Journal of Pharmaceutical Research International

33(61A): 73-87, 2021; Article no.JPRI.82532
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

The Relationship between Oral Microbiome and SARS-CoV-2

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i61A35118

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/82532

Review Article

Received 22 October 2021
Accepted 27 December 2021
Published 28 December 2021

ABSTRACT

The oral microbiome represents an important part of the human microbiome. It has an important function to protect against the colonization of extrinsic bacteria, affecting systemic health. On the other hand, the most common oral diseases such as caries, gingivitis, and periodontitis, are based on microorganisms. After the gut microbiome, the oral microbiome is the second largest microbial population in the body. It has the potential to affect the onset and progression of a variety of localized and systemic disorders, including viral infections, especially those that enter the body through the oropharynx. Pandemics like SARS and coronavirus disease 2019 (COVID-19) have impacted negatively on economies and people around the world in recent years, making viral infection one of the most common and dangerous health problems. Despite being one of many respiratory viruses that use the oropharynx as their primary replication site, the novel pandemic human severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 disease has yet to be determined. PubMed, Medline, Google Scholar, Science Direct, Scopus, and Web of Science databases were among the search engines used up to December 1, 2021. For published data, search terms included 'Microbiome', 'COVID-19,' ' Oral Microbiome changes in COVID-19,' dysbiosis in COVID-19', or 'SARS-CoV-2'. This concise review aimed to see if there was a link between the oral microbiome and SARS-CoV-2.

Keywords: SARS-CoV-2; Oral Microbiome; COVID-19; dysbiosis; salivary microbiome.

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1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has spread rapidly over the world, affecting almost everyone on the planet. COVID-19 was originally discovered in December 2019 in the Wuhan area of China, and it swiftly became a pandemic, spreading to nearly every country in the world within six months. Despite being confined in certain nations, COVID-19 has begun to resurface in others that have had less success with containment or are seeing large rises in the number of cases [1,2].

COVID-19 is caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the World Health Organization in February 2020. SARS-CoV-2 appears to spread mostly by respiratory droplets, which begin as mucosal secretions in infected individuals [3]. Coughing, sneezing, or talking causes these droplets to become aerosolized, which can subsequently spread through the air or onto contaminated surfaces. When infected patients are in enclosed spaces or in close contact with others, respiratory droplets are more contagious [4].

The oral microbiome is the second largest and most complex microbial community in the human body, after the gut microbiome [5]. The microbiota in the oral cavity is the second largest in the human body. The microbial component of a eubiotic oral microbiome can prevent pathogen colonization by competitive exclusion and/or enhancing the immune response [6]. Periodontal inflammation is usually associated to oral microbiome dysbiosis, which has been linked to a variety of local and systemic illnesses, including those caused by viral infections [7,8]. Antiviral compounds (defensins) can be produced by the microbiota against adenoviruses, herpesviruses, papillomaviruses, orthomyxoviruses, and coronaviruses, to name a few [9]. Viruses, on the other hand, can alter the microbiota, causing dysbiosis and disease progression [10].

Early in the pandemic, studies found a relationship between a changed gut microbiome and the severity of COVID-19 [11,12] adding to the expanding body of evidence that the microbiome regulates innate and adaptive immunity to viral infections [13,14]. Furthermore, among COVID-19 patients, a high frequency of coinfection cases with organisms from the oral cavity has been reported [15]. COVID-19 has recently been associated to a decrease in oral microbiome diversity and an increase in the prevalence of dysbiotic organisms [16].

Furthermore, because oral microorganisms are concentrated in pulmonary fluids, and their presence in the lung has been linked to inflammation, the oral microbiome has a significant link with the lung microbiome [17–19]. As a result, the oral microbiome can be used as a proxy for lung microorganisms and as a potential indicator of lung health. For SARS-CoV-2 infection, the oral microbiota has showed promise as a diagnostic tool and predictor of illness severity [16,20,21]. It's also possible that the COVID-19 pandemic illness load might be reduced by targeting the oral microbiota [15,16,20,22]. It is also necessary to characterize the microbiome in COVID-19 illness to see if oral hygiene is a modifiable risk factor for severe disease [23].

SARS-CoV-2 infection and the severity of COVID-19 consequences may thus be linked to the oral cavity. So, the purpose of this review was to summarize previous studies, with a focus on whether the oral microbiota and SARS-CoV-2 had a relationship.

2. ORAL MICROBIOME

The microbiome is the microbial community that lives in our bodies. Joshua Lederberg, a Nobel Laureate, developed the word "microbiome" to define the ecological community of symbiotic, commensal, and pathogenic microorganisms. These bacteria occupy our physical space [24]. Compared to the amount of cells in our bodies, the number of bacteria in our bodies is roughly the same, if not greater than [25].

Various populations of indigenous microbes can be found throughout the human body [26]. Research shows that the gut microbiota plays an essential role in the digestive process as well as fat storage and angiogenesis, as well as the formation and reaction of the immune system and the ability to resist colonization [27–29].

The oral cavity has the second most abundant microbiota just after the gastrointestinal system. In addition, the oral cavity has one of the most diverse and unique populations of microbes in the human body [30,31]. Still, it is understudied in comparison to the gut—a PubMed search as an example for "oral microbiome" yielded 2223 articles, compared to 8942 for "gut microbiome" at the time of writing this study.

The microbiota in the oral cavity is quite varied. The mouth provides an ideal environment for the growth of organized bacterial populations due to its humidity and warmth. These grow as biofilms on the stomatognathic system's hard surfaces (teeth) and soft tissue. It is important to note that these communities are complex organizations that contain a wide range of bacteria species with variable degrees of pathogenicity [32].

The phrase "oral microbiome," "oral microbiota," or "oral microflora" is used to describe these microbiotas in the human oral cavity [33]. Dutchman Antony van Leeuwenhoek was first to discover the oral microbiome, using a microscope he manufactured himself [34]. He noticed his own tooth plaque in 1674 and described it as "small living animalcules prettily moving" [35].

As of October 5, 2021, the enhanced Human Oral Microbiome Database (eHOMD) had data on 700 different prokaryote species discovered in the human oral cavity. Approximately 49% of the phylotypes are officially named, 17% are unnamed (but cultivated), and 34% are only known as uncultivated phylotypes [36,37]. Bacteria in our bodies are nearly the same number as cells in our bodies, if not higher. A milliliter of saliva includes roughly 10^8 microbial cells [38] and studies have shown up to 700 different prokaryotic taxa [39] with a normal healthy microbiome containing between 100 and 200 different bacterial organisms [40]. *Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Bacteroidetes, and Spirochaetes* make up over 96 percent of the microbiome in a healthy human oral cavity, with Actinomyces, *Atopobium*, *Corynebacterium*, *Rothia*, *Bergeyella*, *Capnocytophaga*, *Prevotella*, *Granulicatella*, *Streptococcus*, *Veillonella* [41,42]. The most common genera are *Streptococcus*, *Veillonella*, and *Prevotella*. The palates, gingival surfaces, teeth, lips, cheeks, and tonsils are among the various oral cavity sites that get colonized [43].

