THE MOUTH COVID CONNECTION

The importance of the oral cavity for the coronavirus disease – part II

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Abstract

Dentistry has been disrupted by the pandemic, however, the dental community has risen to the challenges imposed by COVID-19 to maintain delivery of oral healthcare. Untreated oral conditions can adversely affect the systemic environment, influencing respiratory conditions, and COVID-19. Deficient plaque control is detrimental for health, as it increases the risk for oral and respiratory diseases, potentially turning the oral cavity into a reservoir for respiratory and periodontal pathogens. Several studies have linked poor plaque control to worse lung function and pneumonia, particularly in hospitalized patients and institutionalized elderly. COVID-19 patients with poor plaque control can carry the virus for longer periods. Because saliva can be highly infective, pre-treatment oral rinsing has been recommended to decrease the viral load and transmission of COVID-19. Findings from this review suggest that the promotion of oral health and plaque control are vital to prevent respiratory diseases and potentially decrease the severity of COVID-19.

Keywords: mouth covid, saliva covid, oral health covid, oral inflammation

Introduction

The COVID-19 pandemic caused by the novel SARS-CoV-2 has disrupted multiple healthcare professions, including dentistry.[1] The dental community has slowly risen to the challenges imposed by the coronavirus disease in order to maintain the delivery of oral healthcare. Untreated oral conditions can become a challenge, as they can cause pain, affect important functions, such as speech and mastication, decrease general quality of life, and contribute to systemic inflammation.[2] The coronavirus disease is adversely affected by systemic inflammation, this is why dentists have an important role to play in the elimination of infection and inflammation in the mouth.[3] Due to the frequent exposure to body fluids, and close proximity to patients, dental treatments during the pandemic require strict use of personal protective equipment (PPE) and extraordinary infection control measures to decrease the risk of transmission of COVID-19 to dentists, dental staff, and patients.[4]

Findings from previous studies have shown that poor plaque control negatively influences the prevalence and severity of respiratory diseases, such as pneumonia. In a case report from Japan, the persistence of SARS-CoV-2 in saliva samples for extended periods after clinical recovery suggests a link between viral shedding and the oral biofilm.[5] Furthermore, secondary bacterial infection can be a challenge in the context of COVID-19, and the oral biofilm can act as a reservoir for pathogenic bacteria.[6] Given the spread of COVID-19, the extent of its complications, and the link between poor oral hygiene and increased risk for respiratory infections, adequate plaque control can help prevent COVID-19 secondary infection and complications, with special relevance for old age residents and hospitalized patients.[7]

Considering the infectivity of saliva droplets, mouthwashes constitute a promising approach to prevent viral replication in the oral cavity and oropharynx.[8] Oral rinses can potentially inactivate and decrease the number of infective virus particles in mucous membranes.[9] The use of antiseptic oral rinses has been part of routine oral health care, particularly pre- and post-operatively, as a measure to reduce the number of oral microorganisms.[10] During the pandemic, the American Dental Association (ADA), the Center for Disease Control (CDC), and other regulating bodies around the globe have recommended pre-procedural oral rinsing with hydrogen peroxide or iodine before delivery of oral health care to reduce the risk of COVID-19 transmission.[4]

In the first part of this review, SARS-Cov-2 presence in the oral cavity, the role of saliva in the coronavirus disease, diagnostic considerations of COVID-19, and alterations in the oral cavity of COVID-19 patients were discussed. In the second part of this review, the role of the oral cavity in COVID-19 is further explored, including the use of mouthwashes to decrease transmission, the importance of the oral biofilm for respiratory infections, and COVID-19, and the contribution of oral conditions to systemic inflammation.

Poor oral hygiene, oral microbiome, and risk for pulmonary infection

The oral microbiome is composed of more than 700 different species of microorganisms. Poor oral hygiene favors plaque accumulation and increases bacterial load. Because there is a frequent microbial exchange between the lungs and the oral cavity through aspiration and inhalation, oral microorganisms can promote infection of the lower respiratory tract, which can possibly contribute to increased severity of COVID-19.[6,7]

Oral hygiene, respiratory function, and pneumonia

Adequate oral hygiene has been linked to lower incidence and mortality due to pneumonia.[11] In ICU patients, oral hygiene measures resulted in decreased incidence of ventilator-induced pneumonia.[12] In a study on ventilation-associated pneumonia, plaque accumulation, and poor salivary flow were positively associated with increased risk for respiratory infection in critically ill patients.[13]

Analysis of respiratory tract samples from ICU patients on mechanical ventilation detected the presence of the periodontal pathogens *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis*, *Fusobacterium nucleatum, Treponema denticola,* and *Veillonella parvula*. The bacterial load increased with longer intubation time and the authors suggested that oral bacteria can contribute to ventilator-associated pneumonia.[14]

