Print ISSN: 2321-6379
Online ISSN: 2321-595X

Review Article

Association between Periodontitis and COVID-19 Infection: A Review Article

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Abstract

COVID-19 is the largest epidemic of the 21st century. Virus SARS-Cov-2 causes the disease. SARS-CoV-2 (formerly nCov-19) is one of the severe acute respiratory-related coronavirus (SARS-CoV). The virus envelope is composed of a lipid bilayer, in which the membrane (M), the envelope (E), and the spike (S) structural proteins are concentrated. The molar ratio of E:S:M in the lipid bilayer is approximately 1:20:300. Periodontal dysbiosis leads to disruption of local homeostasis and immune mutations that increase microbial colonization, virulence, and disease resistance, and lead to the continuous recruitment of hyperfunctional PMN or hyperactive phenotypes. Similar to what happens in patients with COVID-19, these now inactive PMNs produce high levels of ROS and harmful enzymes as well as increasing levels of proinflammatory cytokines. Innovative methods may explain the strong interaction seen between periodontitis and COVID-19 intensity. Enthusiasm for periodontopathic viruses may exacerbate COVID-19 by inducing angiotensin-converting enzyme 2, a SARS-CoV-2 receptor, and inflammatory cytokines in the lower respiratory tract. Furthermore, it was suggested that periodontopathic viruses may increase the risk of SARS CoV-2 by cutting out its S glycoproteins and that the oral cavity, and especially the periodontal packs may act as a repository. Many studies currently appear to focus on confirming, whether the presence of periodontal disease affects COVID-19-related effects. It would be interesting, however, to see if there were any opportunities for communication between SARS-CoV-2 and the oral microbiome directly or in a phage-mediated manner.

Key words: COVID-19, Periodontitis, Periodontitis and COVID-19 association

INTRODUCTION

COVID-19 is the largest epidemic of the 21st century. Virus SARS-Cov-2 causes the disease. SARS-CoV-2 (formerly nCov-19) is one of the severe acute respiratory-related coronavirus (SARS-CoV).[1] All coronaviruses are zoonotic, starting in animals, and then mutating recombination and adaptation, then passed on to humans. SARS-CoV causes acute respiratory syndrome (SARS), MERS-CoV causes Middle-East Respiratory Syndrome (MERS) and SARS-CoV-2 known as novel coronavirus causes coronavirus 2019, namely, COVID-19.

Access this article online

www.ijss-sn.com

Month of Submission : 03-2022
Month of Peer Review : 04-2022
Month of Acceptance : 04-2022
Month of Publishing : 05-2022

Periodontopathic bacteria stimulate the release of proinflammatory cytokines in the lower respiratory tract, and these cytokines may play a role in COVID-19.[2] It has also been suggested that periodontitis and periodontopathic bacteria can increase the oral colonization with SARS-CoV-2, and as a result, the oral cavity may act as a repository for the virus. The presence of bacteria in periodontal ulcers has been previously shown and it has been shown that periodontal pockets and plaque can carry germs, such as Helicobacter Pylori and Chlamydia pneumonia; and patients with periodontal disease are more likely to develop hospital-acquired pneumonia as a problem. Several approaches may explain the potential for oral diseases to increase lung infections, including the desire for oral diseases in the lower respiratory tract, especially in high-risk individuals.[3]

STRUCTURE AND PROTEIN

Coronaviruses are large, almost circular particles with a distinct local view. Its magnitude varies widely between 80

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and 120 nm. Larger sizes are known from 50 to 200 nm in diameter. The total molecular weight is estimated at 40,000 kDa. They are enclosed in an envelope containing a number of protein molecules. The envelope of lipid bilayer, membrane proteins, and nucleocapsid protects the virus when it is outside the host cell.[4]

The virus envelope is made up of a lipid bilayer, in which the membrane (M), the envelope (E), and the spike (S) structural proteins are concentrated.[5] The molar ratio of E:S:M in the lipid bilayer is approximately 1:20:300. Protein E and M are structural proteins attached to the lipid bilayer to shape the virus envelope and maintain its size. S proteins are required for the interaction of host cells. However, the human coronavirus NL63 is unique in that its M-binding protein binds to the host cell, not its S protein. The diameter of the envelope is 85 nm. The virus envelope on electron micrographs looks like a separate pair of dense electric shells (shells that are almost visible in the electron beam are used to scan the virus particles) [Figure 1].

