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The Interrelation between COVID-19 and Periodontal Disease

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Abstract

The potential causal link between COVID-19 and periodontal disease is indistinct, although further research is needed to fully understand the relationship. There is some evidence to suggest that COVID-19 may increase the risk of developing periodontal disease. COVID-19 may contribute to periodontal disease by causing systemic inflammation throughout the body, which can exacerbate the existing periodontal disease. Additionally, COVID-19 may weaken the immune system, making it easier for oral bacteria to flourish and cause periodontal disease. However, it is important to note that more research is needed to fully understand the relationship between COVID-19 and periodontal disease. While these findings are intriguing, they do not prove causation and other factors could be at play. Therefore, this review focuses to assess the role of periodontal disease as a possible risk factor for the progression of COVID-19 disease, to identify any communal causal etiopathogenesis between the two diseases and to construe the effects of the virus on the periodontium.

Keywords: covid-19, periodontal disease, periodontium, cytokine storm

Introduction

Coronavirus disease (COVID-19) is a severe acute respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hailing from Wuhan, China, with consequent global spread, it was then declared by WHO as a pandemic on March 11th 2020. Coronavirus SARS-CoV-2 is a strain of the severe acute respiratory syndrome-related coronavirus (SARS-CoV), member of the Coronaviridae family and is structurally related to the virus that causes the severe acute respiratory syndrome (SARS) as seen in two preceding instances of the coronavirus disease in the past 18 years, that is, SARS (2002-2004) and Middle East respiratory syndrome (MERS-2012).

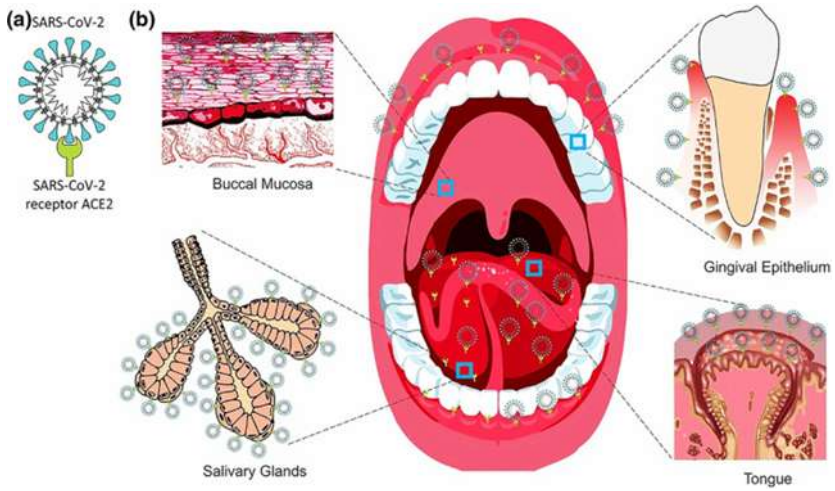
SARS-CoV-2 virus primarily affects the respiratory system, although other organ systems are also involved. Lower respiratory tract infection related symptoms including fever, dry cough and dyspnoea ranging from minimal symptoms to significant hypoxia with Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, further leading to multi-organ damage [1].

Patients with severe COVID-19 and ARDS usually present an exacerbated immune response, characterized by excessive levels of proinflammatory cytokines and widespread tissue damage; the so-called Cytokine Storm Syndrome [2]. In fact, COVID-19 mortality has been associated with elevated serum levels of interleukin-6 (IL-6), C-Reactive Protein (c-RP), D-dimer and ferritin suggesting a clear link between disease severity and a virally driven non-resolving hyperinflammation [3].

The entry of the virus particle can be the nasal and the oral cavity, giving the virus an ideal environment for the attachment, replication and progression of the disease. The periodontal pocket is considered an ambient niche for the virus particle for the replication and it can then migrate systemically using the capillary periodontal complex and reach the respiratory tract (Figure1) [4] . The presence of SARS-CoV-2 in the GCF and the periodontal pocket would be synchronous with the viremia, occurring after an initial colonization of target cells and could be a favorable anatomical niche for the virus and thus acting as a reservoir for SARS-CoV-2 [5].

