ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 4, Issue – 4, July - 2021, Page No. : 518 - 529

Tie-up between covid-19 and periodontal disease – A review

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Citation of this Article: Dr. K. Malathi, Dr. N. Srividya, Dr. Lishamol. K. Thomas, Dr. G. Sandhya, Dr. T. Arivukarasu, "Tie-up between covid-19 and periodontal disease – A review", IJDSIR- July - 2021, Vol. – 4, Issue - 4, P. No. 518 – 529.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

COVID-19 is an emerging health emergency which ruins the well-being of the individual and devastating the global economies. SARS-CoV-2 was first identified in December 2019 with serious respiratory illness called COVID-19 or coronavirus disease 2019 as etiologic factor. Patients with cardiovascular disease, diabetes mellitus and obesity are the higher risk groups. Steady knowledge on the pathogenesis of this disease revealed that the immense destruction and degradation of lung tissue is due to the presence of angiotensin converting enzyme-2 (ACE2) which has an important role in the entry of virus to the host cell. Periodontitis is a polymicrobial and multifactorial oral disease and demonstrated the existence of bi-directional relationships between periodontal disease and systemic conditions. The hyperresponsiveness of the host resulting in the increased release of pro-inflammatory cytokines called the 'cytokine storm' leads to bacterial stimulation and tissue destruction, this shows that there is a potential interrelationship between periodontitis and COVID-19 which advises in improving oral hygiene during the COVID situation. And also, the individuals with periodontal disease are at higher risk of getting COVID-19 associated unfavorable consequences. So, understanding these associations help to deliver appropriate care at early stage.

Keywords: COVID-19, periodontitis, angiotensin converting enzyme-2, cytokine storm, oral hygiene

Introduction

Coronaviruses are a diverse group of viruses infecting different animals, and cause mild to severe respiratory infections in humans. In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS- CoV), appeared in humans and caused lethal respiratory illness. At the end of 2019, SARS- CoV-2 a new coronavirus emerged in the city of Wuhan, China. It is also known as coronavirus disease 2019 (COVID-19), member of the coronaviridae family and was identified as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. There is a lack of effective biomarkers to identify individuals at risk of developing COVID-19.

The role of the oral cavity in COVID-19 has been controversial. While recent evidence suggests that the oral

mucosa is the mode of transmission and pathogenicity of SARS-CoV-2. Systemic inflammation is also a symptom of periodontal disease, or gum disease. Periodontitis is one of the most prevalent chronic inflammatory non-communicable diseases (NCDs), if left untreated lead to tooth loss. The Global Burden of Disease (GBD) study reported that 50% of adults are affected by mild-to-moderate periodontitis, and 10% by the severe form, rendering the sixth most prevalent condition affecting mankind [**2**]. This disease is characterized by destruction of the tooth attachment apparatus and bone loss and chronic non-resolving inflammation in response to a dysbiosis in the subgingival biofilm.

Epidemiologic, experimental and interventional studies have publicized that periodontitis may also impact systemic health. Periodontal disease has been linked to several other serious conditions in addition to COVID-19, including diabetes, heart disease, Alzheimer's and even premature mortality. The chronic inflammation frequently leads to lesser degree of systemic inflammation and increased levels of cytokines, such as Tumour Necrosis Factor-α (TNF-α), Interleukin (IL)-1β, IL-4, IL-6 and IL-10, as well as C-reactive protein and ferritin. The risk factors for periodontitis, such as smoking, stress, unhealthy diet, glycaemic control, genetic and socio-economic determinants. Furthermore, we will discuss the clinical and epidemiological features, diagnosis.

Emergence and Spread

COVID -19, an emerging respiratory tract infection has resulted in over 75 million confirmed cases and almost 1.6 million deaths as of December 22th, 2020. 14% of confirmed cases develop severe conditions requiring hospitalization and oxygen support, and 5% need admission to intensive care units and around 2% die. The case numbers in Europe, the USA and other regions have jumped sharply. One study from France detected SARS-CoV-2 by PCR at the end of 2019, suggesting that it might have spread much earlier, cannot give a solid answer to the origin of SARS- CoV-2, and thus a false positive result cannot be excluded. To address this, further retrospective investigations need to be conducted worldwide with well- validated assays.

