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Covid-19 and Periodontitis- An Intimate Interplay

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Abstract

Coronavirus disease 2019 (COVID-19), caused due to SARS-CoV-2 is an emergent health problem worldwide. While most cases result in mild symptoms (including hyposalivation and an alteration in taste), some cases progress to severe pneumonia and multi-organ failure with the death of the patient, according to the age and the presence of comorbidities. Recent relevant studies have demonstrated the bidirectional association between the severe clinical course of COVID-19 and chronic diseases such as cardiovascular disease, hypertension, diabetes mellitus, obesity, chronic renal disease including periodontitis. Worldwide interest has been raised in seeking a link between COVID-19 and these chronic diseases. COVID-19 pandemic has been reported to have adverse outcomes attributed to the cytokine storm, many of the components of which are common with the cytokine expression profile of periodontitis.

Periodontitis has long been attributed to having its pathophysiology rooted in a cytokine response. Hence there exists a communication that explores the connection between COVID-19 and periodontal disease through a common cytokine connection that forms a basis for recommending maintenance of oral hygiene in the COVID era. It's a wake-up call for patients with periodontitis as having an increased risk of exhibiting COVID-related adverse outcomes. The various hypothesis should be established and robust studies are required to fill these lacunae in knowledge.

Introduction

In December 2019, a series of rapidly spreading acute atypical respiratory diseases occurred in Wuhan, China. It was soon discovered as a novel coronavirus and named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV) due to its high homology (~80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002–2003.**[**1**]** The outbreak of SARS-CoV-2 was zoonotic transmission initially later, recognized that human to human transmission played a major role in the subsequent outbreak.**[**2**]** The World Health Organization (WHO) on March 11, 2020, has declared the novel coronavirus (COVID-19) outbreak a global pandemic.**[**3**]** The SARS-CoV-2 virus primarily affects the respiratory system, although other organ systems are also involved. Lower respiratory tract infection-related symptoms including fever, dry cough and dyspnea were reported in the initial case series from Wuhan, China.**[**4**]** In addition, headache, dizziness, generalized weakness, vomiting and diarrhea were observed.**[**5**]** It is now widely recognized that respiratory symptoms of COVID-19 are extremely heterogeneous, ranging from minimal symptoms to significant hypoxia with ARDS.

Cytokine storms play an important role in severe COVID-19 cases. Cytokine Release Syndrome (CRS) is a systemic inflammatory response that can be caused by infection, some drugs and other factors, characterized by a sharp increase in the level of a large number of pro-inflammatory cytokines.**[**6,7,8**]** CRS is more common in immune system-related diseases and immune-related therapy such as chimeric antigen receptor T-cell (CAR-T) therapy, organ transplantation sepsis and viral infections.**[**9**]** SARS-CoV-2 binds to alveolar epithelial cells. The virus then activates the innate and adaptive immune systems, resulting in the release of a large number of cytokines, including IL-6. In addition, vascular permeability is increased by these pro-inflammatory factors, resulting in a large amount of fluid and blood cells entering the alveoli, resulting in dyspnoea and even respiratory failure.**[**10,11,12**]**

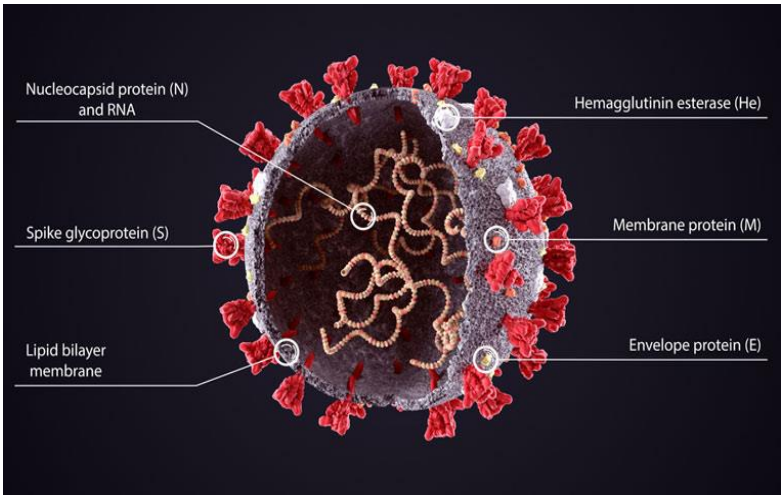
Periodontitis is a chronic inflammatory condition characterized by progressive destruction of bone and soft tissue, seriously affecting a patient's quality of life and causing a tremendous social and economic

