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Covid 19 and periodontal disease - An intriguing relationship

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Abstract

SARS-CoV-2 was originally identified as the cause of a deadly respiratory ailment known as COVID-19 (coronavirus disease 2019) in December 2019. According to the information from the World Health Organization, the first COVID-19 case was reported in Wuhan, China, and since then it has spread all over the world, multiplying faster than any other respiratory disease known until now, with more than 85 million confirmed cases and nearly 2 million deaths (WHO). Periodontal disease is one of the most common dental disorders. It is a systemic inflammatory illness produced by a sequence of dysbiotic events triggered by periodontopathogenic bacteria, which results in the death of periodontal tissues locally and an aggravated proinflammatory condition. Many systemic disorders have been linked to periodontitis and severe Covid-19 infections. Because these illnesses have comparable inflammatory pathways that play a role in their course, it's reasonable to conclude that they share a pathological relationship.

Keywords: COVID-19, SARS-CoV-2, Periodontal disease, Cytokines, ACE2, inflammation

Introduction

Covid-19 is a worldwide pandemic that challenged the functionality of every aspect of life,[1] which is rapidly spreading.[1] At the end of 2019, there was an uncertain etiology for the outbreak of a lower respiratory infection in China's Whuhan Province. The causative virus was named as Novel Corona Virus 2019.[2] Covid-19 is caused by sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and targets human angiotensin-converting enzyme 2 (ACE2)[1] and has been declared pandemic by WHO on march 11th 2020.[3]

Currently, the number of new Covid-19 cases per week has nearly doubled in the past two months, approaching the highest rate of infection seen to date during pandemic, the World Health Organization (WHO).

According to WHO, there are 2.82Cr recorded cases of Covid-19 of which 3.32L cases are showed deaths. Considering the presence of any comorbidity or condition, such as diabetes, hypertension, obesity, asthma, pregnancy, lung illnesses, liver illnesses, oral dysbiosis, ageing, and gender, only a small fraction of those infected develop a critical state.

Oral diseases, such as caries and periodontal disease, are among the most common diseases worldwide, making them an important public health issue that imposes significant health and economic burdens on the socio-economic interface, communities, and individuals. Periodontal diseases are a group of inflammatory pathologies in which microbial agents cause a host response that mediates inflammatory events, which lead to tissue distruction.[4] Periodontal Diseases are frequently caused by a build-up of microbial dental plaque over time, which causes acute or chronic inflammation of the dental supportive tissues.[2]

Periodontal diseases follow the same chronic inflammatory model as other diseases like cardio vascular disease, diabetes, obesity, ageing, and hypertension, and several studies have suggested a bidirectional relationship between periodontal health and these pathologies.[2] This supports the notion that there is a strong link between Periodontal Diseases and systemic health.

The purpose of this article is to put forward the potential link between periodontal disease and Covid-19 through different mechanism, and to elicit ate that there is a two relationship between PD and Covid-19.

Etiology of Covid-19 and Periodontal disease

The virus shares 88 percent sequence identity with two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, but is more distant from the severe acute respiratory syndrome corona virus (SARS-CoV). As a result, it was initially dubbed 2019-novel corona virus (SARS-CoV2).[5] Corona virus is a single stranded, enveloped ribonucleic acid named after its solar corona like appearance caused by 9–12 nm-long surface spikes.[6] On the envelope, the corona viral genome encodes four major structural proteins, one of which is the spike (S) protein, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell.[7] Based on phylogeny, taxonomy, and established practise, the International Committee on Taxonomy of Viruses' Coronavirus Study Group (CSG) finally designated it as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) on 11 February 2020.[8] Soon after, WHO designated the coronavirus caused disease as Corona virus Disease 2019.[9] (COVID-19). According to current data, bats may have been the first to host COVID-19, which may have been transmitted to humans via pangolin or other wild animals sold at the Huanan seafood market, and then spread via human-to-human transmission.[5]

PD is the most common disease affecting the oral cavity after dental caries. It is multifactorial in origin yet is considered a bacterially induced chronic inflammatory disease.[10] Periodontal disease first starts with a microbial infection followed by a hyper - inflammatory host-mediated response that will often destroy the surrounding tissues.[11] Often asymptomatic, the clinical signs of PD include gingival inflammation, formation of deep pockets surrounding the dentition, attachment loss of the supporting tissues, root exposure and loss of

alveolar bone. Ultimately this may lead to tooth loss and negatively impact the quality of life of the individual.