In the absence of adequate plaque control, periodontal pathogens accumulate and the consequent dysbiosis in the oral cavity and periodontal deterioration can negatively affect respiratory function, leading to a higher risk for pneumonia.[15] In a large group of dentate male participants from Northern Ireland, there was a significant association between chronic periodontitis and worse respiratory function, measured as the forced expiratory volume in one-second.[16]

In another study on institutionalized elderly, the risk of pneumonia increased with poor oral hygiene, as it led to the accumulation of the respiratory pathogens *H. influenzae and P. aeruginosa* in the tongue and dental calculus, suggesting that plaque and calculus removal can decrease the risk for pneumonia.[17] These findings have been corroborated by many studies that report lower risk for respiratory infections linked to adequate oral hygiene in both hospitalized and care-home patients.[18–21]

In a systematic review, oral hygiene decreased incidence and mortality from pneumonia in elderly hospitalized individuals and nursing home residents. The authors concluded that in every 10 deaths from pneumonia, one can be prevented through simple oral hygiene measures.[22]

COVID-19, secondary infections, and poor oral hygiene

The development of COVID-19 complications in young and otherwise healthy individuals has led to the search for alternative risk factors. In a study from Zhou et al (2020), half of the COVID-19 related deaths were associated with secondary infection.[23] Results from other studies on the use of antibiotics further confirm the high prevalence of bacterial infections and their negative impact on mortality rates of COVID-19.[24,25]

While many studies have included antibiotics in their treatment approaches, few have discussed potential sources for bacterial infection in COVID-19.[7] The literature provides compelling evidence on the detrimental role of poor oral hygiene in general health in healthy individuals and in those who suffer from chronic diseases, such as diabetes and cardiovascular disease, which are comorbidities for COVID-19.[26]

In COVID-19 patients, the risk for co-infection is likely to increase with poor oral hygiene, coughing, and mechanical ventilation, as those mechanisms can facilitate the entrance of oral microorganisms into the upper and lower respiratory tract. It has also been suggested that lung hypoxia, which is typically present in COVID-19, can promote the growth of anaerobic and facultative oral bacteria in the lungs.[6] Segal et al. (2016) has reported that 50% of bronchoalveolar lavage samples from healthy subjects contained oral bacteria, suggesting a close relationship between the oral microbiome and the lungs. In COVID-19 patients and pneumonia patients, high levels of

Capnocytophaga, Veillonella, and other oral bacteria were detected in bronchoalveolar lavage samples.[27]

In Japan, eight COVID-19 patients were followed-up after hospital admission. All patients had underlying systemic diseases, had overcome the acute phase of the disease, but remained positive for the virus for an average of 15.1 days. However, in two patients, the viral shedding period was much longer than the average (44 and 53 days). Those two patients did not perform oral hygiene during their hospital stay due to mental and psychological issues. After the introduction of monitored daily oral hygiene, both patients tested negative after 4-9 days.[5]

Thus, previous research provides evidence that dental plaque can function as a viral and bacterial reservoir, increasing the risk for pulmonary infection in COVID-19 patients. Bao et al. suggest that lung hypoxia, a common COVID-19 symptom, can be beneficial for oral facultative and anaerobe bacteria in the respiratory tract.[6] The importance of plaque control cannot be underestimated, particularly in the context of transmissibility, hospitalization, and mechanical intubation.

Based on findings from studies on dental plaque and respiratory conditions, adequate oral hygiene is vital to decrease the risk of lung infection, including COVID 19, particularly in hospitalized patients and home care residents. Poor oral hygiene can influence lung conditions directly through changes in the oral microbiome that favor the accumulation of periodontal and respiratory pathogens. It can also increase the risk of lung disease indirectly by promoting periodontal disease and consequent systemic inflammation.

Oral rinses for the prevention of transmission and infection of COVID-19

Oral rinses have been investigated due to their potential to decrease the viral load, severity of the disease, and transmission, given that: the virus accumulates in the oral cavity, nasal and pharyngeal area before symptoms develop; salivary glands present high expression of ACE-2 receptor; and saliva droplets represent a crucial route of transmission.[28] Previous studies on coronaviruses indicate that oral rinses targeting the viral lipid envelope can have a virucidal effect.[9]

Chlorhexidine (CHX)

As a well-known disinfectant and antiseptic, CHX presents broad-spectrum antimicrobial activity against gram- bacteria, some viruses, and fungus.[29,30] Although pre-treatment oral rinse with CHX has been suggested to reduce transmission of microorganisms through dental aerosols,[31] the efficacy of its antiviral properties has not been fully investigated. A 30-second exposure to 0.12% CHX has been shown to inactivate certain enveloped viruses in vitro, such as herpes simplex, cytomegalovirus, influenza A, parainfluenza, and hepatitis.[32] A study from Wood and Payne (1998) demonstrated that CHX was not able to inactivate human coronaviruses.[33] Recently, CHX mouthwash effectively decreased the viral load of SARS-CoV-2 in the saliva of two hospitalized COVID-19 patients. However, this effect was transient and the viral load increased again after 2-4 hours.[34] At this point, the benefits of CHX in the reduction of SARS-CoV-2 in the oral cavity are controversial.