burden. Severe periodontitis affects more than 700 million people (11% of the world's population), making it one of the most prevalent chronic inflammatory diseases worldwide.[13] In addition, an increasing amount of clinical and experimental evidence indicates the potential direct relationship between periodontitis and several systematic diseases including diabetes, rheumatoid arthritis, atherosclerosis, Alzheimer's disease and even cancers.[14,15,16] The pathogenesis of periodontitis involves a complex interplay between periodontopathogens and host immunity, greatly influenced by genetic and environmental factors. The role of the cytokine network in the pathogenesis of periodontitis has been well established. Pro-inflammatory cytokines from IL-1, IL-6 and TNF families are secreted by host periodontal cells and immunocytes after stimulation by pathobionts, which activates and recruits specific immune cell subsets and causes direct tissue damage.[17]

Hence there exists a communication that explores the connection between COVID-19 and periodontal disease through common cytokine association. Understanding of this association underscores the importance of keeping periodontal disease under check and the value of maintaining meticulous oral hygiene in the COVID-19 era. It also points towards the possibility of the presence of periodontal disease as a predisposing factor towards COVID-19 related adverse outcomes.

SARS-CoV-2 virus Structure and Pathophysiology

The coronaviruses are made up of four structural proteins, namely, the spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins. The S protein is seen to be protruding from the viral surface and is the most important one for host attachment and penetration.[18] This protein is composed of two functional subunits (S1 and S2), among which S1 is responsible for binding to the host cell receptor and the S2 subunit plays a role in the fusion of viral and host cellular membranes.[19]



ACE-2 has been identified as a functional receptor for SARS-CoV and is highly expressed on the pulmonary epithelial cells.[20] It is through this host receptor that the S protein binds initially to start

the host cell invasion by the virus.[21] The virus is transmitted via respiratory droplets and aerosols from person to person. Once inside the body, the virus binds to host receptors and enters host cells through endocytosis or membrane fusion. The mean incubation period was 5.2 days. The combined case-fatality rate was 2.3%.[22,23]