Oral microbiome composition and activity may shift substantially over time and space, and they vary in parallel with the host's growth. In addition to the host and diet, the reaction to pH changes, the interactions between bacterial species, and, over a longer period of time, gene mutations and horizontal gene transfer that impart new features on the strain all contribute to these multiplex, nonequilibrium dynamics [44]. A biofilm is the most common form of the oral microbiota. Maintaining oral homeostasis, protecting the oral cavity, and halting disease development are all critical aspects of oral hygiene. The identification of the microbiome and the neighbours with whom it regularly interacts is vital for the mechanistic understanding of the primary participants [45].

The study of the oral microbiota is a new and promising area of investigation. An imbalance in oral microbiota can lead to both oral and systemic illnesses. It is found in biofilms throughout the mouth and generates an ecology that supports health in a stable condition. Pathogens can develop and cause disease, however, when there are specific imbalances in this state of equilibrium. Dysbiosis is the result of oral microbiota disruption [22].

3. HOW THE ORAL MICROBIOME MAY CAUSE LUNG INFECTION (THE ORAL-LUNG AXIS: ORAL CAVITY AND THE RESPIRATORY TRACT)

The oral microbiome is not a separate biome; it is part of a microbiome network that covers the human body, forming a micro-biosphere. The oral cavity has a lot of control over activity in other parts of the body since it is the entry point for almost all ingested material and has a lot of vascularity. It's no surprise, then, that the oral microbiome has been associated with a variety of systemic diseases and oral ailments [37]. Poor dental health has been linked to a range of systemic disorders in previous studies [46–48]. Furthermore, in recent studies, periodontal pathogens and their products were found to spread to other tissues and contribute to the development of systemic illnesses such as hospital-acquired pneumonia, chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disease, atherosclerosis, cerebrovascular illness, and stroke (Fig. 1) [49–52].

Several theories have been offered to explain how periodontal bacteria might infect organs that are far away from the mouth (Fig. 2). Gingival epithelial ulceration, bacterial invasion, and immune cell influx contribute to periodontitis, leading to inflammatory damage to periodontal tissues and deterioration of the supporting alveolar bone. Because of the prolonged inflammatory response, bacterial products, host inflammatory chemicals, and pathogenic oral bacteria escape into the bloodstream and are transported to distal tissue sites. Once in the systemic circulation, periodontally generated

materials have the potential to aggravate a range of systemic disorders, either directly in situ or indirectly through amplification of the systemic inflammatory response [54].

Early research analysing the healthy lung microbiome from bronchoalveolar lavage fluid found a lot of overlap between the oral and lung microbiota [55]. Because the two anatomic regions are adjacent and micro-aspiration is widespread even among healthy individuals, this parallelism is biologically feasible [56]. Interestingly, the nasal microbiota exhibits fewer similarities with the lung microbiome than the oropharyngeal microbiota [17]. This backs with the idea that salivary flow and micro-aspiration are the major mechanisms that promote the growth of the lung microbiome's population. Although the oral and lung microbiotas are extremely similar in composition, the lung is likely to have its own resident bacteria and may eradicate other common mouth bacteria such *Prevotella* species [17,19].

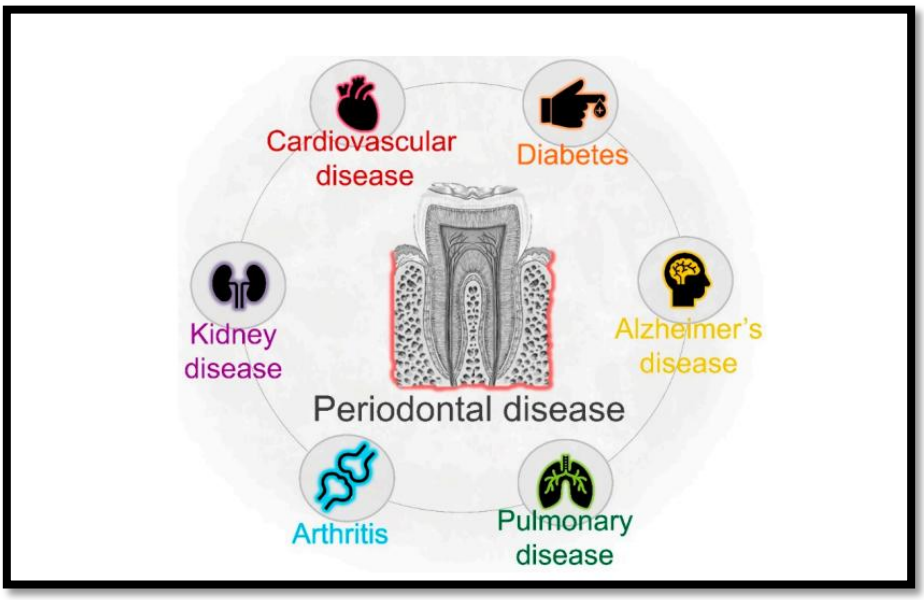

Fig. 1. The chronic periodontal disease raises the risk of several systemic disorders [53]

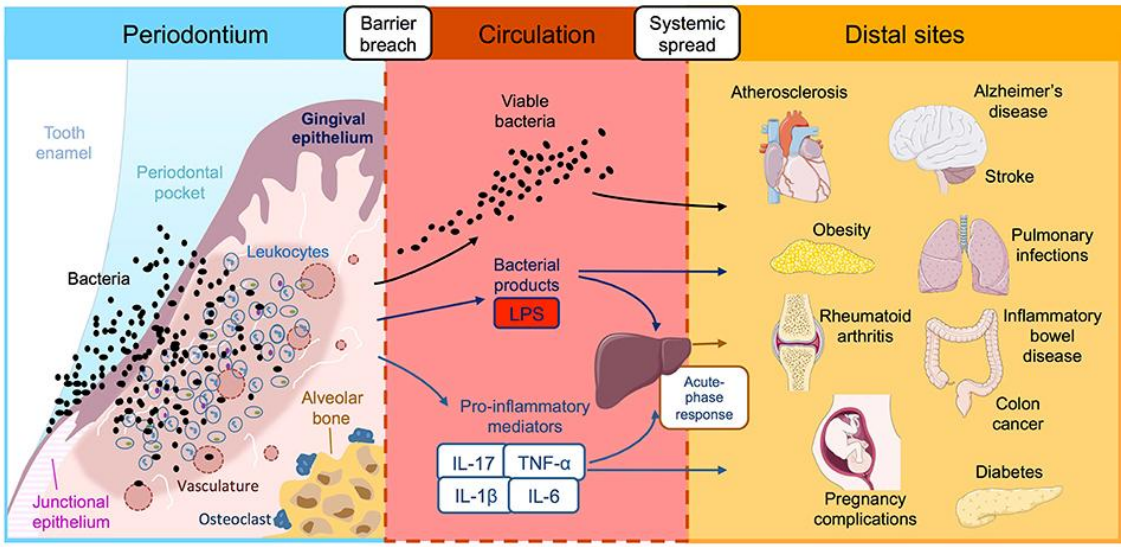

Fig. 2. To understand how periodontal bacteria can spread to other parts of the body, theories have been proposed [54]