Spikes are a very distinctive feature of coronaviruses and have a look-like corona- or halo-like structure.[6] On average, a coronavirus cell has 74 surface spikes. Each spike is about 20 nm long and is composed of a S protein trimer. The S protein is made up of S1 and S2 subunits. The homotrimeric protein S is a Class I protein compound that mediates receptor binding and membrane bonding between the virus and the host cell. The S1 subunit forms the head of the spike and has a receptor-binding domain (RBD). The S2 subunit forms a stem that tightens the spike in the virus envelope and in protease activity allows for coagulation. These two subunits remain illegally connected as they are exposed to the virus site until they attach to the host cell membrane. In operation mode, three S1s are attached to two S2 units. The subunit complex is broken down into individual units, where the virus binds and binds to the host cell under the action of protease compounds such as the cathepsin family and the transmembrane protease serine 2 (TMPRSS2) host cell.

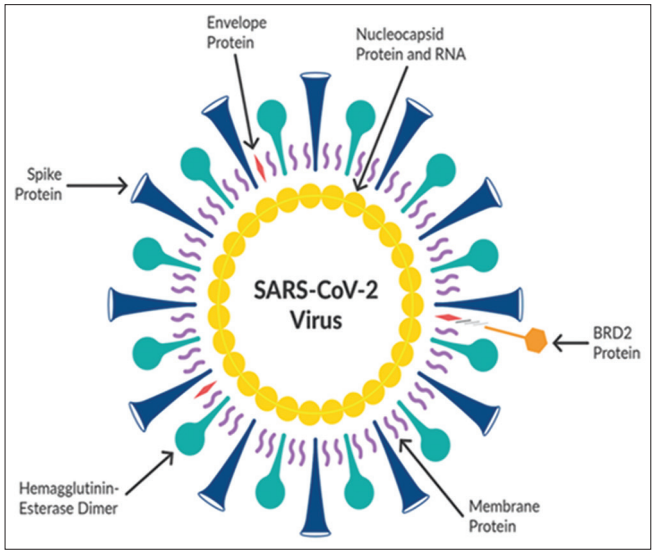

Figure 1: Structure of SARS-CoV-2 virus

BIOMARKERS OF PERIODONTITIS

Periodontitis is associated with elevated serum levels of systemic inflammatory biomarkers, proteolytic and microbial biomarkers such as IL-1, IL-6, IL-10, TNF, CRP, Cystatin, ACP ALP, AST, ALT, Lactoferin, Translactoferin, MMP-8, MMP 9, MMP10, MMP13, Osteopontin, Fibronectin, Platelet derived factor, Vascular endothelial growth factors, IgG, and IgM. These can be found in saliva, GCF, and serum. They are all responsible for the destruction of soft and strong tissue and affect the health of the system.[7]

BIOMARKERS FOR COVID-19

Systematic reviews and meta-analysis of Mahat *et al.* (2021)[8] have shown significant serum concentrations in CRP, ESR, PCT, IL-6, IL-10, IL-2R, ferritin, SAA, and NLR in COVID-19 difficult. Patients compared with those with weak COVID-19 patients. Similarly, they found increased levels of CRP, PCT, IL-6, ferritin, and NLR in non-survivors compared with survivors. These inflammatory parameters can help physicians quickly identify serious patients with COVID-19, which is why it is easier to start effective treatment. In addition, these inflammatory parameters can be used to predict the transition from mild to acute/critical changes in COVID-19 patients.