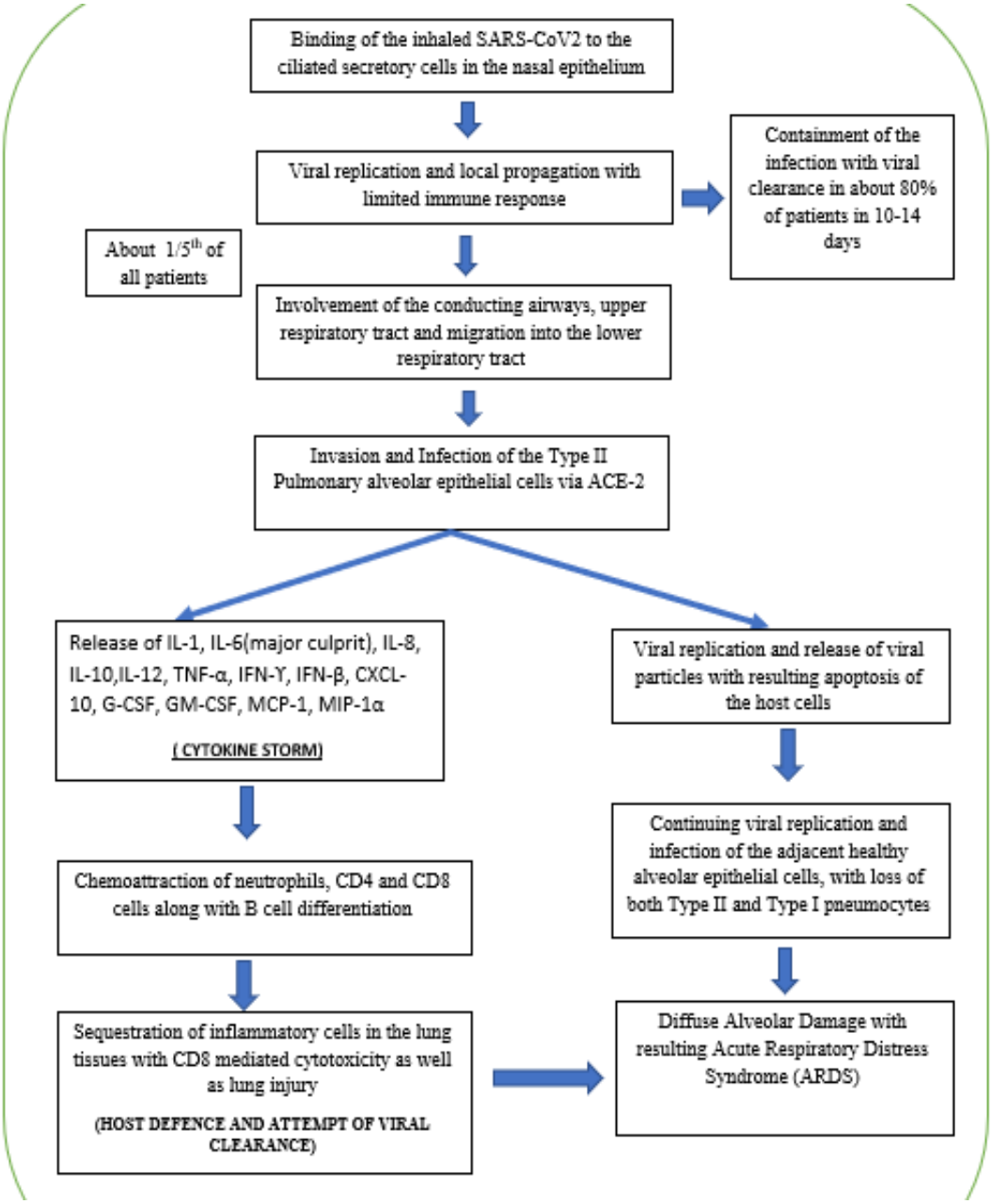


Figure 1. Pathophysiology of COVID-19 Virus

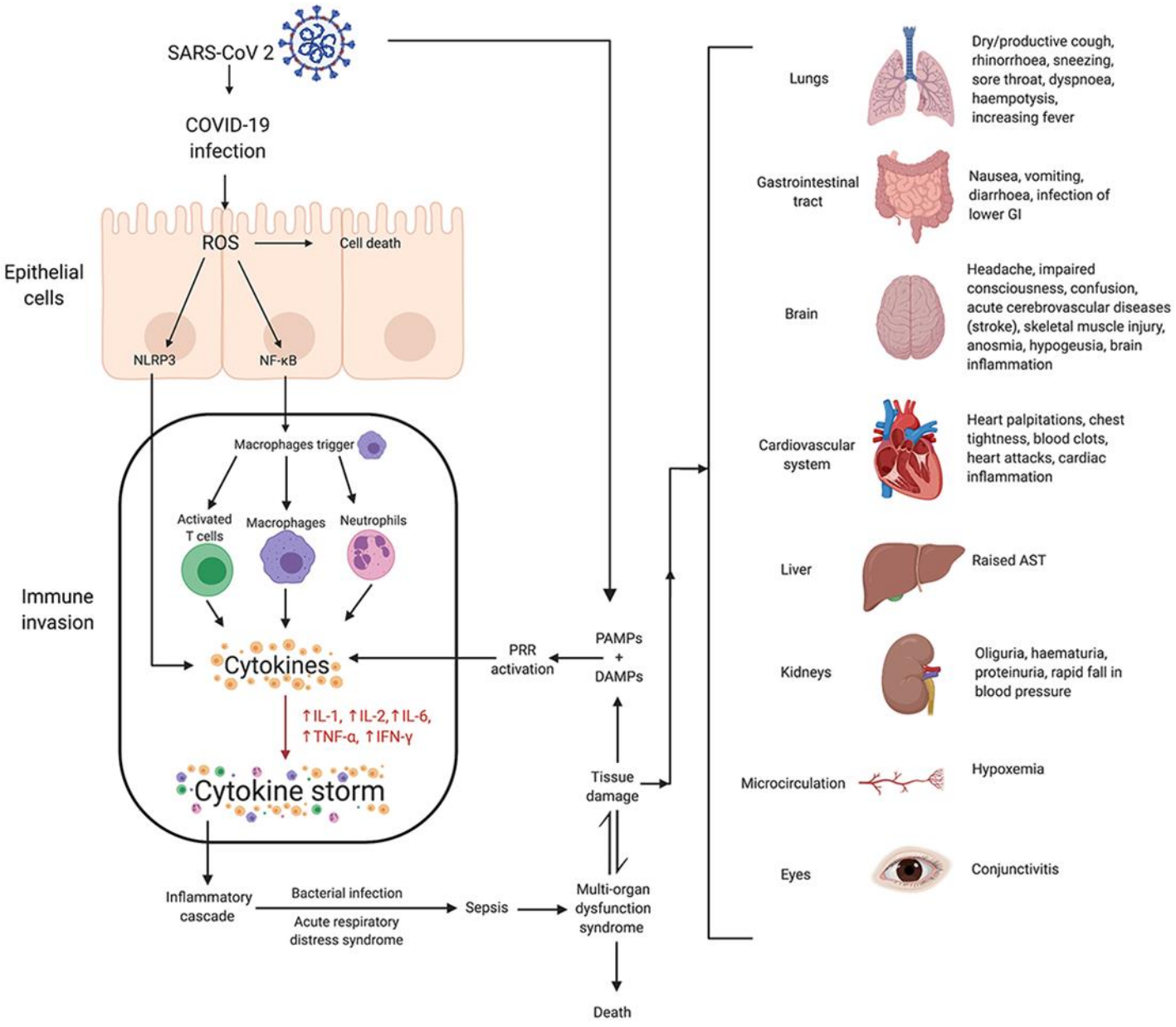


Figure 2. Mechanisms of SARS-CoV-2 associated cytokine storm and associated damages.

Periodontal Disease Pathophysiology

For ages, periodontal disease has been considered a silent pandemic with complex multi-factorial pathophysiology along with evidence-based claims of immune-mediated pathogenesis. In a healthy state, local challenge and a mild host immune response are balanced. Both the commensal microbiota and mechanical stimulation caused by mastication participate in the training of local mucosal immunity. In

this state, there is an appropriate number of infiltrating neutrophils in the gingival sulcus, as well as some resident immune cells in the gingival tissue, including Th17 cells and innate lymphoid cells.**[**24**]**