The structure of the healthy lung microbiota is compatible with the neutral theory of community ecology, an ecological model. The lung microbiota, according to this theory, is the result of random migration of bacteria from the oral microbiota, random bacterial reproduction in the lung, and random lung bacteria clearance. Micro-aspiration, inhalation of germs from the air, and mucosal dispersion all contribute to lung immigration. Coughing, mucociliary clearance, and immune/host defences contribute to elimination. According to the neutral theory, the lung environment has less impact on which lung taxa live or die after immigration to the lung than random events like immigration, growth, or elimination. As a result, if the lung microbiota follows the neutral theory, the composition should closely resemble that of the source (oral) microbiota. Any lung taxonomic abundance that does not match stochastic microbial immigration from the oropharynx or removal represents "non-neutral" reproduction or elimination in the lung environment. Only 1% of human bacterial populations followed the neutral theory, according to a large study that included all of the records from the Human Microbiome Project [57,58]. Surprisingly, the healthy lung appears to be one of the few human locations that adhere to the neutral theory, implying that the mouth and lungs share a microbial habitat [55].

There has been an upsurge in research on the connection between oral health problems and lung disease in recent years. In addition to periodontal disease, there is a link between periodontal disease and respiratory illness (Fig. 3) [59,60].

Periodontal pockets, which are spaces beneath the gum line where bacteria may thrive and reproduce, are associated with a greater accumulation of dental plaque [61]. As a result of a build-up of dental plaque in periodontal pockets (holes or gaps beneath the gum line that are present in sickness), bacteria can multiply and reproduce [62]. Pneumonia, asthma, COPD, and bronchiectasis can all be exacerbated by aspirating oral infections into the lower respiratory tract [63].

Proinflammatory mediators can be maintained in periodontal tissues, aggravating pre-existing systemic inflammation in conditions like COPD, asthma, and pulmonary fibrosis [54,64]. TNF-, for example, has been found to be elevated in the sputum of patients with COPD, as well as during COPD and asthma exacerbations [65,66]. Matrix metalloproteinases (MMP), such as MMP-9, have been linked to the deterioration of periodontal connective tissue and enamel and lung parenchyma, which may play a role in asthma, COPD and idiopathic pulmonary fibrosis etiology [67,68]. Interleukin -6b (IL-6) in the sputum is linked to a faster loss in lung function and more frequent COPD exacerbations [69]. Aspiration of these molecules from a painful oral cavity can exacerbate daily respiratory symptoms, cause disease exacerbations, and even harm the lung parenchyma.

There are two other main mechanisms that link periodontal inflammation with respiratory illness, including bacteriaemia and the transmission of bacterial products. The gingival epithelial barrier is destroyed during established periodontal inflammation, resulting in ulcerations. As a result, the proximity of subgingival Gram-negative bacteria to the circulation favours their systemic spread. Transient bacteraemia can, however, occur as a result of teeth brushing, flossing, eating, and dental operations [70,71]. In the oral cavity and damaged periodontal tissues, respiratory infections can be detected. As a result, patients with active periodontal disease and poor dental hygiene may have a higher risk of developing a lung infection [72–74].

Active bacteria can also enter the circulation through bacterial-derived chemicals and toxins. Although Gram-negative oral bacteria provide a chronic danger to the host's immune system, they also provide a steady supply of Lipopolysaccharide (LPS) and toxins that can reach the bloodstream. Gram-negative oral bacteria [75]. Systemic inflammation can result from low quantities of LPS, which can lead to an imbalance in blood coagulation and organ failure [76,77]. In patients with periodontitis, C-reactive protein levels are raised [78]. C-reactive protein and IL-6 levels can be reduced by periodontal therapy, demonstrating the systemic effects of an inflammatory disease in the mouth can be reversed [79].

4. POTENTIAL ORAL RESERVOIRS OF SARS-COV-2

The global threat posed by COVID-19 has prompted extraordinary research efforts to learn more about SARS-CoV-2 infection, transmission, and early detection [80]. However, as a point of entry and outflow, the oral cavity is an underappreciated interface for learning more

about SARS-CoV-2 infection mechanics and their impact on oral and systemic health. Furthermore, tissue reservoirs in the oral cavity may produce biological changes locally and distally, resulting in worsened disease consequences and a longer recovery time. First, SARS-CoV-2 infects host cells by binding to angiotensin-converting enzyme 2 (ACE2), a receptor prevalent in lung cells and numerous extrapulmonary organs [81]. In the lungs, the heart, the digestive tract, the kidney's proximal tubule, and arterial smooth muscles, ACE2 is abundant [82].

Additionally, whereas oral epithelial cells express ACE2, particularly in the tongue and gingiva, the oral mucosa plays a critical role in preventing SARS-CoV-2 infection. According to published bulk-seq RNA datasets, ACE2 appears to be expressed on the oral mucosa [83]. It's possible that patients with SARS-CoV-2 infection have higher levels of ACE2 in their tongue epithelial cells, or that SARS-CoV-2 has infected their neurons or glia directly, as well as many other symptoms, including pain in the tongue and gustatory dysfunction, including loss of smell and taste [84,85]. Moreover, ACE2 expression in the nasal epithelium is age-dependent, with lower expression in children, which could explain why older people have a greater COVID-19 prevalence [86]. The viral spike (S) protein of SARS-CoV-2 has to be degraded by proteases such as transmembrane protease serine 2 (TMPRSS2) and furin for adsorption and fusion with host cells during infection with SARS-CoV-2 [87–90]. The ACE2 receptors are also found in periodontal fibroblasts, and higher protease levels caused by chronic periodontitis can enhance the risk of viral infection [91]. Moreover, ACE2 shedders and endopeptidase expression in discrete sections of the oral mucosa indicated that the mucosa might serve as a reservoir for the virus [92].

Huang et al. also found anti-SARS-CoV-2 antibodies and ACE2- and viral RNA-positive epithelial cells in saliva taken from COVID-19 patients who had recovered completely. It was discovered that several cells in the small salivary gland ducts and acini expressed the ACE2 gene [20]. This study also found ACE2 in cells from the submandibular gland duct and minor salivary glands [93]. Polymerase chain reaction (PCR) discovered SARS-CoV-2 RNA in cancerous lesions on the tongue and in the submandibular gland tissues of pre-symptomatic persons who were later found to have COVID-19 [94]. Infection with SARS-CoV-2 occurs in the oral cavity, according to these findings, and it is transmitted by saliva.