There are several studies that were put forward stating that Periodontal Disease and Covid-19 have common risk factors like age, gender, diabetes mellitus, CVD, obesity, pregnancy, chronic obstructive pulmonary disease(COPD), smoking, asthma, HIV, cancer, liver disease, Rheumatoid arthritis and oral dybiosis.[12] This is also indicates that there is a potential relation between PD and Covid-19, and the latter can be affected by the periodontal pathogens outside the etiological niche and cause chronic inflammation.[12]

Etiopathogenesis of Covid-19

The path of transmission of virus is linked to contact or faecal – oral transmission, coughing, and sneezing, still on respiratory droplets[13].

The crucial effect is that patients' symptoms are associated with the onset of the disease [14] and contagiousness can persist for up to 2 or 3 weeks after recovery[15]. Moreover, patients' symptoms and disease manifestations are diversified for every person affected; indeed, mild or subclinical symptoms are related to infective patients[16]

The immune response of Covid-19 occurs in 2 phase

1. Body directly acts on the viral infection.
2. Cytokine storm reaction that causes damage to lungs, gastric mucosa, brain and other structure.

(Fig.1: Schematic illustration of the pathobiology of COVID-19.[17] and 2: Schematic illustration of the pathobiology of Periodontitis.[18])

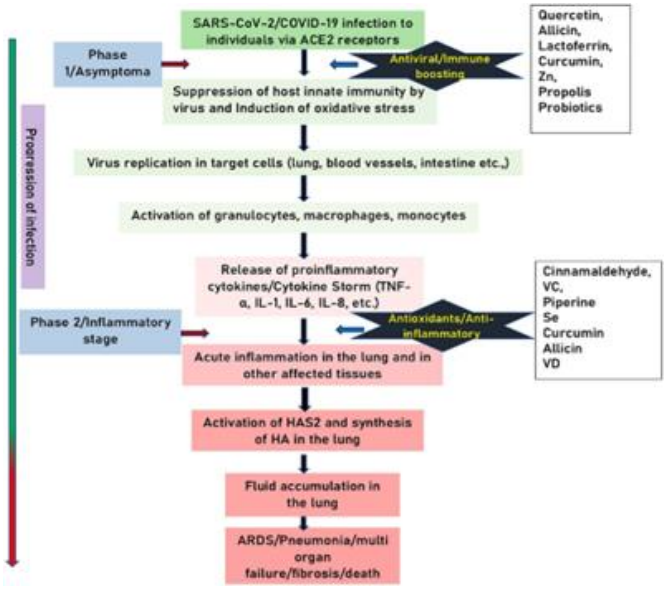

Fig 1: Schematic illustration of the pathobiology of COVID-19. (Page RC et al,1998)[18]

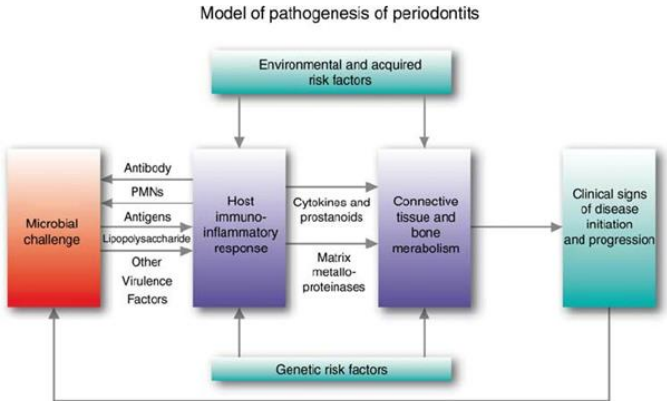

Fig 2: Schematic illustration of the pathobiology of Periodontitis (Zhu N et al,2020).[19]

Covid-19 and Disruption of Oral Biosis

Periodontal tissue consists of commensals which play major role in physiology of oral cavity, which leads to host microbial network[19] when a disease occurs this host-microbial network leads to dysbiosis and increased burden to the host before causing systemic impact.[20]

There is increased risk of bacterial superinfection in Covid-19 patients due to bacterial pathogen present in the periodontal region. Bacteria present in patients with severe COVID-19 infection are usually organisms in the mouth like Prevotella, Staphylococcus, and Fuso bacterium.[21] Prevotella intermedia could be a common

pathogenic bacterium that's involved within the onset and progression of periodontitis. Other bacterial species such as Streptococci, Fusobacterium, Treponema, and Veillonella also play a very important role within the progression of disease.[22]