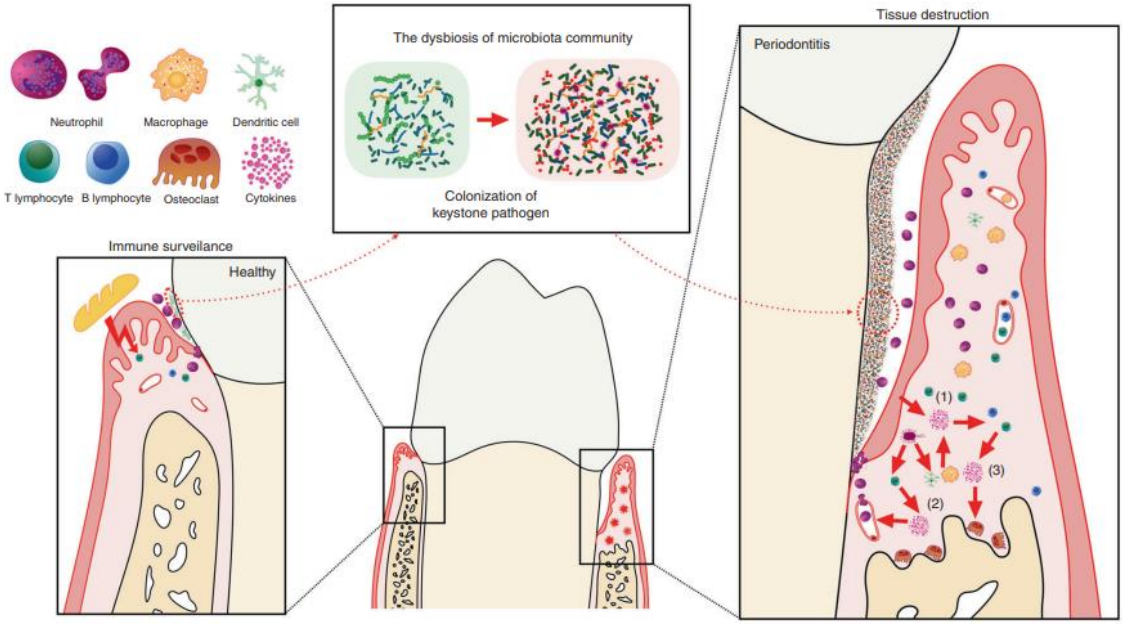


Figure 3. The homeostasis of periodontal tissue, the pathogenesis of chronic periodontitis and roles of the involved cytokines.

However, if the immune pathogenicity of the local microbiota is elevated by the colonization of keystone pathogens, which over-activate the host immune response, tissue destruction is initiated.**[**24**]** The interaction between the microbiota and all host cells leads to the first wave of cytokine secretion:

- Mainly participates in the amplification of pro-inflammatory cytokine cascade (IL-1, IL-6, TNF-α..)
- The recruitment, activation and differentiation of specific immune cells.
- Release of cytokines from differentiated immune cells such as Murine mononuclear phagocyte (MNPs) and Antigen-presenting cells (APCs) after stimulation by the microbiome.
- They can activate or promote other effector cells, such as osteoclasts and neutrophils, which exert pro-inflammatory or anti-inflammatory effects by secreting cell-specific cytokine clusters
- Among these cell subsets, Th1 and Treg cells mainly act as protectors, while Th2/B and Th17 cells exert complex effects that may lead to tissue destruction or protection under certain circumstances.