Figure 1: Oral Niches for Sars-CoV-2 Virus Particles

Adapted from Brandini et al 2021[4]



Periodontal disease has long been regarded as a silent pandemic which has a complex multi-factorial pathophysiology with evidence-based claims of immune mediated pathogenesis [6].

Periodontal disease is a chronic inflammatory disorder delineated by the breakdown of supporting structures – alveolar bone, gingiva, and periodontal ligaments – of teeth and gums. Periodontitis is known to be the sixth most common inflammatory disease in humans, affecting 20-50% the global population [7]. Due to the inflammatory nature of chronic periodontitis, there is a release of proinflammatory mediators in systemic circulation as a response to bacterial plaque. There is also a low-grade systemic inflammation induced by these mediators, resulting in a covert peripheral inflammation in susceptible individuals. The disease has a perceptible impact on general systemic health and could even aggravate other systemic disorders such as diabetes mellitus, hypertension, rheumatoid arthritis [8].

Pathophysiology Of COVID-19 And Periodontal Disease:

The recent COVID-19 pandemic has been reported to have adverse outcomes related to the establishment of a cytokine storm, many of which are common with the cytokine expression profile of periodontitis.

The possible link between the two inflammatory diseases

1. Cytokine Storm
2. Increased ACE 2 receptor induction

The pathophysiology of SARS-CoV-2 infection is characterized by rapid virus replication and aggressive inflammatory responses that can lead to acute respiratory distress syndrome (ARDS).

Several diseases, such as diabetes, obesity, vascular diseases and lung diseases including pneumonia and chronic obstructive pulmonary disease (COPD) have been strongly associated with periodontitis, even though the mechanisms or causal associations have not been completely established. The interaction between the subgingival polymicrobial biofilm and the host cells lead to the release of pro-inflammatory cytokines, especially interleukin-1 (IL-1), IL-6 and

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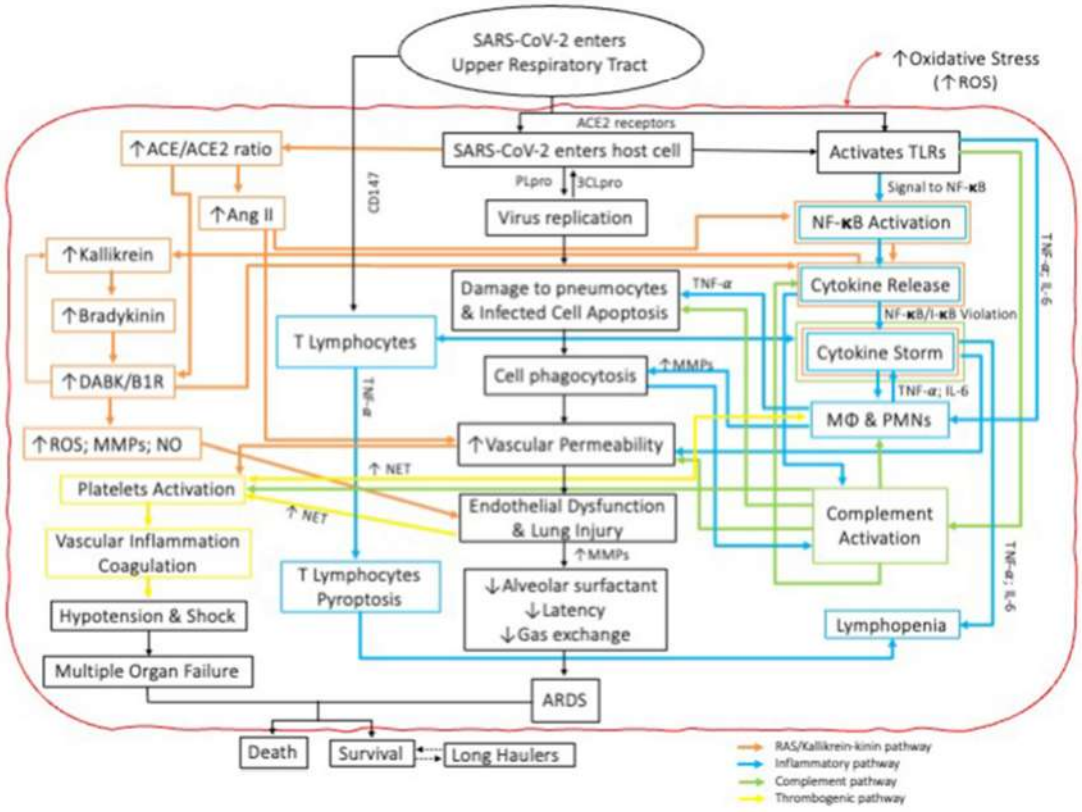
tumor necrosis factor (TNF) with important clinical outcomes on periodontal tissues and repercussion to the systemic inflammatory burden [9].