Animal Host

Bats are important natural hosts of alphacoronaviruses and beta coronaviruses. The discovery of diverse bat coronaviruses suggests that bats are possible reservoirs of SARS- CoV-2 and wildlife is the infected pangolins showed clinical signs and histopathological changes, including interstitial pneumonia and inflammatory cell infiltration in diverse organs [**3**]. SARS- CoV-2 also uses and identifies ACE2 from pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit and dog.

Structure

As a novel betacoronavirus, SARS- CoV-2 shares 79% genome categorization distinctiveness with SARS- CoV. The pneumonia patients of the Wuhan were observed and found that strains of SARS-CoV-2 had a measurement of 29.9 kb [**4**]. SAR-CoV2 is an enveloped, non-segmented, positive sense RNA virus which is seen in the sarbecovirus, ortho corona virinae subfamily which is widely spread in humans and other mammals. Its dimensions are about 65-125 nm, single strands of RNA with crown-like spikes on the external surface. Structurally, SARS-CoV-2 has four main structural proteins includes 1) spike (S) 2) glycoprotein, 3) small envelope (E) glycoprotein, 4) membrane (M) glycoprotein, 5) nucleocapsid (N) protein, and 6) several accessory proteins.

Approximately 5days	<10 YEARS	ASYMPTOMATIC	Incubation Period
Approximately 8days	<50 Years	MILD DISEASE	Fever, Fatigue Pneumonia, Ground Glass Opacities
Approximately 8days	>60 Years	SEVERE	Dyspnea, Co-Existing Illness
Approximately16 Days	>68 Years	CRITICAL	ARDS, Cardiac Injury, MultiOrgan Failure

Pathogenesis

The pathogenesis of SARS- CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure.

Binding to epithelial cells in the respiratory tract,

SARS- CoV-2 starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs.

May trigger a strong immune response.

Patients of older age (>60 years) and with serious pre-existing diseases have a greater risk of developing acute respiratory distress syndrome and death. Multiple organ failure has also been reported in some COVID-19 cases. Histopathological changes in patients with COVID-19 showed bilateral diffused alveolar damage, hyaline membrane formation, and exudative inflammation desquamation of pneumocytes and fibrin deposits in lungs. Immunohistochemistry assays detected SARS- CoV-2 antigen as well as in type I and type II pneumocytes, alveolar macrophages and hyaline membranes in the lung lower respiratory tracts [**5**].

Immune Responses

COVID-19 patients revealed that there was an increase in the total number of neutrophils, Interluekin-6 (IL-6) serum and c-reactive protein about 38%, 52% and 86%, respectively and 35% decrease of total lymphocytes. The entry of the virus into the host cell triggers stimulation of the host's immune response which will first be encountered by innate immune system cells via antigen presenting cells. APC have Pattern Recognition Receptors (PRR) including Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and other small free molecules. They recognize PAMP comprised nucleic acids, carbohydrate moieties, glycoproteins, lipoproteins and other small molecules that are found in the structural components of viruses.

Toll like receptor 4 (TLR-4) +outer component of CoV the protein spike

MyD88, NF-kB transcription factors and the pathogen-activated protein kinases (MAPKs) pathway

Prion flammatory proteins

Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure, which is considered the main cause of death in patients with COVID-19. It also releases excess of pro-inflammatory cytokines such as IFN- α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF β, and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 from immune effector cells causing hyperinflammation which eventually leads to ARDS cytokine storm syndrome.