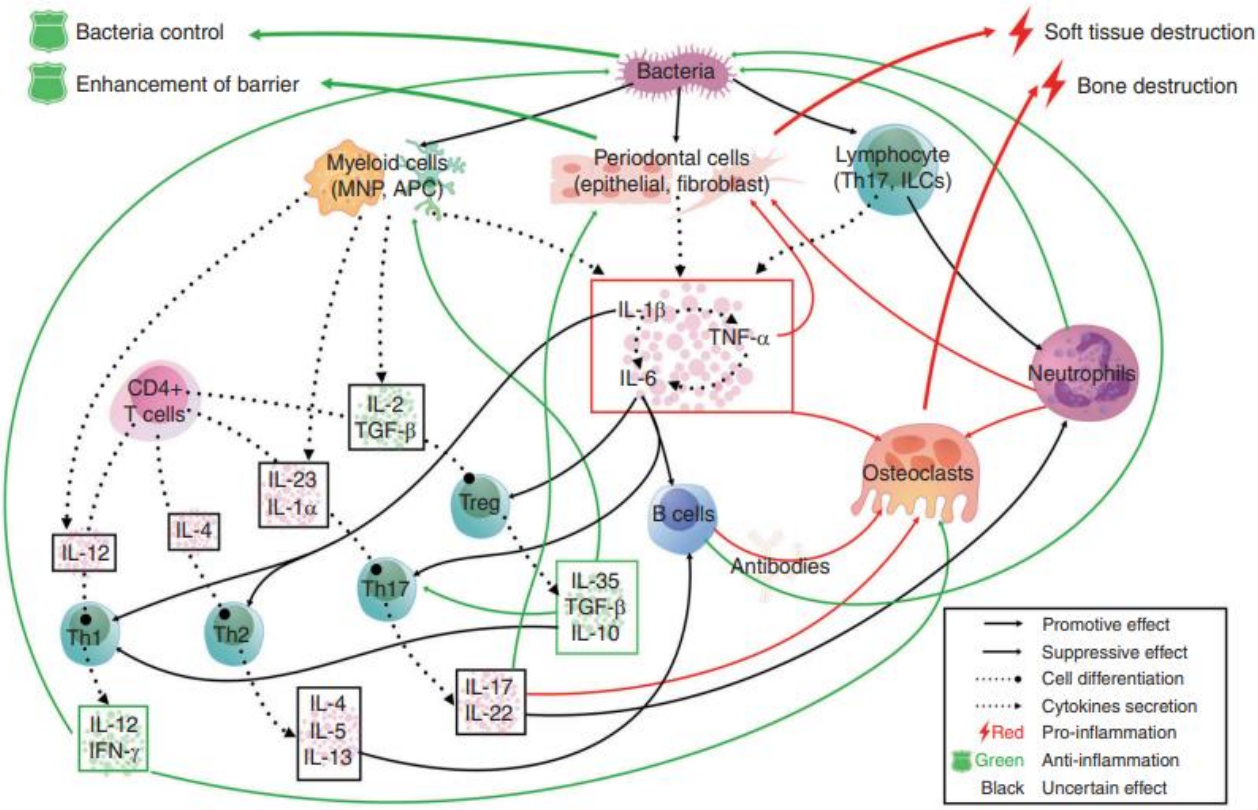


Figure 4. Cytokine network in the pathogenesis of periodontitis.

About two decades ago, there was a particular interest in confirming associations between periodontitis and systemic disease. Very interestingly, the strict relationship between periodontitis, diabetes and IL-6 was demonstrated by a recent in vivo experimental study: coexistent diabetes and periodontitis significantly reduced leptin and IL-18 and significantly increased IL-6 than controls, concluded that periodontitis is able to induce changes indicative of systemic inflammation.**[**25**]** Chronic periodontitis has been shown to be a risk factor for cardiovascular disease, diabetes mellitus, respiratory disease, rheumatoid arthritis and other conditions. The systemic inflammatory burden of periodontitis is well-documented also thanks to the evidence of high sensitivity C-reactive protein (hsCRP).

Interlink Between Covid-19 And Periodontitis

Hypotheses depending on the most recent literature demonstrated for periodontitis, several events would seem to correlate with the clinical behavior of COVID-19 with a patient's periodontal status. By causing ulceration of the gingival epithelium, periodontitis could reduce the protective function of the oral epithelial cells, thereby exposing the patients to an elevated risk of invasion by SARS-CoV-2.**[**26**]**

Concurrently, ACE2, TMPRSS2 and furin, which are expressed in the aforementioned oral epithelial cells and the proteases produced by periodontopathic bacteria, could cleave the protein S of the virus, thereby favoring infection. It, therefore, follows that the presence of periodontopathic bacteria could increase the risk of SARS-CoV-2 infection.[27]