For some patients with COVID-19, the binding of the SARS-CoV-2 spike protein to the ACE2 leads to a massive immune response with an increased release of cytokines, especially IL-6 implicated in multi-organ damage and risk of death [10]. This dysregulated inflammatory response also occurs in periodontal disease and can cause hyperstimulation of the immune system [11], which could aggravate the severity of SARS-CoV-2 infection due to the cytokine storm.

The possible mechanism of the progression of the SARS-CoV-2 viral infection given by Cardoso et al., 2021 shows a hyper stimulated immune response resulting in the cytokine storm leading to an increase in the oxidative stress (Figure 2) [12].

Figure 2: Possible Pathogenic link of Cytokine storm between the two diseases

Adapted From Cardoso et al 2021[12]



This cytokine connection forms a translational basis for recommending maintenance of oral hygiene in the COVID era and to red flag patients with periodontitis as having an increased risk of exhibiting COVID related adverse outcomes.

In severe cases of COVID-19, patients are hospitalized for a long period and need mechanical ventilation, requiring different types of medication and in many cases, oral hygiene is neglected. Consequently, persistent alterations in the oral microbiome and the increased burden of pro-inflammatory cytokines can impose detrimental effects on the periodontium.

Importance/Relevance For The Current Scenario:

The Coronavirus Disease 2019 is an active, progressive and highly transmissible disease that has proved to be fatal. This emerging infection has resulted in over, a total of 76,10,71,826 confirmed positive cases, including 68,79,677 deaths, which have been reported to the World Health Organization (WHO) as of March 20th, 2023.

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The COVID-19 outbreak is a stark reminder of the ongoing challenge of emerging and re-emerging infectious pathogens and the need for constant surveillance, prompt diagnosis and robust research to understand the basic biology of new organisms and our susceptibilities to them, as well as to develop effective countermeasures especially in patients with a systemic history like diabetes and a periodontal history.

With the constant mutations of the virus particle that is from alpha, beta, gamma, delta to the more recent Omicron variant, we are at an endless battle against the invisible enemy, thus we need to seize the opportunity to gain important information, achieve a better understanding of the pathogenesis of this disease which will be invaluable in navigating our responses in this uncharted arena and make the world safe again.

Summary Of Literature:

Periodontal disease and COVID-19 have an interlinking mechanism wherein each disease accrues to the progression of the other. There are various inflammatory mechanisms shared in a common pool with each other thereby instantiating the fact that COVID-19 and periodontal disease could be a risk factor for each other.