Activation of endosomal receptors, TLR-3, TLR recognize the RNA or dsRNA genome of coronavirus recruit TRIF adapter protein

TRIF activates IRF3 and NF-kB transcription factors induce proinflammatory cytokines

PAMP introduced through TLR-4 recruits TIR- domain containing adaptor protein- inducing interferon β (TRIF) adapter proteins which is mediated by TRIF- related adaptor molecule (TRAM) and TIRAM [**6**]. This in turn secretes proinflammatory cytokines which is the primary reaction in the first line of defence against virus infection. Type I INF & IFNAR receptors form complexes and activates JAK-STAT pathways. JAK1 and tyrosine kinases-2 (TYK2) further phosphorylate STAT1 & 2 with its complexation with IRF9, migrate into the nucleus and

activates the transcription of IFN-stimulated genes (ISGs) with its viral replication can prevent the severity of the disease. However, excess releasing of pro-inflammatory cytokines from immune effector cells causes hyperinflammation which will eventually lead to ARDS.

a) specific IgM that can only last 12 weeks, but IgG with a longer period

b) Formation of CD4 T cells and CD8 memory that can last for four years.

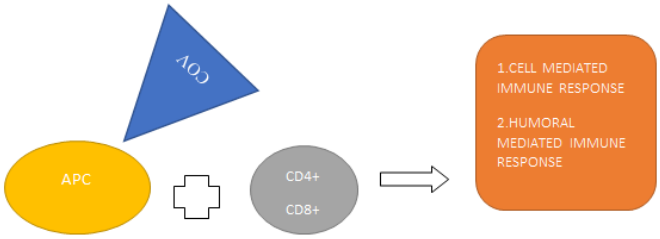

Figure 1

II Antigen of CoV

Attaches to CD4 + T-helper cells by MHC class 1

Releases IL-12 as a co-stimulatory molecule

Stimulate Th1 cell activation

Releases interleukin-12 and IFN-α

Increase in MHC Class I and NK cell activation

Leads to resistance of viral replication

Produces proinflammatory cytokines via NF-k signaling pathway

IL-17 is a proinflammatory cytokine increased

Recruit neutrophils and monocytes to infection and activate several other pro-inflammatory cytokines and chemokines

Immuno-Evasion of Coronaviruses

There are many ways for the virus to affect and get away from the immune system which starts from the entry to the host. During the recognition, the double vesicles formed causes shield recognition of cytosolic PRRs to dsRNA as an intermediate product of replication virus. Apart from this the virus has 8 proteins blocks INF by evading the immune system. Nsp1 suppress INF-I through host translational machinery inactivation, RNA-Host degradation and inhibits phosphorylation of STAT1 to induce replication and dissemination of viruses at an early stage and leads to increased severity of disease. In addition to this, protein accessories of SARS-CoV can be utilized to avoid immune responses. For example, the virus gene segment on ORF3b and ORF6 in which ORF3 antagonizes the INF signaling pathway and inhibits the effector cell activation to eradicate and inhibit viral replication and ORF6 inhibit JAK-STAT signaling pathway by binding to karyopherin-a2, and tethers karyopherin-b1 on internal membranes to lead to blocking nuclear translocation of the transcription factor STAT1 [7].

Hypothetical model for the oral-vascular-pulmonary route of infection

The hypothesis is based on primary vascular pathological radiological evidence, formation of a viral reservoir in the oral cavity (and saliva), translocation of the virus from saliva to the gingival sulcus/periodontal pocket and survived within the sub-gingival plaque biofilm, thus evading the oral mucosal immune response and the viral binding of the ACE2 receptor on the endothelium of pulmonary vessels.