Various studies have shown:

- Subgingival component epithelial cells of periodontal pockets express high levels of CD147[28,29] and thus, periodontitis could facilitate SARS-CoV-2 infection through the CD147 route.
- Periodontopathic bacteria are aspirated into the lungs, the expression of ACE2 increases in the bronchus and the lungs (also in the oral cavity) due to bacterial and pathogenic factors, such as endotoxins, and that this overexpression could increase the risk of a SARS-CoV-2 infection.[29]
- The culture supernatant of the periodontopathic bacterium Fusobacterium nucleatum has been shown to upregulate the ACE-2 receptor of the SARS-CoV2 in alveolar epithelial cells.[30]Colony Stimulating Factor (CSF) induced the production of IL-6 and IL-8 by alveolar epithelial cells; CSF also strongly induced the expression of IL-6 and IL-8 by bronchial epithelial cells of pharyngeal mucosa. These findings suggest that when patients with mild COVID-19 frequently aspirate periodontopathic bacteria, SARS-CoV-2 infection is promoted, and lower respiratory tract inflammation can become severe in the presence of viral pneumonia.[30]
- Periodontitis was associated with a higher risk of intensive care unit admission, need for assisted ventilation and death of COVID-19 patients, and increased blood levels of biomarkers linked to worse disease outcomes.[31]
- In patients with periodontal disease during SARS-CoV-2 infection, the periodontal condition could be aggravated due to the downregulation of ACE2 and an increase in ACE and Ang II, thereby resulting in the involvement of several pro-inflammatory factors.[32,33]
- Periodontopathic bacteria have been found in the metagenome of severe COVID-19 patients[34]; indeed, it is commonplace to find bacterial superinfections in patients with severe cases of COVID-19.[35]
- Finally, a recent study has demonstrated that intensive periodontal treatment reduced the risk of pneumonia in COVID-19 patients.[36]
- Another possible mechanism, which could explain the association between periodontal disease and a severe COVID-19 course, could be the overproduction of phlogistic molecules, such as IL-6 and IL-17, in healthy patients and patients with chronic diseases such as diabetes. It should be considered that periodontitis, independently of any other pathology, raises IL-6. Therefore,

and irrespective of the concept that IL-6 is the cause of severe cases of COVID-19 or a reliable biomarker for COVID-19**[**37**]**, periodontitis could modify the level of IL-6 in COVID-19 patients.

- It can also be hypothesized that in those COVID-19 patients, also suffering from diabetes and periodontitis, levels of IL-6 in circulation deriving from all three pathologies could be envisaged.

The above evidence held strong co-relation between periodontitis with IL-6 and COVID-19 with IL-6 release, at least in diabetic patients, that seeds the scientific community to simulate hypotheses, as follows:

1. Can periodontitis be a risk factor involved in the more aggressive clinical manifestation of COVID-19 in some, at least diabetic patients?

2. Can periodontitis induce such a chronic inflammatory status, that forms stable increasing levels of cytokines like IL-6, the main culprit for the adverse events in COVID-19?

3. Is it beneficial to clinically evaluate and monitor the periodontal status of diabetic SARS-COV-2 positive patients over time, in order to check IL-6 production?

Conclusion

Considering the common pathway of inflammatory response points towards the possible association between Periodontitis and COVID-19 related adverse outcomes. Encouraging the experimental studies in the following fields based on the evidence, are suggested to elucidate these potential relationships and their pathophysiologic and clinical impact on the worldwide community. Understanding of this association highlights the importance of keeping periodontal disease under check and the value of maintaining meticulous oral hygiene in the COVID-19 era. It also points towards the possibility of the presence of periodontal disease as predisposing towards COVID-19 related adverse outcomes.

Conflicts of Interest: The author declares no conflict of interest.

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