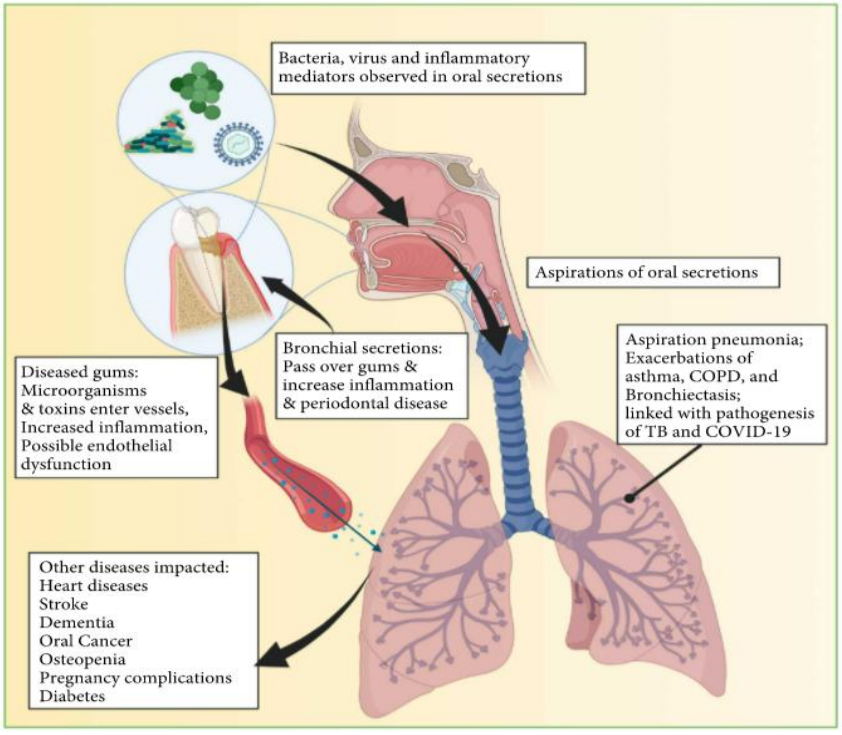

Fig. 3. Several mechanisms could relate respiratory disease to periodontitis [60]

In the gingival sulcus, a well-established microbial niche where enzymes and inflammatory chemicals are produced, bacteria may be more likely to settle and spread SARS-CoV-2 [95]. SARS-CoV-2 is also suspected to be present in gingival crevicular fluid (GCF), which is released by infected periodontal cells or terminal capillary complexes in periodontal tissues and subsequently combined with saliva to reach the oral cavity [96].

SARS-CoV-2 can accumulate in the mouth and spread to other organs, such as the respiratory and digestive systems, if the oral cavity serves as a major reservoir for the virus (Fig. 4) [97].

5. ORAL MICROBIOME ALTERATIONS IN SARS-COV-2 INFECTED PATIENTS

Viral infection has been linked to lung microbiome microbial variation in previous research [98]. Similarly, viral infections, such as SARS-CoV-2, can disrupt the local microbiome, resulting in dysbiotic communities [99]. This section and Table 1 described the alterations in the oral microbiome associated with SARS-CoV-2 infected patients.

Pseudomonas and Bacillus species were shown to increase considerably in the oropharyngeal microbiota of pneumonia patients with influenza virus infection compared to those without influenza virus infection. Prevotella, Veillonella, and Neisseria species, on the other hand, have declined dramatically in number [100]. Fusobacterium periodontium was shown to be significantly reduced in the nasopharyngeal microbiota of COVID-19 patients recently [101]. If SARS-CoV-2 infection in the mouth causes microecological imbalance and dysbiosis, additional investigation is needed. Secondary infections, such as superinfections and coinfections, might enhance patient mortality if they are exposed to SARS-CoV-2 [102]. Opportunistic infections, including those caused by bacteria and fungus, can have an impact on how COVID-19 is diagnosed and treated [103,104]. Researchers have shown that other viruses that may infect the respiratory and systemic systems of an infected person, including SARS-CoV-2 [105].

Analysis of both oral and gastrointestinal microbiomes of SARS-CoV-2 patients throughout hospitalization was conducted by Wu et al. to determine the possible ramifications and implications of these changes. Patients' viral loads and illness severity were linked to microbial species, suggesting the possibility of a microbiome-based treatment for COVID-19 prevention and treatment, according to the researchers [106].

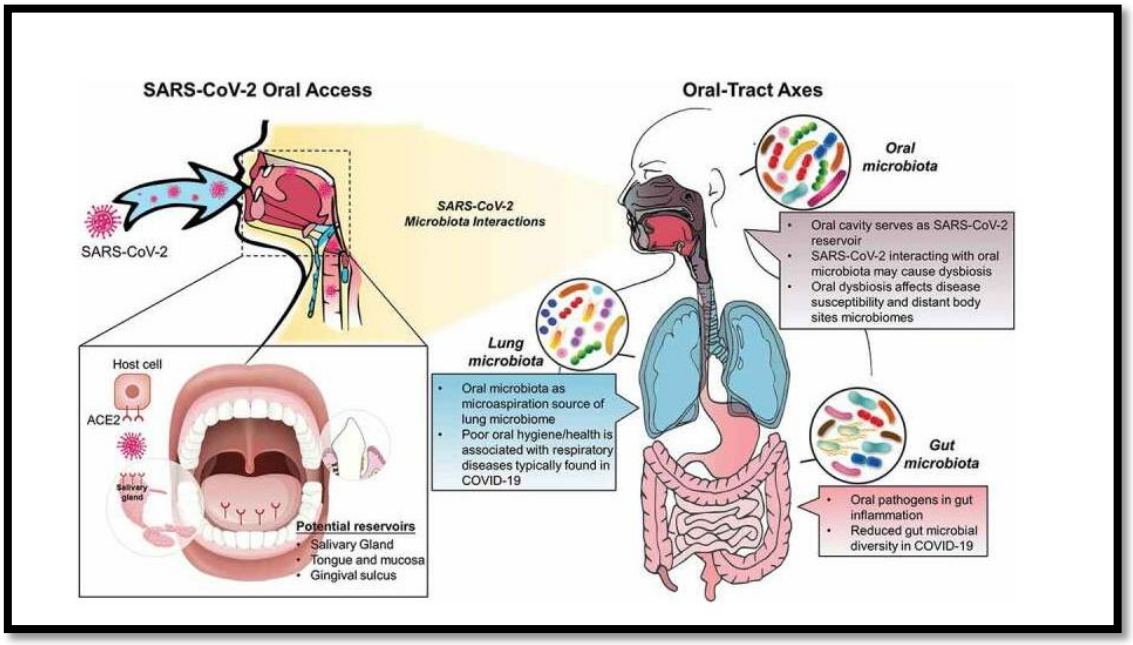

Fig. 4. The implications of oral SARS-CoV-2 infection on local and distant microbiomes across the 'oral-tract axes' [97]