Povidone-iodine

Povidone-iodine has been widely used as an antiseptic and mouthwash because of the antimicrobial and virucidal properties of iodine against non-enveloped and enveloped

viruses. Multiple in vitro studies have demonstrated the effectiveness of povidone-iodine in the inactivation of coronaviruses.[35] In vitro, povidone-iodine was able to inactivate SARS-CoV-2 when exposed for at least 15 seconds with a minimum concentration of 0.5%.[36] Contrary to CHX, oral rinsing with povidone-iodine has not been linked to teeth discoloration nor taste alterations, with substantivity in the oral cavity estimated at 4 hours. The contra-indications for povidone-iodine include allergy to iodine, active thyroid disease, pregnancy, and radioactive iodine therapy.[9]

Quaternary ammonium compounds

Different quaternary ammonium compounds have been used in mouthwashes, including benzalkonium chloride, cetylpyridinium chloride, and dequalinium chloride, due to their effect on cell surface lipids and proteins and plaque inhibiting effect. Cetylpyridinium chloride (CPC) has been shown to destroy influenza virus' envelope in vitro and in vivo and to decrease the incidence of upper respiratory infections in healthy adults.[37,38] However, the literature is scarce regarding the virucidal effects of these quaternary compounds on SARS-CoV-2.

Ethanol

Oral rinses containing ethanol (21-26%) combined or not with essential oils, such as eucalyptol, menthol, and thymol have shown inactivation of enveloped viruses such as herpes simplex, and influenza virus, both in vitro and in clinical studies.[39,40] In a study from Meiller et al., when used as an oral rinse, Listerine (ethanol-based mouthwash) reduced the load of Herpes Virus in saliva and the effect lasted for at least 30 min, suggesting a potential beneficial effect against SARS-CoV-2.[40]

Hydrogen peroxide

Hydrogen peroxide is an oxidative agent that has been used in dentistry for many years. Through the production of free oxygen radicals, hydrogen peroxide can destroy viral lipid membranes. However, in lower concentrations, it is quickly broken down by salivary catalase. In a study on periodontitis treatment, regular use of 1%–1.5% hydrogen peroxide was not linked to side effects on the oral mucosa.[41] Hydrogen peroxide has shown virucidal activity against coronaviruses when used as a surface disinfectant,[42] and because SARS-CoV2 seems to be susceptible to oxidation, it has been suggested that rinsing with 1% hydrogen peroxide can decrease the viral load in saliva.[4]

During the pandemic, oral rinsing with 1% hydrogen peroxide or 0.2% povidone-iodine has been recommended as a pre-procedure oral rinse by the American Dental Association and other regulatory bodies from different countries.[43]

Comparative studies

When hydrogen peroxide (1.5% and 3.0% for 30 seconds) was compared to povidone-iodine (at least 0.5% for a minimum of 30 seconds) in vitro, it was marginally effective as opposed to the high effectiveness of povidone-iodine.[44] In a recent in vitro study from Germany, eight commercially available mouthwashes were evaluated for their ability to inactivate SARS-CoV-2. All evaluated products had a beneficial effect on viral load, but the most effective were the formulations containing ethanol, povidone-iodine, and dequalinium and benzalkonium chloride, which nearly eliminated the virus in saliva.[45] Povidone-iodine (0.5% for a minimum of 30 seconds) presents the highest amount of

evidence in terms of anti-viral activity against SARS-CoV-2 in vitro. Oral rinses containing hydrogen peroxide, ethanol, and dequalinium/benzalkonium chloride also seem to have been effective in vitro virucidal effects. In conclusion, there is a scarcity of clinical data on the efficacy of mouthwashes in COVID-19 patients and clinical trials are warranted.