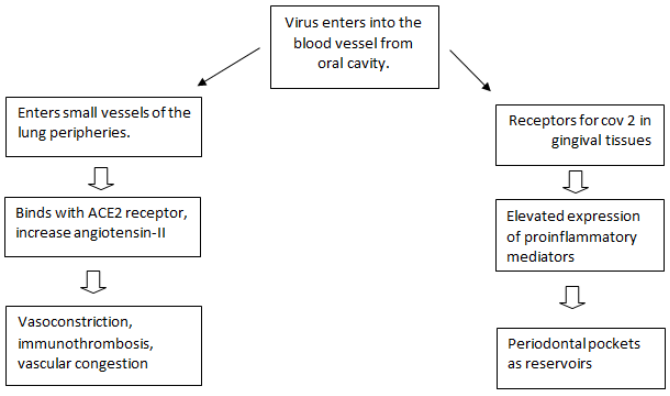

Figure 2

Risk Factors

1. Age And Gender

Additional risk factors with age are considered a process that causes degenerative changes at the cellular level and sometimes leads to various other diseases including periodontal disease. Another critical factor for the disease is altered immune response which was not as strong as young people. Men are more prone to periodontal disease due to their behavioral and environmental factors in immune function. In a similar way, men are more prone to become seriously ill by COVID-19 than women and it was proposed that the difference of immune response to SARS-CoV-2 between men and women favours the inflammatory range.

2. Diabetes Mellitus

Increasing evidences like chest tomography and other clinical parameters supports an association between severe covid-19 and diabetes mellitus. Diabetes mellitus (DM) is a chronic disease associated with in a bilateral way with periodontal disease. The proposed mechanisms to understanding this association includes alterations in vascular, cellular, and host repair processes. Patients with COVID-19 may have affected the expression of the angiotensin-converting enzyme 2 (ACE-2) in the lungs and receptor is greater in diabetic than in no diabetic. This is because of diabetic patients will be under the treatment with ACE inhibitors and angiotensin II type I receptor blockers (ARBs). In both diseases the immune response is affected by host factors, external and internal environmental factors. Diabetes mellitus is a risk predictor for COVID-19 and periodontal disease and the later could be useful to identify risk groups COVID-19.

3. Hypertension And Cardiovascular Disease (CVD):

Hypertension is a health disorder that is considered as a main risk factor for cardiovascular disease. In periodontal disease, proinflammatory cytokine regulate and increase levels of C- reactive protein. Detection of high-density CRP a marker in CVD and hypertension and the presence of CRP is the link between periodontal disease and CVD. Treatment of hypertension with ARBs increases expression of ACE-2. Expression of ACE-2 in hypertension and periodontitis may represent a major risk factor for severe COVID-19.

4. OBESITY:

In obesity, the production of reactive oxygen species that generate oxidative stress is increased. It also alters the periodontal microbial composition which in turn shows elevated levels of periodontal pathogens. The main consequence of obesity is a systemic inflammation state and periodontal disease. There is an induction of an increased inflammatory systemic state triggered by the dissemination of bacterial products and proinflammatory cytokines. Obesity increases the risk of developing severe COVID-19 and the association between covid-19 and obesity could be decreased expiratory reserve volume, functional capacity, and respiratory system compliance. Apart from this, augmented inflammatory factors reported in obesity could contribute to amplify the response of the patient and develop severe COVID-19.

5. Pregnancy

In pregnancy mother's immune system is suppressed to allow gestational development. Increased progesterone levels trigger the gingival response causing dysbiosis, periodontopathogens growth occur affecting the supporting structures of the teeth. Immunosuppression, high progesterone and estrogen levels, and the physiological adaptive changes predispose pregnant women to respiratory infections diseases, but one less than 10% developed severe disease. Very few cases of covid-19 have confirmed in pregnant women.

6. COPD

Patients with pre-existing COPD have a four-fold increased risks to develop severe covid-19 illness. Increased risk of expression of ACE-2 in airway is the main reason for it. The association with COPD and periodontal disease can be the risk group to develop severe COVID-19.

7. Smoking

It is a major risk factor in periodontal disease and covid-19 progresses, 1.4times more probable to have severe covid-19 symptoms. The relationship between smoking and severity of covid-19 is not clear.

8. Asthma

It could be a risk indicator for periodontal disease adults and could be a risk factor for severe covid-19 diseases. In asthma patients with increased expression of ACE-2 and TMPRS2 could indicate increased susceptibility for SARS-CoV2 infection and COVID-19 morbidity.

9. HIV

It is believed that the degree of immunosuppression may contribute to a higher susceptibility to SARS-CoV2 infection.