Table 1. Summary of oral microbiome alterations in SARS-CoV-2 infected patients

COVID-19 patients	Oral microbes	Reference
Saliva	*P. pallens, Streptococcus infantis, Streptococcus parasanguinis*, clade 411, *Streptococcus sanguinis, Actinomyces* sp., HMT180, *Treponema* spp.	Miller et al. [107]
pregnant women with COVID-19	*Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Tannerella species*	Butera et al.[113]
Endotracheal aspirates or bronchoalveolar lavages	*Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae*	Kreitmann et al. [114]
bronchoalveolar lavage fluid	*Veillonella*, *Prevotella*, *Campylobacter*, *Treponema*, Fusobacterium	Shen et al. [115]
bronchoalveolar lavage specimens and tongue-coating samples	*Veillonella*, *Prevotella*, *Campylobacter*, *Treponema*, *Fusobacterium*	Ren et al. [116]
Nasopharyngeal swab samples	*Fusobacterium nucleatum*	Wolff et al. [117]
Bronchoalveolar lavage fluid	*Veillonella infantium*	Wu et al. [118]

SARS-CoV-2 and saliva microbiome may be linked in COVID-19 patients and controls, according to Miller et al. They used 16S rRNA sequencing and reverse transcription PCR to determine the SARS-CoV-2 virus load in saliva of COVID-19 patients and controls to compare microbiome diversity and taxonomic composition (RT-PCR). There were no significant differences in the microbiome of COVID-19 patients' saliva compared to controls. SARS-CoV-2 viral load revealed substantial changes in the abundance of multiple taxa, including *Streptococcus* and *Prevotella*. Changes in saliva microbiome as a result of SARS-CoV-2 viral load might reveal biologically significant bacterial-viral linkages affecting clinical outcomes in COVID-19 illness, the researchers found [107]. Two additional investigations, however, found that the diversity of the oral microbiome in COVID-19 patients was much lower than in healthy controls, and that butyrate-producing bacteria was also reduced in these patients [16,108].

Ma et al. studied the oropharyngeal microbiome of 31 COVID-19 patients, 29 influenza B patients, and 28 healthy controls to determine the level of microbial diversity and relative bacterial abundance. Specifically, they looked at the oropharyngeal microbiome's unusual topography in COVID-19 and examined the linkages between the oropharyngeal microbiome's modified oropharyngeal microbiome and COVID-19 severity. They concluded that the severity of COVID-19 was associated to changes in the oropharyngeal microbiota and functional abnormalities in the pharynx [57].

Even when the COVID-19 virus is eliminated, the microbiome dysbiosis persists. After release from the hospital, several individuals tested positive for SARS-CoV-2 RNA, according to previous study [109]. Re-detectable positives have no recognized cause. If the microbiome is negatively affected by SARS-CoV-2 infection, convalescent individuals may be more susceptible to reinfection or persistent viremia because their immune systems are malfunctioning [106].

Pregnancy brings about a variety of physiological and microbial changes, including an increase in dangerous bacteria in the mouth that can lead to gingivitis [110]. These three bacteria are frequent in pregnancy and have been connected to the development of gingivitis, according to several research. Postpartum, there is a significant decrease in the number of these same dangerous species: *Porphyromonas gingivalis, Tanerella forsythia, and Aggregatibacter actinomycetemcomitans* prevalence decreases significantly after delivery [111]. When *Fusobacterium nucleatum* was discovered in patients with COVID-19, researchers concluded that this bacterium had been introduced through bacteria translocation. Patients with COVID-19 had the same pathogenic microorganism in their colon mucus and bronchoalveolar washing fluid [112]. Pregnancy-related changes in the oral microbiota and their possible oral consequences in COVID-19 patients were examined by Butera and his colleagues. Pathogenic bacteria such as *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum* grew in pregnant women, and *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Tannerella* species grew selectively because they use progesterone as a source of nutrition, according to the research findings [113].

6. RELATIONSHIP BETWEEN COVID-19 SEVERITY AND ORAL MICROBIOME

SARS-CoV-2 and *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* have both been discovered in the bronchoalveolar lavage (BAL) fluid and sputum of infected patients, despite the fact that bacterial superinfection or secondary bacterial pneumonia in COVID-19 patients has been reported only seldom [119,120]. Other pneumonia-causing pathogens such as *Staphylococcus aureus, Haemophilus influenzae, or Streptococcus pneumoniae* are also shown to be superinfected in patients with COVID-19 who require invasive ventilation for acute respiratory distress (ARDS) [114]. Secondary bacterial infection is more likely in COVID-19 exacerbation patients because of elevated neutrophil counts and the widespread use of antibiotics in SARS-CoV-2 patients. Patients with COVID-19 have recently been shown to have oral bacteria such *Veillonella, Prevotella, Campylobacter, Treponema, and Fusobacterium* in their BAL fluid [115,116].

The concept that interactions between host and viral microorganisms may play a crucial role in the beginning and course of COVID-19 will be examined below, based on the idea that poor oral hygiene might exacerbate lower respiratory tract inflammation in COVID-19 patients. For the old and ill, who are known to be more vulnerable, this is especially true. Because of their impaired swallowing and coughing reflexes, these individuals are at an increased risk of aspiration.

As a result, patients are more likely to require more dental care in the future. SARS-CoV-2 and mild COVID-19 infections may not be confined to the following. SARS-CoV-2 infection or mild COVID-19 aggravated by aspiration may have been caused by aspiration of oral bacteria, which is prevalent in the lower respiratory tract inflammation associated with aspiration, according to the researchers [121].

In addition, a retrospective case-control study has just been published. Study participants were divided into two groups: those with COVID-19-related problem and those who did not. Gum disease/periodontitis has been linked to a three-fold increased risk of ICU admission, a four-fold increased risk of assisted breathing, and an 8.81-fold increased risk of mortality in COVID-19 patients, regardless of any concurrent risk factors, according to the researchers. They stated that the aged patients are more prone to COVID-19 pulmonary problems because to increased aspiration, as the elderly have poor swallowing and cough reflexes. Chronic periodontitis complicates mild COVID-19 patients, according to a new retrospective case-control study [122].

Haran et al. aimed to investigate if the duration of COVID symptoms was linked to the oral microbiota. Tongue swabs were administered to patients exhibiting signs of COVID-19 infection. As long as symptoms remained, infections were monitored until they disappeared. Metagenomic sequencing was used to assess the bacterial composition. The microbiota and clinical features associated with long-term COVID symptoms were discovered using random forest modelling. For example, the Prevotella and Veillonella genera (both of which generate LPS) have greater concentrations of inflammation-promoting microorganisms than healthy individuals. The oral microbiota of long-term COVID patients resembles that of patients with chronic fatigue syndrome. Their findings reveal a link between long-term COVID and oral microbiota, indicating that disruption of the oral microbiome may have had a role in this draining condition [123].

