients with COVID-19 potentially leads to the aggravation of COVID-19 through the induction of inflammatory cytokine production, ACE2 expression, and cleavage of the S protein of SARS-CoV-2. Management of oral hygiene is therefore important in patients with mild COVID-19 as it may help prevent the aggravation of COVID-19.

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 [27,28]. Clinical trials for tocilizumab, which suppresses IL-6 production that is associated with rheumatoid arthritis, are in progress [28].

It has been reported that heat-inactivated periodontopathic bacteria can induce the production of inflammatory cytokines, such as IL-6 and IL-8, by pharyngeal, bronchial, and alveolar epithelial cells in a density-dependent manner [29], where these bacteria induce cytokine production higher than that by *S. pneumoniae*. When the periodontopathic bacterium *F. nucleatum* is introduced into the murine trachea, it causes a remarkable increase in IL-6 and KC protein levels in the lower respiratory tissues and serum, indicating that the bacterium can induce pro-inflammatory cytokine production *in vivo* [29]. Moreover, gingipain, a protease produced by *P. gingivalis*, is determined to be the main etiological factor that causes pneumonia in mice [30]. Therefore, periodontopathic bacteria, even when lacking infectivity, are a potent pro-inflammatory stimulant for the lower respiratory tract through aspiration. If patients with mild COVID-19 aspirate periodontopathic bacteria frequently, COVID-19 symptoms may become more severe in combination with viral pneumonia.

The basis of research on the onset of infectious disease is the analysis of the pathogenicity of the microorganism involved at the time of onset. However, in some infectious diseases, multiple pathogens are known to be involved during onset and aggravation. Even in cases of severe pneumonia caused by influenza, symptoms are often aggravated due to the secondary bacterial infection that follows the primary viral infection [31]. Symptoms of SARS and Middle East respiratory syndrome may have been aggravated by the combined infection with viruses and bacteria [32,33]. Similarly, the involvement of secondary bacterial infection has also been suggested in the aggravation of COVID-19 [34,35].

Although bacteria such as *P. aeruginosa* and *Klebsiella pneumoniae* have 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 TMPRSS2 and furin for adsorption and fusion with the host cells [2,3,38]. Although ACE2, TMPRSS2, 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,

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 via respiratory epithelial cells (data not shown), it is important to ensure the involvement of periodontopathic bacteria in the aggravation of COVID-19. However, as far as poor oral hygiene may be contributing to the aggravation of COVID-19, treating periodontal disease and maintaining good oral hygiene are crucial for maintaining overall health.

Conflict of interest

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

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