10. Cancer

Cancer is a malignant neoplasm and patients with cancer are more susceptible to develop severe COVID-19 illness. In cancer patients, the immune response is suppressed by treatments and nutritional deterioration which in turn induces dysbiosis breakdown and increases the possibility of respiratory infections. Patients with lung cancer are more likely to develop severe covid-19. So, cancer patients with periodontal disease could represent a group at risk for severe covid-19.

11. Liver Disease

COVID-19 because the novel coronavirus binds hepatocytes and cholangiocytes using the ACE-2 receptor in patients with liver disease (LD). So, pre-existing LD patients would be more vulnerable to severe COVID-19 disease. The patients with liver disease and periodontal disease could help to identify a group at risk for severe. Lipopolysaccharide from Porphyromonas gingivalis induces liver inflammation products released from periodontal pathogens in a periodontal disease stimulates cytokine that are involved in the progression of liver disease.

12. Rheumatoid Arthritis

Rheumatoid arthiritis (RA) is a chronic inflammation and the relation between rheumatoid arthirits and periodontal disease exists. People with rheumatoid arthirits get worse when they have periodontal disease. P. gingivalis is known to produce an enzyme that causes citrullination and periodontal bacteria have been isolated from synovial fluid. Association between periodontal disease and RA and possible inflammatory and bacterial underlying mechanisms could affect the outcome in patients with COVID-19. It has been reported that the patients with rheumatoid arthirits have twice the risk of infectious disease and it also increases mortality when there is bronchopulmonary infection.

Periodontal Perspective

The disease of periodontium is a globally wide spread. Periodontitis is considered to start as plaque induced gingivitis, a reversible condition that is left untreated ay develop into chronic periodontitis. It is distinguished by loss of attachment and alveolar bone is regarded as irreversible and is classified by staging and grading systems. Probable associations between periodontal infection and systemic diseases were well-documented. Periodontal pathogens and their products including IL-6 could enter the bloodstream, thereby causing several systemic diseases [**8**]. And also, periodontopathic bacteria were found in the bronchoalveolar lavage fluid of patients suffering from pneumonia and diabetes could increase the

risk of developing pneumonia. There are several microbial exchanges between the oral cavity and the lungs.

Two hypotheses have been proposed; (1) cytokines and enzymes produced during a periodontal disease may alter the respiratory epithelium and oral mucosa, thereby favours infection; and (2) the aspiration of oral pathogens into the lungs. Thus, poor oral hygiene can increase the risk of respiratory infections at an elderly people. However, specific mechanisms and pathological pathways have been identified directly linking periodontitis to these comorbidities, such as translocation of pathogens to blood (eg- bacteraemia), systemic inflammation, and induced autoimmune damage. Moreover, there is an evidence that periodontal treatment leads to an improvement of glycaemic control, improves the balance of lipids, improved renal function associated with diabetes and as well as biomarkers associated to atherosclerosis, such as serum CRP, IL-6, fibrinogen and IL-1 β level.

Association between covid-19 and periodontitis

The mechanism which could explain the association between periodontitis and covid-19 diseases are of two types: (1) the direct contact of virus with the periodontal tissues, also due to the high expression of ACEII and CD147, as (2) the similar overexpression of several cytokines, a COVID-19 'cytokine storm', with elevated serum levels of IL-1 beta, IL-6, IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, GM-CSF, GCSF, IFN-gamma, TNF alpha, MIP1A, MIP1B, MCP1 and IP10. IL-6 and IL-17 has high levels in the serum of COVID-19 patients, which is also over expressed in periodontitis. When SARS-CoV-2 infects the respiratory tract, it induces a release of IL-1β and IL-6. Induction of interstitial pneumonia, which is in turn linked to an overproduction of IL-6. An increase in IL-17, and fourteen other cytokines levels were positively correlated with lung injuries. There was an increase in IL-17-producing cells in the gingival tissue of the gingivitis and periodontitis patients and there is an increase in levels of IL-17 in the serum.