There are many reasons that support the contribution of oral bacteria in the relationship with respiratory infections like COVID-19. They are as follows:

- Inhalation of oral microbiota into the alveoli of lungs.
- Biomarkers related to periodontitis alter the surface of mucosa to allow the secretion and expression of receptors, thereby creating adhesion and colonization sites for respiratory pathogens.
- Enzymes associated with periodontitis can alter the saliva membrane of bacteria, preventing them from being removed from the oral mucosa surface.
- Pro-inflammatory mediators and other cytokines related to periodontal disease may change respiratory epithelial cells, and promotes the invasion of respiratory pathogens.[1]

Moreover, the study showed that 80% of patients with severe COVID-19 had high bacterial load.[23] These complications of COVID-19 infection rely on immune response. It's been reported that patients with severe COVID-19 had higher levels of inflammatory markers. They reported in higher neutrophil count and lower lymphocyte count, it's common for a bacterial super infection that means in severe activity disease of COVID-19.[24]

Inflammation process in Covid-19

Eke et al;2015 stated that PD is an chronic inflammatory noncommunicable disease, in response to dysbiosis in subgingival biofilm.[25] PD have demonstrated increased number of cytokines and chemokines, tumor necrosis factor-α, interleukin (IL)-1β, IL-4, IL- 6 and IL-10 as well as C-reactive and Ferrittin protein producing cell in periodontitis.[2]

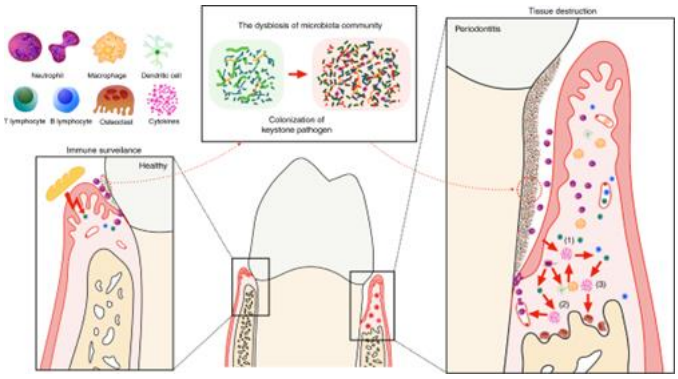

Fig.3: Schematic representation of cytokine storm in periodontal diseases[26]

Schematic representation of cytokine storm in periodontal diseases[27]

Similarly, there is also evidence stating that the Covid-19 patients who were hospitalized in intensive care unit showed elevated serum levels of IL-1β, IL-4, IL- 6 and IL-10; Th17, IFN-gamma, GM-CSF, GM-CSF, IL-8,TNF- α, MIP1B, MCP1,MIP1A and IP10 were observed.[4] The cytokine storm observed in Covid 19 is very similar to the cytokine imbalance in periodontal disease.

This cytokine storm activation also suggested expression of high levels of Angiotensin converting enzyme-2 (ACE2) after infection.[28]

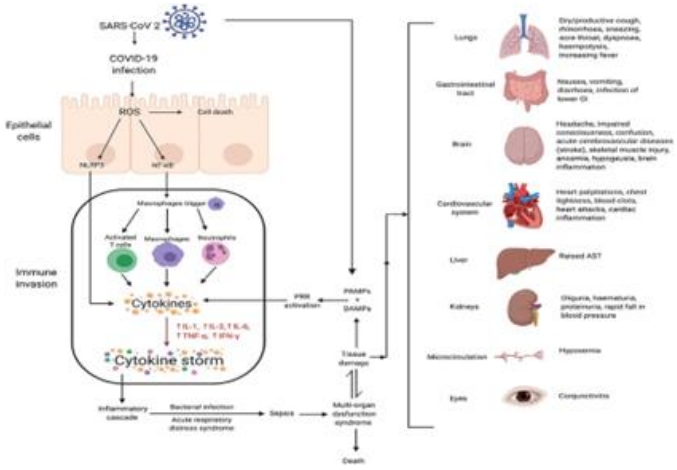

Fig. 4: Mechanism of COVID-19 associated cytokine storm and associated damages.27

Mechanism of COVID-19 associated cytokine storm and associated damages28

This cytokine storm activation also suggested expression of high levels of Angiotensin converting enzyme-2 (ACE2) after infection.[28]