A study by Marouf et al., 2021 suggested that periodontitis was significantly associated with a higher risk of complications from COVID-19, including ICU admission, need for assisted ventilation and death and increased blood levels of markers linked worse COVID-19 outcome such as D-dimer, WBC and CRP therefore we need to understand better the risk factors influencing the outcome of COVID-19 infections and highlight the importance of periodontal health in the prevention and perhaps even management of COVID-19 complications. This case-control study of 568 patients with COVID-19 showed that patients with periodontal disease were 3.5 times more likely to be admitted to an intensive care unit, 4.5 times more likely to need mechanical ventilation and had 8.8 times more chance of death compared to those with good periodontal health [13].

COVID-19 complications were significantly higher among patients with moderate-to-severe periodontitis compared to those with milder or no periodontitis. Periodontitis shares common risk factors with most chronic inflammatory diseases known to influence COVID-19 severity. The increased prevalence and severity of periodontitis and associated poor oral hygiene might contribute to the aggravation of SARS-CoV-2 infection. Gingival bleeding and dental plaque accumulation were also found to be more frequent among the COVID-19 patients [14].

A study done by Takahashi et al., 2020 stated that aspiration of periodontopathic bacteria might aggravate COVID-19 by inducing the expression of angiotensin converting enzyme 2 (ACE2), a receptor for SARS-CoV-2, and inflammatory cytokines in the lower respiratory tract [15]. Also, it was suggested that periodontopathic bacteria might enhance SARSCoV-2 virulence by cleaving its S glycoproteins and that the oral cavity, and especially periodontal pockets could act as a viral reservoir [16].

Gupta and Sahni et al.,2020 detailed the Neutrophil Extracellular Trap (NETosis) production is involved in the pathogenesis of both diseases and that the strong Th17 response in severe periodontitis could exacerbate the cytokine storm in COVID-19 [17]. All these hypothetical pathways could also foresee an increased incidence of periodontal lesions, especially necrotizing periodontal disease (NPD) during this pandemic [18].

The possibility of periodontal diseases during COVID-19 may be increased, as the enzymes ACE2 and TMRPSS, which are required for SARS-COV-2 invasion, are also present in tissues such as the tongue and periodontal pocket. Likewise, increased NLRP3 activation and cytokine expression during periodontitis may further exacerbate COVID-19. NLRP3 provides the ability to further increase the cytokine storm during both COVID-19 and periodontitis. This increases the likelihood that damage to periodontal tissues, and the effects on entire systems will be more severe. Therefore, modulation of the immune system is important for the protection of both oral and other tissues. Melatonin, along with its antioxidant and anti-inflammatory properties, is thought to reduce COVID-19 and periodontal damage by preventing NLRP3 activation and cytokine expression and pyroptosis [19].

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Patients with periodontal disease are at increased risk of SARS-CoV-2 infection due to elevated levels of furin and cathepsin in the oral cavity. It could also be hypothesized that COVID- 19 complications could occur with increased frequency in patients with periodontal disease due to the significant increase of CD14+ CD16+ monocytes. This could be explained on the basis of the fact that nonclassical monocytes when challenged with infectious stimuli can produce up to three-fold higher levels of the proinflammatory cytokines such as TNF [20].

It is hence plausible that a patient with periodontal disease having high circulating levels of nonclassical monocytes could also harbour macrophages of the same phenotype as the nonclassical monocytes in various tissues. With reference to a patient with periodontal disease having SARS-CoV-2 infection, it can be hypothesized that the lung would definitely have a higher population of macrophages with a nonclassical trait. Hence, the cytokine storm phenomenon following SARS-CoV-2 entry into the lung could manifest in a more intense fashion in the abovementioned scenario. High-circulating levels of cytokines and proinflammatory mediators in patients with periodontal disease could add a synergistic effect if these patients are afflicted by SARS-CoV-2, thereby abnormally raising the concentrations of cytokines.

With respect to the clinical periodontal manifestations of COVID-19, as of today, there is an insufficient number of clinical cases with confirmed COVID-19 to draw any conclusions. Gingival inflammation appears to be common in patients suspected of having COVID-19, but there is insufficient evidence that this gingival inflammation is secondary to CoV-2 SARS infection and it is widely known that gingivitis is very common. However, lesions of the oral cavity have been reported in COVID-19, such as vesiculobullous lesions [21].