PERIODONTITIS AND SYSTEMIC DISEASES

Gupta *et al.* suggested that a strong Th17 response to severe periodontitis could exacerbate the cytokine storm in COVID-19 (Gupta and Sahni, 2020).[10] Periodontitis is characterized by chronic unresolved inflammation in response to dysbiosis in subgingival biofilm (Curtis *et al.*, 2020).[11] Chronic inflammation often leads to low systemic levels and elevated levels of cytokines, such as Tumor Necrosis Factor-α (TNF-α), Interleukin (IL) -1β, IL-4, IL-6 and -IL-10 (Chapple *et al.*, 2013; Acharya *et al.*, 2017),[12,13] as well as CRP and ferritin (Thounaojam, 2019).[14] Periodontitis may affect the systemic health. In fact, periodontitis has been independently associated with several NCDs, such as diabetes, heart disease, and even premature death (Sanz *et al.*, 2018; Genco and Sanz, 2020).[15,16] Periodontitis shares many risk factors with other NCDs, such as smoking, stress, unhealthy diets,

glycemic control, or genetic and socioeconomic factors (Pihlstrom *et al.*, 2005; Petersen and Ogawa, 2012).[17,18] However, specific paths and pathological methods have been identified that link to specifically periodontitis these diseases, such as viral transmission (e.g., bacteremia), systemic inflammation, and autoimmune damage caused (Schenkein, Papapanou, Genco, and Sanz, 2020).[19] In addition, there is evidence that periodontal treatment leads to improved glycemic control in patients with type 2 diabetes (Teeuw *et al.*, 2010),[20] and metabolic syndrome (Montero *et al.*, 020),[21] as well as improved kidney function associated with diabetes (Chambrone *et al.*, 2013).[22]

There are many studies that have investigated the link between periodontal disease and various diseases that have important areas of interest: Heart disease, diabetes, and the adverse pregnancy outcome. Interactions between periodontitis and many other diseases and conditions have also been reported, including respiratory illness; chronic kidney disease; arthritis; mental retardation; obesity; metabolic syndrome; and cancer. A person with a systemic disease or illness is more susceptible to COVID-19 and the complications may become lethal.

Serious cases of COVID-19 are often complicated by Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock, leading to multiple organ damage (Yang, Yu, *et al.*, 2020).[23] Patients with severe COVID-19 and ARDS (Mehta *et al.*, 2020)[24] often exhibit improved immune responses, characterized by elevated levels of proinflammatory cytokines and widespread tissue damage; so-called cytokine storm syndrome (Yang, Shen, *et al.*, 2020).[25] COVID-19 mortality is associated with elevated serum levels of interleukin-6 (IL-6), C Reactive Protein (CRP), D-dimer, and ferritin (Ruan *et al.*, 2020),[26] suggesting clear interactions between the severity of the disease and the hyperinflammation driven by the unresolved virus. The severity of COVID-19 infection has been associated with patients suffering from comorbidities (e.g., high blood pressure, diabetes, and cardiovascular disease) (Wu *et al.*, 2020),[27] age and obesity. However, certain risk factors that lead to poor clinical outcomes have not yet been fully elucidated.

ASSOCIATION BETWEEN PERIODONTITIS AND COVID-19 INFECTION [FIGURE 2]

Periodontal dysbiosis leads to disruption of local homeostasis and immune mutations that increase microbial colonization, virulence, and disease resistance, and result in the continuous recruitment of hyperfunctional PMN or hyperactive phenotypes. Similar to what happens in patients with COVID-19, these now inactive PMNs produce high levels of ROS and harmful enzymes as well as increasing levels of proinflammatory cytokines. These actions lead to severe damage to the connective tissue in the affected teeth leading to pain, bleeding, and eventually loss of teeth.