Oral cavity as a source of inflammation

Periodontitis

Elevated levels of pro-inflammatory cytokines, particularly interleukin 6 (IL-6), have been linked to respiratory complications in COVID-19 patients. In hospitalized COVID-19 patients, IL-6 levels above 80 pg/ml were a strong predictor for respiratory failure and the consequent need for mechanical ventilation.[46] As highlighted in a previous review from our group, because serum IL-6 levels are elevated as a consequence of gingival inflammation, untreated periodontitis can be an overlooked source of inflammation. Hence, because periodontal treatment can decrease systemic IL-6 levels, it should be regarded as an essential part of general healthcare to decrease inflammation and the risk for lung complications in COVID-19 patients.[3]

Pulpitis and periapical lesions

Pulpitis and periapical lesions are typically caused by infection originating from caries lesions. In vitro studies report that pulp cells and cells from periapical lesions increase IL-6 production when exposed to bacterial products.[47] IL-6 has been identified in inflamed pulp and periapical tissues and its expression seems to be proportional to the

size of the lesion and clinical symptoms.[48] A meta-analysis has reported increased local and serum CRP, IL-1, and IL-6 expression in patients with periapical lesions.[49] Collectively, these data indicate that periapical lesions can contribute to systemic inflammation. [50,51]

Mucosal lesions

Oral lichen planus is a T-cell mediated autoimmune disorder characterized by erosive or white lesions in the oral mucosa, being associated with higher IL-6 levels in saliva and serum (particularly ulcerative forms).[52] In a study from Larsen et al. (2017), patients with oral lichen planus, oral lichenoid lesions, and generalized stomatitis presented higher IL-6 levels than healthy controls, with oral lichen planus presenting the highest expression of IL-6 (average of 89.6 pg/ml).[53] Topical corticosteroid treatment of oral lichen planus has been reported to decrease IL-6 levels.[54]

Cytokines have also been implied in the pathophysiology of oral cancer, particularly oral squamous cell carcinoma (OSCC), which accounts for over 90% of all cancers in the oral cavity. Higher serum and saliva IL-6 levels have been associated with increased severity and worse prognosis of OSCC.[50,55]

Sleep apnea

Obstructive sleep apnea, defined as repetitive closure of the upper airway during sleep, leads to interrupted sleep, lower alveolar ventilation, and hypoxia. This sleep disorder has been linked to increased risk for periodontal disease, inflammation in the oral mucosa and upper airways, and systemic inflammation, characterized by higher

expression of pro-inflammatory markers in serum. Furthermore, patients with sleep apnea present an elevated risk for cardiovascular disease.[56,57] Thus, given the serious local and systemic consequences of sleep apnea, which include changes in the airways, it can potentially increase the risk for COVID-19 complications.

Even though most studies on the link between oral diseases and systemic inflammation have focused on periodontitis, other conditions have the potential to further increase IL-6 levels, although these associations have been investigated to a lesser degree. Thus, the importance of maintaining good oral health goes beyond the oral cavity. It does not only affect the capacity to eat and chew and the nutritional intake, but it can also negatively affect general health, particularly COVID-19, through mechanisms that involve local chronic infection and inflammation. As the literature on the importance of cytokine storms for COVID-19 increases, so does the responsibility of dental practitioners in preventing and treating oral conditions that can improve general inflammation.

Take-home message

Oral hygiene. Deficient plaque control can cause oral dysbiosis, leading to the accumulation of periodontal and respiratory pathogens in the oral cavity, higher risk for periodontal disease, pneumonia, potentially contributing to increased severity of COVID-19. The oral biofilm can also harbor SARS-CoV-2, which is important in the context of viral transmission and infection.

Oral rinses. Authorities around the world, including the ADA, recommend pre-treatment oral rinsing to decrease the viral load, severity, and transmission of COVID-19. The two

most recommended agents are povidone-iodine (0.2%) and hydrogen peroxide (1%), although the evidence is still limited.

Oral inflammation. Oral conditions such as periodontitis, periapical lesions, oral lichen planus, oral cancer, and obstructive sleep apnea can lead to systemic inflammation, which can be detrimental to COVID-19. Untreated oral diseases need to be regarded as potential hidden sources of systemic inflammation.

Oral care. Interventions to restore oral health and prevent disease are crucial to maintaining oral and general health. Measures to control plaque, remove calculus, eliminate infection and inflammation are essential to decrease the risk for respiratory infections and the severity of COVID-19.

Conclusion

Given the importance of the oral cavity and saliva for the coronavirus disease, mouthwashes are a promising approach to decrease the viral load according to in vitro studies, but there is an urgent need for clinical studies. Poor oral hygiene is highly detrimental for oral health and it also has a negative impact on lung conditions, potentially increasing the prevalence and severity of pneumonia and COVID-19. Dental plaque and calculus can function as a reservoir for respiratory pathogens, which can increase the risk for secondary bacterial infection in COVID-19. Finally, the mouth can become a source of inflammation if oral diseases and conditions are left untreated, with the potential to contribute to COVID-19 complications and other respiratory diseases. Findings from this review suggest that dentists have a crucial role to play in the promotion of oral health during the pandemic.

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