A pro-inflammatory protein Galectin-3 is an acute phase protein elevated in severe periodontitis. Gal-3 is involved in several mechanisms such as: inflammation, angiogenesis, cell growth, host defence and others. Morphology of Gal-3 was observed to be similar to the SARS-CoV-2 spike protein. The presence of could increase the risk of SARS-CoV2 infection. By causing ulceration of the gingival epithelium, protective function of the oral epithelial cells is reduced and exposing the patients to an elevated risk of invasion by SARS-CoV-2. ACE2, TMPRSS2 and furin, expressed have ulcerated oral epithelial cells to in the aforementioned oral epithelial cells and the proteases produced by periodontopathogenic bacteria could cleave the protein S of the virus, thereby favouring infection. Periodontitis could facilitate SARS-CoV-2 infection through the CD147 route as the epithelial cells of the periodontal pocket express high levels of CD147 [**9**]. When periodontopathic bacteria are aspirated into the lungs, the expression of ACE2 increases in the bronchus and the lungs and this overexpression could increase the risk of a SARS-CoV-2 infection. The culture supernatant of the periodontopathic bacterium Fusobacterium Nucleatum (CSF) induced the production of interleukin (IL) -6 and IL-8 by alveolar epithelial cells. The 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.

1. Entry factors for SARS-CoV-2 in oral and gingival tissues

- The invasion of host cells by SARS-CoV-2 is mediated by ACE2 receptors, furin, and trans membrane protease serine protease 2 (TMPRSS2).

- These mediators, which are key elements for infection, are expressed abundantly in the nasal airways and oral cavity, including gingival tissues, minor salivary glands, and tongue
- cells of the sulcular epithelium do express ACE2, TMPRSS2, and furin. This indicates the potential for the gingival sulcus to be a target for SARS-CoV-2 infection [10].
- Thus, several niches in the oral cavity can become infected by the virus, including the gingival sulcus.

2. Presence of SARS-CoV-2 in the oral cavity and periodontal tissues

- There is strong evidence from several studies confirming the presence of SARS-CoV-2 in saliva, minor salivary glands, tongue, and gingival crevicular fluid [11].
- Huang et al suggests that the virus can persist in saliva or in the nasopharynx for over two months
- In asymptomatic individuals, viral clearance was observed after 0.5 to 3.5 weeks
- The salivary viral load has been linked to loss of taste, overall disease severity and mortality, being a better predictor of poor outcome than patient age or viral load in the nasopharynx

3. Periodontal pockets as a reservoir for viruses

- viral RNA was detected in the gingival crevicular fluid of 64% of COVID-19 positive patients
- It has been speculated that viral particles in the oral cavity can migrate into the gingival sulcus/periodontal pockets, where the conditions are favorable for their survival
- Sub-gingival plaque biofilm can provide a unique environment for viruses and micro-ulcerations pocket epithelium facilitates the passage of microorganisms and viral particles to the underlying connective tissue and gingival capillary complex, reaching the systemic circulation [12].
- poor oral hygiene and periodontitis increase the risk for development of severe COVID-19 with poor outcomes

4. Oral and nasal cavities as entry points for microorganisms

- In periodontitis patients, the risk for viral invasion is to increased due to potential disruption of the pocket epithelium which favours bacterial entrance to the systemic circulation [13].
- Even in healthy patients, the permeable nature of the junctional epithelium can facilitate viremia
- Other potential sources of transmucosal transfer - the floor of the mouth (including salivary ducts) and Kiesselbach's plexus (Little's area) of the nose.

5. The potential role for viral-bacterial synergy in the periodontal environment

- the co-presence of SARS-CoV-2 with periodontal bacteria may exacerbate periodontal tissue damage [14]
- In periodontitis patients, it can be speculated that

  i) a viral-bacterial synergy might facilitate penetration of SARS-CoV-2 through the pocket epithelium,

  ii) such an interaction can help viruses evade the immune response

6. Potential role of local and systemic inflammatory response

- In periodontitis, the host response to microorganisms in the subgingival biofilm is mediated by the expression of pro-inflammatory cytokines, particularly tumour necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)
- peripheral blood neutrophils of periodontitis patients are hyper-reactive with respect to cytokine release (IL-1β, IL-8, IL-6, TNF-α) when FcγR and Toll-like

R4 receptors are challenged, relative to non-periodontitis controls [15].