Several studies have suggested the role of IL-6 in the pathogenetic pathways of COVID-19. when SARS-CoV-2 enters the respiratory tract, it triggers the release of proinflammatory cytokines, including interleukin (IL)-1beta and IL-6. One of the mechanisms by which coronavirus kills can be the introduction of interstitial pneumonia, which is linked to excessive IL-6 production. Similarly, IL-17 has high levels in the serum of patients with COVID-19. In a recent study, an increase in IL-17, and 14 other cytokines, levels were positively associated with Murray's high rate of lung damage. Indeed, species of coronavirus have been shown to improve the adhesion of streptococcus to the epithelial cells of the respiratory tract, causing complications such as pneumonia and inflammatory lesions in the lungs and subsequent inhibition of bacterial expression. Finally, recent research has shown that intensive periodontal treatment reduces the risk of pneumonia in COVID-19 patients.[28]

PERIODONTITIS AND COVID-19 SEVERITY

Innovative methods may explain the strong interaction seen between periodontitis and COVID-19 intensity. Takahashi *et al.* suggested that periodontopathic viral cravings may exacerbate COVID-19 by inducing the expression of angiotensin converting enzyme 2, the SARS-CoV-2 receptor, and inflammatory cytokines in the lower respiratory tract (Takahashi *et al.*, 2020).[29] Furthermore, it was suggested that periodontopathic viruses may enhance the risk of SARS-CoV-2 by differentiating its S glycoproteins (Madapusi Balaji *et al.*, 2020; Takahashi *et al.*, 2020)[29,30] and that oral cavity, and especially periodontal pockets may act as a viral reservoir (Badran *et al.*, 2020; Bao *et al.*, 2020).[3,31] In patients with periodontitis, the expression of gingival epithelium CD-147 increases which may increase SARS-CoV-2 infiltration into cells. Similarly, microRNA-146a and 155 increase in the oral cavity during periodontitis, altering the antiviral host response. Gupta *et al.* have suggested that the production of Neutrophil Extracellular Trap is involved in the formation of both diseases (Gupta and Sahni, 2020).[10]

All of these approaches may also predict an increase in periodontal lesions, particularly necrotizing periodontal disease (NPD) during the epidemic (Patel and Woolley, 2020).[32]

Marouf *et al.* (2021)[33] found that the fatal effects of COVID-19 were significantly associated with higher