A study done by Eghbali et al., 2020 suggested that the most common oral manifestation was dry mouth, which was reported in 75 of the cases. 71 patients reported changes in taste sensation 67 patients developed pseudomembranous structure, white plaque or hairy tongue on the intraoral mucosa. The other manifestations were Erosions, erythema, ulcers, necrotizing ulcerative periodontitis. The oral symptoms often appeared after general symptoms such as fever and asthenia, but can still be the initial or only sign of COVID-19. Thus, a careful clinical intraoral examination must be performed on COVID-19 positive patients [22].

Hence, it is essential to maintain periodontal health and good oral hygiene as an important measure for the prevention and management of COVID-19 and its complications.

Host modulation therapy used for periodontitis as a potential strategy for the prevention of ARDS a deadly outcome of COVID-19 which includes medications like Tetracycline, Sub-antimicrobial-dose doxycycline slow-release form, Resveratrol, Curcumin and Resolvins could reduce morbidity, mortality, and possibly longer-term sequelae of COVID-19. The rationale for this proposed treatment approach is based on the use of some or all the compounds identified above to inhibit the cytokine storm/ARDS, including PMN-mediated hyperinflammatory responses and tissue destruction and including the development of thromboembolic disorders [12].

Thus, it can be concluded from the above-described literature that there is a positive relationship between COVID-19 and periodontal disease because of the various mechanistic fallouts hence periodontists may have a role in preventing or minimizing the spread of COVID-19 disease wherein periodontal management and oral hygiene reinforcement can reduce the microbial load in the oral cavity thereby reducing the risk and exacerbation of COVID-19 infection.

Research Gaps Identified:

- Studies on the effect and the causal link between the two diseases are not enough to establish a connection between them.
- Interventional studies focused on the influence of periodontitis and periodontal management on COVID-19 infections, would help better understand the pathophysiology link.
- Furthermore, understanding the mechanisms underpinning the relationship between periodontitis and COVID-19 complications is a promising area of research that may produce mechanistic targets, risk stratification and novel interventions.

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Conclusion:

The proposed aetiological mechanisms of Coronavirus disease 19 and Periodontitis may be optimistic with many authors giving theoretical evidence about the connection between the two inflammatory diseases but this needs to be substantiated with further clinical studies.

The exacerbation of either of the disease in milieu of the other is possible and can be strategized to be taken care of, especially in patients with a history of moderate to severe periodontitis who have been affected by the virus need special periodontal management like oral hygiene reinforcement along with supplements like mouthwashes and host modulating therapy targeting to reduce the cytokine storm would be highly advised.

It is seen from the above literature that the two inflammatory diseases prove to be adversaries to each other and can be detrimental in nature, an ethiopathogenic relation can be identified and robust treatment protocols can be fabricated keeping in mind the periodontal health for the better management of the patients affected by COVID-19 with periodontitis. Literature suggests that patients treated with COVID-19 need to be periodontally assessed every six months to prevent any detrimental effects of the virus which may lead to the advancement of their oral and overall health.

Recommendations For Future Research:

Future studies in clinical or experimental research including the new variants can be investigated to better understand their impact at the periodontal level. Interventional studies focused on the influence of periodontitis and periodontal treatments on COVID-19 infections, would help better understand the causal connections between them. Furthermore, understanding the mechanisms supporting the relationship between periodontitis and COVID-19 complications is a promising area of research that may produce mechanistic targets, risk stratification and novel interventions. Clinical trials assessing the periodontal status along with host modulating therapy in patients with COVID-19 are needed to establish the links more firmly between SARS-CoV-2 infection and periodontal disease. Thus clinical, experimental and longitudinal approaches are particularly useful to provide reliable scientific evidence in the current pandemic scenario.

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