- Severity of COVID-19 has also been linked to systemic inflammation
- In COVID-19 patients, the risk for respiratory failure was 22 times higher in patients who presented high IL-6 levels upon hospital admission

7. Links between periodontitis and oral hygiene with other respiratory conditions

- Evidence suggests that periodontitis can increase the risk for respiratory diseases such as pneumonia, and chronic obstructive pulmonary disease (COPD) [16].
- In hospital settings, adequate plaque control measures and dental treatment have been shown to reduce the incidence and severity of pulmonary infection

8. Shared risk factors between COVID-19 and periodontitis

- Periodontitis and poor outcome in COVID-19 share many risk factors, such as patient age, sex, Smoking, diabetes, cardiovascular disease, obesity, COPD, Down syndrome, physical disability or learning difficulty and dementia

9. Higher severity of COVID-19 in patients with poor oral hygiene/periodontal disease

- COVID-19 patients showed an association between periodontitis and COVID-19 severity
- Dental plaque could provide a constant source of viral delivery to the vasculature during the acute phase of COVID-19.

Diagnosis

Early diagnosis is crucial for controlling the spread of COVID-19. Molecular detection of SARS- CoV-2 nucleic acid is the gold standard. SARS- CoV-2 has been detected from a variety of respiratory sources, including throat swabs, posterior oropharyngeal saliva, nasopharyngeal swabs, sputum and bronchial fluid, the viral load is higher in lower respiratory tract samples. Chest CT was used to quickly identify a patient when the capacity of molecular detection was overloaded including bilateral multilobed ground- glass opacities with a peripheral or posterior distribution. SARS- CoV-2 serological tests detecting antibodies to N or S protein could complement molecular diagnosis, particularly in late phases [17]. However, the extent and duration of immune responses are still unclear, and available serological tests differ in their sensitivity and specificity, all of which need to be taken into account when one is deciding on serological tests and interpreting their results or potentially in the future test for T cell responses.

Management:[18]

1. **Inhibition of virus entry**

- Umifenovir (Arbidol)- between the S protein and ACE2 and inhibit membrane fusion
- Camostat mesylate- blocks entry of SARS- CoV-2 into human lung cells
- Chloroquine and hydroxychloroquine – unclear

2. **Inhibition of virus replication**

- Remdesivir - several international phase III clinical trials continuing to evaluate.

3. **Immunomodulatory agents**

- Dexamethasone- reduced mortality by about one third
- Tocilizumab and sarilumab- treatment of severe COVID-19 by attenuating the cytokine storm.
- Eculizumab-

Clinical Significance

- From the oral cavity, if SARS-CoV-2 can reach the lungs through the blood, causing immune-thrombosis driven disease in the pulmonary vessels, then early measures to decrease transmission to the lungs in this way must be considered in the management of COVID-19 [19].

- This concept potentially highlights the importance of active oral healthcare and adequate daily oral hygiene measures in the management of COVID-19