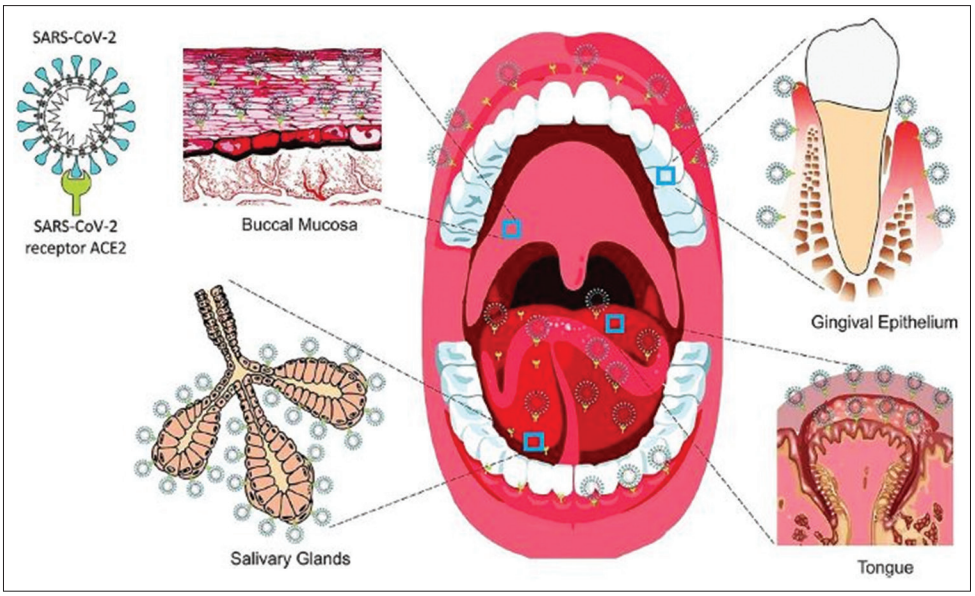

Figure 2: The interaction between angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2 spike protein (s) will allow viral entry, replication, and activation of innate antiviral response including proinflammatory cytokine production and infiltration of immune cells. This may result in manifestation of signs and symptoms in the oral cavity of COVID-19 patients. (b) Different sites of the oral cavity where virus and its receptors are reportedly detected including periodontal tissues, buccal mucosa, tongue, and salivary glands. COVID-19, coronavirus disease 2019; SARS-COV-2, severe acute respiratory syndrome-coronavirus-2[28]

Table 1

Time period	Biomarkers
<7 days	Total leucocyte count and lymphocyte count normal or slightly low↑LDH, AST, ↑ ALT, ↑ CK, 1 CK-MB- may be early markers of severe disease and mortality.
7–14	Total leucocyte count and lymphocyte count progressively fall to reach nadir at 8–9 days. Thrombocytopenia may occur. ↑ IL-6, IL-10, IL-1RA, and MCP-1
>14 days	Increasing total leucocyte count, lymphocyte, and platelet count predict recovery while reducing counts predict mortality.

ALT: Alanine transaminase, AST: Aspartate transaminase, CK: Creatine kinase, IL-6: Interleukin-6, LDH: Lactate dehydrogenase, MCP: Monocyte chemoattractant protein. (Samprathi *et al.* 2021).[9]

concentrations of D-dimer, WBC and CRP, and lower concentration of lymphocytes in the blood. Furthermore, patients admitted to the ICU and those in need of ventilation reported higher blood pressure levels of CRP and D-dimer. These results are consistent with the previous studies reporting high levels of inflammation in deceased patients with COVID-19 (Ruan *et al.*, 2020).[26] Interestingly, our COVID-19 cases with periodontitis also had higher levels of WBC and CRP in the serum than those without periodontitis, which may indicate a potential link through systemic inflammation. Effective treatment of periodontitis has been shown to improve the serum markers of systemic inflammation (CRP, IL-6) (D'Aiuto *et al.*, 2013),[34] as well as systemic metabolic control (Montero *et al.*, 2020) 21. If a causal link is established between the periodontal and the increased levels of adverse effects in COVID-19 patients, then establishing and maintaining periodontal health may be an important part of the care of these patients.

COVID-19 VACCINES

The purpose of these vaccines is to prevent infection with COVID-19. These are WHO, Moderna, Covishield, Pfizer/BioNTech, Janssen (Johnson and Oxford/Astra Zeneca, Johnson), Covaxin, BBIBP-Corv (Vero Cells), and Sinovac CoronaVac vaccines. There are also several vaccines that are under clinical evaluation. Although the current vaccines have proved to be very effective in combating (SARS-CoV-2) which has caused the epidemic, recent data have highlighted the emergence of a few mutant species. There has been uncertainty as to whether current vaccines will protect against this alternative [Table 1].

CONCLUSION

There is a direct link between periodontal disease and the effects associated with COVID-19. However, as periodontal disease manifests and determines the systemic health, it may also play an indirect role in increasing the rate of illness directly related to the poor prognosis of COVID-19-related adverse effects. Maintaining oral hygiene continues to be important during the COVID-19 period, not only due to the direct link between periodontal inflammation and the COVID-19 but also due to the indirect system effects it may

have, to ultimately determine COVID-19-related prognosis and identification of the potential patients at risk.

Many studies currently appear to focus on confirming whether the presence of periodontal disease affects COVID-19-related effects. It would be interesting, however, to see if there were any communication between SARS-CoV-2 and the oral microbiome directly or in a phage-mediated manner.

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How to cite this article: Kirar V, Dahiya R, Gullia K, Kaur P, Sharma G, Vashisth V. Association between Periodontitis and COVID-19 Infection: A Review Article. Int J Sci Stud 2022;10(2):7-11.

Source of Support: Nil, **Conflicts of Interest:** None declared.