Role of ACE2 in Covid-19 and Periodontal Diseases

ACE2 is related to renin-angiotensin system (RAS) which play an important role in counteracting ACE function. They act as enhancers and diminishers in regulating the activities and vital responses like blood pressure regulation, inflammation response, organ protection, oxidative stress and diuresis. Its role is associated in forming two opposite axes

1. the angiotensin-converting enzyme 2–angiotensin 1–7–Mas receptor (ACE2–Ang1–7–MasR) – down regulating function, blocking oxidative stress, cell proliferation, hyper tension, and inflammatory response
2. the angiotensin-converting enzyme (ACE)e–angiotensin II (Ang II) –angiotensin receptor type 1(AT1) axis – aimed at initiating the inflammatory process, inducing chemotaxis of inflammatory cells and mediator.[8]

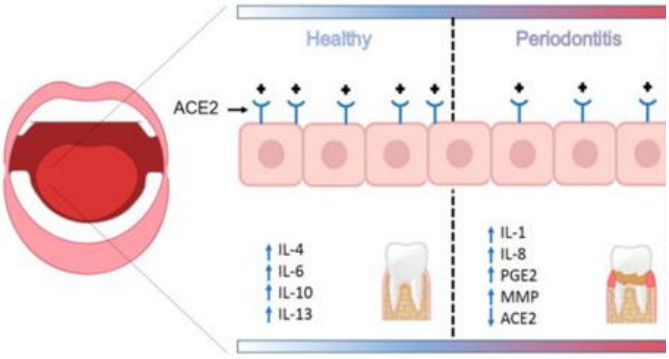

Fig.5: ACE2 expression in Periodontitis[29]

ACE2 expression in Periodontitis (Belouzard, S.et al,2009)[30]

There are study that shown that there is presence of ACE2 and RAS system in oral cavity, mostly in cells of periodontal structure.[29] Hence, the regulation of inflammatory pattern that occurs due to ACE2 is a resonse to periodontal disease.[8]

ACE2 also play an major role in entry of SARS-CoV 2 into cells, mechanism is correlated with endocytosis and internalization of ACE2.[8] Recent a study was conducted Liu Y et al, which reported increase in Ang II, which is correlated to viral load due to binging between ACE2 and SSARS-CoV 2.

Viral replication leads the immune system to downregulate ACE2 expression, giving rise to several acute inflammatory injuries.[30] An ACE2–SARS-COV-2 connection could potentially result in reduced ACE2 levels at the cell surface, decreasing the degradation of Ang II, and generating Ang1–7.[31] Moreover, a reduction in ACE2 through its internalization may increase the Ang II/Ang1–7 ratio, which could exacerbate the inflammatory pattern of the SARS-CoV-2 infection.[8]

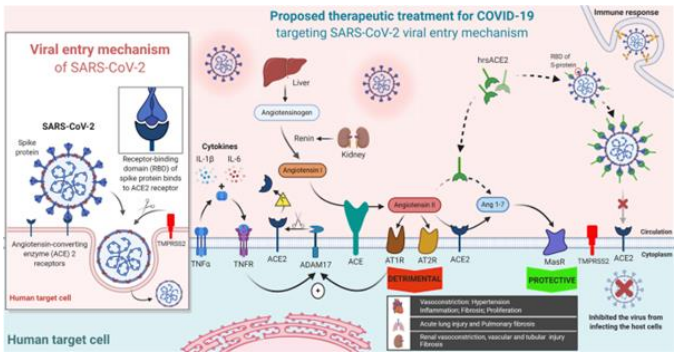

Fig.6: Schematic diagram of the renin-angiotensin system in COVID-19[32]

Schematic diagram of the renin-angiotensin system in COVID-19[32]

The ACE2 also regulates the pro-inflammatory and anti-inflammatory through formation of ACE2-Ang1-7-MasR axis which in-turn downregulates the cytokines which are also present in relation to Covid-19 and PD.[15]

Therefore, the presence of ACE2 in both the disorders indicate the possible link between the two diseases.

Conclusion

The objective of the study was to put forward the potential link between periodontal disease and Covid-19 through different mechanism, and to elicit ate that there is a two relationship between PD and Covid-19. Based on the data collected and summarized it seems apparent that periodontal have an indirect effect on covid-19. The presence of common etiological factors, cytokines and chemokines, tumor necrosis factor-α (TNF- α), interleukin (IL)-1β, IL-4, IL- 6 and IL-10 C-reactive protein, as well as ACE2 indicate the possible association of PD and Covid-19. Hence, further intensive clinical research on this topic is needed to have an in-depth knowledge.

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