Recommendations for Good General Oral Healthcare

- Adequate daily home oral care habits are essential for oral and general health, as it decreases the risk for dental caries, gingivitis, and periodontitis.
- If proven to be correct, the concept of the oral-vascular pulmonary infection route may mean that these simple measures could reduce the risk of developing severe COVID-19 lung disease [20].
- Well-established mouthwashes containing specific ingredients, which inactivate SARS-CoV-2 in vitro, could potentially help mitigate transmission and decrease the risk of severe lung disease in COVID-19.
- 0.05%-0.1% Cetylpyridinium Chloride (CPC): 15 ml for 30 seconds twice a day. In vitro and invivo studies indicate that mouthwash products containing CPC are able to inactivate SARS-CoV-2. These products are generally considered to be safe, with staining of the tongue and teeth being rarely reported [23].
- 0.147% Ethyl lauroyl arginate (ELA): 20 ml for 30 seconds twice a day. In vitro results suggest virucidal activity of ELA against SARS-CoV-2
- 0.2%, 0.4% or 0.5% Povidone-Iodine (PVP-I): 10 ml for 30 seconds twice a day. The use of PVP-I is supported by in vitro and in vivo studies. Contraindications: allergy,hyperthyroidism, thyroid dysfunction, pregnancy, lactation, and treatment with radioactive iodine.
- mouthwashes should not replace daily oral hygiene measures – after tooth brushing – before and after social interactions.
- Clinical trials are also required to specifically address the potential for mouthwashes to mitigate the development of COVID-19 lung disease, and hence the severest form of the disease.

Discussion

COVID-19 is a disease caused by novel coronavirus named SARS-CoV-2 that damages the lungs and other organs. ARDS, SARS and MERS are the other disease by other coronaviruses that cause respiratory syndromes. The nasal and oral cavities are entry points which provides favourable conditions for viral replication, with saliva functioning as a reservoir for SARS-CoV-2. The presence of poor oral health could act as a risk factor to identify individuals more likely to develop COVID-19 lung disease, or those who might progress to severe disease leading to intensive care admission, mechanical ventilation, or death. The co-morbid presence of periodontitis has been shown to represent an independent risk factor for other systemic inflammatory diseases that are characterized by hyper-inflammation and oxidative stress. Determining viral load within blood samples taken simultaneously from the jugular vein and a peripheral site is suggested here as a possible means of corroborating the role of the proposed anatomical pathway.

Periodontitis has been shown to affect systemic health in multiple studies and has been independently associated with increased risk of most chronic NCDs such as cardiovascular diseases, diabetes, hypertension, chronic renal disease, pneumonia and cancer. Takahashi et al suggested that aspiration of periodontopathic bacteria might aggravate COVID-19 by inducing the expression of angiotensin-converting enzyme 2, a receptor for SARS-CoV-2, and inflammatory cytokines in the lower respiratory tract [21]. Also, it was suggested that periodontopathic bacteria might enhance SARS-CoV-2 virulence by cleaving its S glycoproteins that the oral cavity, and especially periodontal pockets could act as a viral reservoir. Gupta et al indicated that Neutrophil

Extracellular Trap production is involved in the pathogenesis of both diseases al suggested that the strong Th17 response in severe periodontitis could exacerbate the cytokine storm in COVID-19 [22].

All these hypothetical pathways could also foresee an increased incidence of periodontal lesions, especially necrotizing periodontal disease (NPD) during this pandemic. Successful treatment of periodontitis has been shown to improve serum markers of systemic inflammation (C-reactive protein, IL-6) as well as systemic metabolic control. In consideration of people in areas of the world where specific mouthwashes may not be available or affordable, there may be even simpler measures to consider. A recent study reported that saltwater rinsing can reduce gingival inflammation, and even mouth rinsing with boiled water (which has been allowed to cool) has shown positive effects on plaque and oral mucosa in hospitalized elderly patients [23]. This suggests that simple measures can help decrease the salivary viral load in areas of the world where mouthwash products are not readily available. It is sincerely hoped that, if proven correct, this concept provides a rationale for the use of oral healthcare measures which are cheap (or even free) and are available worldwide, and that these measures may help prevent the development of lung disease, mitigate deterioration to severe COVID-19, and reduce mortality.

Conclusion

In summary, we conclude that coronavirus has unique and complete components. Its immune-evasion components that contribute to evade from recognition of the immune system lead infectivity and fatality to host. It is now well-known that the pathogenesis of disease-induced coronaviruses, the development of therapy will be more specific. For example, the development of serine protease inhibitor or RBD based vaccine also became coronavirus therapy approach. However, further research is necessary to develop these findings for clinical application in patients.

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