7. CONCLUSIONS

Several cases of SARS-CoV-2 are co-infected with other infections, some of which originate in the oral cavity, during the global pandemic. Until today, little research has been done on coronaviruses and oral microbiomes, and there is still a lot to learn. Therefore, all medical practitioners must grasp the "oral microbiome-virus-host interaction" from the same perspective and understand systemic disorders influenced by the oral microbiota. We highlighted current data and offered a conceptual framework for the potential association between SARS-CoV-2 infection and the oral microbiota in this study. Therefore, microbiome research is far from complete, and we should proceed with care and patience before fully utilizing its medical potential without a thorough grasp of its nature. The present COVID-19 pandemic and future pandemics that we have yet to encounter can be rapidly responded to through medical and dental teamwork.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Xu S, Li Y. Beware of the second wave of COVID-19. Lancet. 2020;395(10233): 1321-1322.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-534.
3. Varadhachary A, Chatterjee D, Garza J, et al. Salivary anti-SARS-CoV-2 IgA as an accessible biomarker of mucosal immunity against COVID-19. MedRxiv. Published online; 2020.
4. Meselson M. Droplets and aerosols in the transmission of SARS-CoV-2. N Engl J Med. 2020;382(21):2063.
5. Caselli E, Brusaferro S, Coccagna M, et al. Reducing healthcare-associated infections incidence by a probiotic-based sanitation system: A multicentre, prospective, intervention study. PLoS One. 2018;13(7): e0199616.
6. Soffritti I, D'Accolti M, Fabbri C, et al. Oral microbiome dysbiosis is associated with symptoms severity and local immune/inflammatory response in COVID-

19 patients: A cross-sectional study. Front Microbiol. 2021;12:1397.
7. Baghbani T, Nikzad H, Azadbakht J, Izadpanah F, Kashani HH. Dual and mutual interaction between microbiota and viral infections: a possible treat for COVID-19. Microb Cell Fact. 2020;19(1):1-25.
8. Cagna DR, Donovan TE, McKee JR, et al. Annual review of selected scientific literature: A report of the Committee on Scientific Investigation of the American Academy of Restorative Dentistry. J Prosthet Dent. 2019;122(3):198-269.
9. Pfeiffer JK, Sonnenburg JL. The intestinal microbiota and viral susceptibility. Front Microbiol. 2011;2:92.
10. Lynch S V. Viruses and microbiome alterations. Ann Am Thorac Soc. 2014;11(Supplement 1):S57-S60.
11. Zuo T, Liu Q, Zhang F, et al. Depicting SARS-CoV-2 faecal viral activity in association with gut microbiota composition in patients with COVID-19. Gut. 2021;70(2):276-284.
12. Yeoh YK, Zuo T, Lui GC-Y, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021;70(4):698-706.
13. Trompette A, Gollwitzer ES, Pattaroni C, et al. Dietary fiber confers protection against flu by shaping Ly6c− patrolling monocyte hematopoiesis and CD8+ T cell metabolism. Immunity. 2018;48(5):992-1005.
14. Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity. 2017;46(4):562-576.
15. Bao L, Zhang C, Dong J, Zhao L, Li Y, Sun J. Oral microbiome and SARS-CoV-2: beware of lung co-infection. Front Microbiol. 2020;11:1840.
16. Ren Z, Wang H, Cui G, et al. Alterations in the human oral and gut microbiomes and lipidomics in COVID-19. Gut. 2021;70(7): 1253-1265.
DOI:10.1136/gutjnl-2020-323826
17. Bassis CM, Erb-Downward JR, Dickson RP, et al. Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. MBio. 2015;6(2):e00037-15.
18. Segal LN, Clemente JC, Tsay J-CJ, et al. Enrichment of the lung microbiome with oral taxa is associated with lung inflammation of a Th17 phenotype. Nat Microbiol. 2016;1(5):1-11.
19. Venkataraman A, Bassis CM, Beck JM, et al. Application of a neutral community model to assess structuring of the human lung microbiome. MBio. 2015;6(1):e02284-14.
20. Huang N, Pérez P, Kato T, et al. SARS-CoV-2 infection of the oral cavity and saliva. Nat Med. 2021;27(5):892-903.
21. Ward D V, Bhattarai S, Rojas-Correa M, et al. The intestinal and oral microbiomes are robust predictors of COVID-19 severity the main predictor of COVID-19-related fatality. medRxiv. Published online 2021.
22. Deo PN, Deshmukh R. Oral microbiome: Unveiling the fundamentals. J oral Maxillofac Pathol JOMFP. 2019;23(1):122.
23. Patel J, Sampson V. The role of oral bacteria in COVID-19. The Lancet Microbe. 2020;1(3):e105.
24. Kilian M, Chapple ILC, Hannig M, et al. The oral microbiome–an update for oral healthcare professionals. Br Dent J. 2016;221(10):657-666.
25. Scotti E, Boué S, Sasso G Lo, et al. Exploring the microbiome in health and disease: Implications for toxicology. Toxicol Res Appl. 2017;1: 2397847317741884.
26. Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human–microbe mutualism and disease. Nature. 2007;449(7164):811-818.
27. Tappenden KA, Deutsch AS. The physiological relevance of the intestinal microbiota-contributions to human health. J Am Coll Nutr. 2007;26(6):679S-683S.
28. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? Br J Dermatol. 2008;158(3):442-455.
29. Flint HJ, Duncan SH, Scott KP, Louis P. Interactions and competition within the microbial community of the human colon: links between diet and health. Environ Microbiol. 2007;9(5):1101-1111.
30. Consortium HMP. Structure, function and diversity of the healthy human microbiome. Nature. 2012;486(7402):207.
31. Li K, Bihan M, Yooseph S, Methe BA. Analyses of the microbial diversity across the human microbiome. PLoS One. 2012; 7(6):e32118.
32. Gomes-Filho IS, Passos JS, Seixas da Cruz S. Respiratory disease and the role of oral bacteria. J Oral Microbiol. 2010;2:10.3402/jom.v2i0.5811.
DOI:10.3402/jom.v2i0.5811

33. Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F. Oral microbiomes: more and more importance in oral cavity and whole body. Protein Cell. 2018;9(5):488-500.
34. Yamashita Y, Takeshita T. The oral microbiome and human health. J Oral Sci. 2017;59(2):201-206.
35. Patil S, Rao RS, Amrutha N, Sanketh DS. Oral microbial flora in health. World J Dent. 2013;4(4):262-266.
36. Zhu J, Tian L, Chen P, et al. Over 50,000 metagenomically assembled draft genomes for the human oral microbiome reveal new taxa. Genomics Proteomics Bioinformatics. Published online 2021.
37. Willis JR, Gabaldón T. The human oral microbiome in health and disease: from sequences to ecosystems. Microorganisms. 2020;8(2):308.
38. Marsh PD, Do T, Beighton D, Devine DA. Influence of saliva on the oral microbiota. Periodontol 2000. 2016;70(1):80-92.
39. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. J Bacteriol. 2010;192(19):5002-5017.
40. Paster BJ, Olsen I, Aas JA, Dewhirst FE. The breadth of bacterial diversity in the human periodontal pocket and other oral sites. Periodontol 2000. 2006;42(1):80-87.
41. Bik EM, Long CD, Armitage GC, et al. Bacterial diversity in the oral cavity of 10 healthy individuals. ISME J. 2010;4(8):962-974.
42. Verma D, Garg PK, Dubey AK. Insights into the human oral microbiome. Arch Microbiol. 2018;200(4):525-540.
43. Krishnan K, Chen T, Paster BJ. A practical guide to the oral microbiome and its relation to health and disease. Oral Dis. 2017;23(3):276-286.
44. McLean JS. Advancements toward a systems level understanding of the human oral microbiome. Front Cell Infect Microbiol. 2014;4:98.
45. Jia G, Zhi A, Lai PFH, et al. The oral microbiota–a mechanistic role for systemic diseases. Br Dent J. 2018;224(6):447-455.
46. Pizzo G, Guiglia R, Russo L Lo, Campisi G. Dentistry and internal medicine: from the focal infection theory to the periodontal medicine concept. Eur J Intern Med. 2010;21(6):496-502.
47. Kumar PS. From focal sepsis to periodontal medicine: a century of exploring the role of the oral microbiome in systemic disease. J Physiol. 2017;595(2): 465-476.
48. Li X, Kolltveit KM, Tronstad L, Olsen I. Systemic diseases caused by oral infection. Clin Microbiol Rev. 2000;13(4): 547-558.
49. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. Ann Periodontol. 2003;8(1):54-69.
50. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol. 1996;67:1123-1137.
51. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. Oral Dis. 2008;14(3):191-203.
52. Sfyroeras GS, Roussas N, Saleptsis VG, Argyriou C, Giannoukas AD. Association between periodontal disease and stroke. J Vasc Surg. 2012;55(4):1178-1184.
53. Aquino-Martinez R, Hernández-Vigueras S. Severe COVID-19 Lung Infection in Older People and Periodontitis. J Clin Med. 2021;10(2):279.
54. Konkel JE, O'Boyle C, Krishnan S. Distal consequences of oral inflammation. Front Immunol. 2019;10:1403.
55. Charlson ES, Bittinger K, Haas AR, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. Am J Respir Crit Care Med. 2011;184(8):957-963.
56. Gleeson K, Maxwell SL, Eggli DF. Quantitative aspiration during sleep in normal subjects. Chest. 1997;111(5):1266-1272.
57. Gaeckle NT, Pragman AA, Pendleton KM, Baldomero AK, Criner GJ. The oral-lung axis: the impact of oral health on lung health. Respir Care. 2020;65(8):1211-1220.
58. Li L, Ma ZS. Testing the neutral theory of biodiversity with human microbiome datasets. Sci Rep. 2016;6(1):1-10.
59. Hobbins S, Chapple ILC, Sapey E, Stockley RA. Is periodontitis a comorbidity of COPD or can associations be explained by shared risk factors/behaviors? Int J Chron Obstruct Pulmon Dis. 2017;12:1339.
60. Kouanda B, Sattar Z, Geraghty P. Periodontal Diseases: Major Exacerbators of Pulmonary Diseases? Pulm Med. 2021;2021.
61. Heinrich J, Thiering E, Jörres RA, Schulz H, Kühnisch J, Standl M. Lung function

and oral health in adolescents. Eur Respir J. 2019;53(3).
62. Diaz PI. Microbial diversity and interactions in subgingival biofilm communities. Periodontal Dis. 2012;15:17-40.
63. Atamas SP, Chapoval SP, Keegan AD. Cytokines in chronic respiratory diseases. F1000 Biol Rep. 2013;5.
64. Reis C, Da Costa AV, Guimarães JT, et al. Clinical improvement following therapy for periodontitis: Association with a decrease in IL-1 and IL-6. Exp Ther Med. 2014;8(1): 323-327.
65. Aaron SD, Angel JB, Lunau M, et al. Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(2): 349-355.
66. Thomas PS. Tumour necrosis factor-α: The role of this multifunctional cytokine in asthma. Immunol Cell Biol. 2001;79(2): 132-140.
67. Demedts IK, Brusselle GG, Bracke KR, Vermaelen KY, Pauwels RA. Matrix metalloproteinases in asthma and COPD. Curr Opin Pharmacol. 2005;5(3):257 -263.
68. Franco C, Patricia H-R, Timo S, Claudia B, Marcela H. Matrix metalloproteinases as regulators of periodontal inflammation. Int J Mol Sci. 2017;18(2):440.
69. Donaldson GC, Seemungal TAR, Patel IS, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest. 2005;128(4):1995-2004.
70. Kinane DF, Riggio MP, Walker KF, MacKenzie D, Shearer B. Bacteraemia following periodontal procedures. J Clin Periodontol. 2005;32(7):708-713.
71. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008; 117(24):3118-3125.
72. Scannapieco FA, Ho AW. Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III. J Periodontol. 2001;72(1):50-56.
73. Mojon P. Oral health and respiratory infection. Journal-Canadian Dent Assoc. 2002;68(6):340-345.
74. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol. 1999; 70(7):793-802.
75. Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. Ann Periodontol. 1998;3(1):108-120.
76. Slofstra SH, ten Cate H, Spek CA. Low dose endotoxin priming is accountable for coagulation abnormalities and organ damage observed in the Shwartzman reaction. A comparison between a single-dose endotoxemia model and a double-hit endotoxin-induced Shwartzman reaction. Thromb J. 2006;4(1):1-7.
77. Levi M, Keller TT, van Gorp E, ten Cate H. Infection and inflammation and the coagulation system. Cardiovasc Res. 2003;60(1):26-39.
78. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol. 2008;35 (4):277-290.
79. D'Aiuto F, Parkar M, Andreou G, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res. 2004;83(2):156-160. DOI:10.1177/154405910408300214
80. Carvalho T. COVID-19 research in brief: december, 2019 to June, 2020. Nat Med. 2020;26(8):1152-1154.
81. Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci. 2020;117(21):11727-11734.
82. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. Published online. 2020;1-8.
83. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):1-5.
84. Lechien JR, Chiesa-Estomba CM, Hans S, Barillari MR, Jouffe L, Saussez S. Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. Ann Intern Med. 2020;173(8):672-675.
85. Cooper KW, Brann DH, Farruggia MC, et al. COVID-19 and the chemical senses: supporting players take center stage. Neuron. Published online; 2020.
86. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. Jama. 2020;323(23):2427-2429.

87. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. Published online; 2020.
88. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020; 11(1):1-12.
89. Izaguirre G. The proteolytic regulation of virus cell entry by furin and other proprotein convertases. Viruses. 2019;11 (9):837.
90. Song J, Li Y, Huang X, et al. Systematic analysis of ACE2 and TMPRSS2 expression in salivary glands reveals underlying transmission mechanism caused by SARS-CoV-2. J Med Virol. 2020;92(11):2556-2566.
91. Balaji TM, Varadarajan S, Rao USV, et al. Oral cancer and periodontal disease increase the risk of COVID 19? A mechanism mediated through furin and cathepsin overexpression. Med Hypotheses. 2020;144:109936.
92. Lin B, Zhong M, Gao H, et al. Significant expression of FURIN and ACE2 on oral epithelial cells may facilitate the efficiency of 2019-nCov entry. BioRxiv. Published online; 2020.
93. Usami Y, Hirose K, Okumura M, Toyosawa S, Sakai T. Brief communication: immunohistochemical detection of ACE2 in human salivary gland. Oral Sci Int. 2021;18(2):101-104.
94. Guerini-Rocco E, Taormina SV, Vacirca D, et al. SARS-CoV-2 detection in formalin-fixed paraffin-embedded tissue specimens from surgical resection of tongue squamous cell carcinoma. J Clin Pathol. 2020;73(11):754-757.
95. Gomes-Filho IS, Cruz SS da, Trindade SC, et al. Periodontitis and respiratory diseases: A systematic review with meta-analysis. Oral Dis. 2020;26(2):439-446.
96. Gupta S, Mohindra R, Chauhan PK, et al. SARS-CoV-2 detection in gingival crevicular fluid. J Dent Res. 2021;100(2): 187-193.
97. Xiang Z, Koo H, Chen Q, Zhou X, Liu Y, Simon-Soro A. Potential implications of SARS-CoV-2 oral infection in the host microbiota. J Oral Microbiol. 2020;13(1): 1853451. DOI:10.1080/20002297.2020.1853451
98. Shenoy MK, Iwai S, Lin DL, et al. Immune response and mortality risk relate to distinct lung microbiomes in patients with HIV and pneumonia. Am J Respir Crit Care Med. 2017;195(1):104-114.
99. Kalantar-Zadeh K, Ward SA, Kalantar-Zadeh K, El-Omar EM. Considering the effects of microbiome and diet on SARS-CoV-2 infection: nanotechnology roles. ACS Nano. 2020;14(5):5179-5182.
100. Leung RK, Zhou JW, Guan W, Li SK, Yang ZF, Tsui SW. Modulation of potential respiratory pathogens by pH1N1 viral infection. Clin Microbiol Infect. 2013;19(10):930-935.
101. Moore SC, Penrice-Randal R, Alruwaili M, et al. Amplicon based MinION sequencing of SARS-CoV-2 and metagenomic characterisation of nasopharyngeal swabs from patients with COVID-19. MedRxiv. Published online 2020.
102. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. The Lancet Microbe. 2020;1(1):e11.
103. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol. 2020;127:104364.
104. Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021;27(1):83-88.
105. Blanco JL, Ambrosioni J, Garcia F, et al. COVID-19 in patients with HIV: clinical case series. lancet HIV. 2020;7(5):e314-e316.
106. Wu Y, Cheng X, Jiang G, et al. Altered oral and gut microbiota and its association with SARS-CoV-2 viral load in COVID-19 patients during hospitalization. npj Biofilms Microbiomes. 2021;7(1):1-9.
107. Miller EH, Annavajhala MK, Chong AM, et al. Oral Microbiome Alterations and SARS-CoV-2 Saliva Viral Load in Patients with COVID-19. Microbiol Spectr. 2021;9(2): e0005521-e0005521. DOI:10.1128/Spectrum.00055-21
108. Iebba V, Zanotta N, Campisciano G, et al. Profiling of oral microbiota and cytokines in COVID-19 patients. Front Microbiol. Published online. 2021:1603.
109. Tao W, Wang X, Zhang G, et al. Re-detectable positive SARS-CoV-2 RNA tests in patients who recovered from

COVID-19 with intestinal infection. Protein Cell. 2021;12(3):230-235.
110. Wang J, Zheng J, Shi W, et al. Dysbiosis of maternal and neonatal microbiota associated with gestational diabetes mellitus. Gut. 2018;67(9):1614-1625.
111. Emmatty R, Mathew JJ, Kuruvilla J. Comparative evaluation of subgingival plaque microflora in pregnant and non-pregnant women: A clinical and microbiologic study. J Indian Soc Periodontol. 2013;17(1):47.
112. Collins L, Diamond T. Fusobacterium nucleatum causing a pyogenic liver abscess: a rare complication of periodontal disease that occurred during the COVID-19 pandemic. BMJ Case Reports CP. 2021;14(1):e240080.
113. Butera A, Maiorani C, Morandini A, et al. Assessment of Oral Microbiome Changes in Healthy and COVID-19-Affected Pregnant Women: A Narrative Review. Microorg . 2021;9(11). DOI:10.3390/microorganisms9112385
114. Kreitmann L, Monard C, Dauwalder O, Simon M, Argaud L. Early bacterial co-infection in ARDS related to COVID-19. Intensive Care Med. 2020;46(9):1787-1789.
115. Shen Z, Xiao Y, Kang L, et al. Genomic diversity of severe acute respiratory syndrome–coronavirus 2 in patients with coronavirus disease 2019. Clin Infect Dis. 2020;71(15):713-720.
116. Ren LL, Wang YM, Wu Z-Q, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020;133(9):1015.
117. Wolff L, Martiny D, Deyi VYM, Maillart E, Clevenbergh P, Dauby N. COVID-19-Associated Fusobacterium nucleatum Bacteremia, Belgium. Emerg Infect Dis. 2021;27(3):975-977. DOI:10.3201/eid2703.202284
118. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269.
119. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
120. Alhazzani W, Evans L, Alshamsi F, et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med. 2021;49(3):e219-e234.
121. Takahashi Y, Watanabe N, Kamio N, Kobayashi R, Iinuma T, Imai K. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. J Oral Sci. 2021;63(1):1-3.
122. Marouf N, Cai W, Said KN, et al. Association between periodontitis and severity of COVID-19 infection: A case–control study. J Clin Periodontol. 2021;48 (4):483-491.
123. Haran JP, Bradley E, Zeamer Al, et al. Inflammation-type dysbiosis of the oral microbiome associates with the duration of COVID-19 symptoms and long COVID. JCI insight. 2021;6(20):e152346. DOI:10.1172/jci.insight.152346

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/82532