REVIEW

Periodontal Disease as a factor in morbidity of Covid-19: A Review.

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Abstract

Background: Covid-19 is a worldwide pandemic causing considerable morbidity and mortality. Many studies have shown the influence of periodontal health on systemic disease.

Aims: This article explores the association between periodontal disease (PD), oral dysbiosis and cytokine storm requiring protocol of maintainence of oral hygiene in covid patients and also in healthy individuals during the pandemic. Covid patients need to be motivated to maintain proper oral hygiene measures to avoid risk of Covid related adverse outcomes.

Methods: Data was collected and analyzed from recently published literature and electronic database searches of PubMed and Google Scholar.

Results: Covid-19 leads to increased release of cytokines from host cells termed as cytokine storm, many of the components of which are common with the cytokine expression profile of periodontitis. It has been shown that periodontitis was significantly associated with increased risk of complications from the Covid-19 including ICU admission, need for assisted ventilation and death.

Conclusion: Plaque control is important to prevent exchange of microorganisms between the oral cavity and the lungs and to reduce the chances of worsening respiratory disease during Covid-19 infection. Understanding this association may definitely help to identify individuals at high risk and deliver appropriate care at early stages.

Keywords: Covid-19, Periodontal, cytokine storm, virus, stress, plaque, respiratory.

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Introduction

Covid-19 disease, the virus of which is called SARS-CoV-2 is a dangerously spreading and continuously evolving disease all over the world. Reports of the first Covid-19 cases started in the Wuhan city of China in December 2019. Later it developed into a global threat and the outbreak was deemed a pandemic by the World Health Organization on March 11, 2020. The initial cluster of infections is reported to have originated in a seafood and wildlife market in Wuhan, where the sale of wild animals could have been the source of zoonotic infection. Bats are considered likely reservoir hosts for SARS-CoV-2. Pangolins were considered as the intermediate hosts between bats and humans because of the similar resemblance of the pangolin coronavirus to SARS- CoV-2. Initially it was named 2019 novel coronavirus (2019-nCoV) and later changed to the now officially known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV-2). [1]

SARS-CoV-2 is a single stranded RNA virus. It expresses a spike protein (S-protein) that mediates adhesion to and invasion of host cells.[2] The SARS-CoV-2 S-protein binds specifically to angiotensin-converting enzyme 2 (ACE-2) which is expressed in the lungs, kidneys and on myocardial cells. ACE-2 is also found intra-orally, especially on salivary glands and the tongue.[3] The common clinical symptoms are fever, headache, sore throat, anosmia, dysgeusia/ageusia cases and nearly dry cough, abdominal pain, vomiting, diarrhoea. These symptoms can be mildly or strongly felt in most and nearly 4% of confirmed cases develop into severe medical conditions requiring hospitalization including oxygen support, 5% of patients need intensive care units admission and around 2% mortality is exhibited (NCPERE, 2020).[4,5] Severe cases tend to get complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, leading to multi-organ damage. Patients with severe Covid-19 and ARDS usually shows exacerbated immune response which are usually characterized by excessive levels of pro-inflammatory cytokines leading to widespread tissue destruction which may be described as the cytokine storm syndrome. In fact, Covid-19 mortality has been linked with elevated serum levels of interleukin-6 (IL-6), C Reactive Protein (CRP), D-dimer and ferritin suggesting a clear association between sever-

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ity of the disease and a virally driven non-resolving hyperinflammation.[6]

ORAL MANIFESTATIONS OF COVID -19

Earlier, it was reported that Covid-19 affects respiratory, gastrointestinal and neurological systems, but further research showed that oral, olfactory and integumentary systems are also involved. In the oral cavity mucosal lesions, taste changes and gingivitis have been reported. Oral mucosal lesions reported in Covid-19 include ulcers, erosions, blisters, plaque-like lesions, reactivation of herpes simplex virus 1(HSV1), and geographical tongue with depapillation.

Oral mucosal lesions tend to disappear (6 days–2 weeks) or reduce in size with time. Oral lesions can be a preliminary sign of Covid-19 infection or a warning sign of peripheral thrombosis. Ulcers, erosions and blood crust on labial mucosa along with palatal and gingival petechiae have also been reported. Angina bullosa are blood filled blisters are observed on soft palate, tongue and cheek. They are brown–black single or multiple lesions and may appear after initiation of therapies for Covid-19. Aphthous-like lesions appeared as multiple shallow ulcers with erythematous halos and yellow-white pseudomembranes on the both keratinized and nonkeratinized mucosal tissue. The most common sites of oral involvement include tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%). Oral lesions were nearly equal in both the genders (49% female, 51% male). Latency time between appearance of systemic symptoms and oral lesions was between 4 days before up to 12 weeks. After the onset of systemic symptoms, the persistence of oral lesions can be between 4 days upto 12 weeks. Kawasaki-like lesions showed the longest latency period. Gingival involvement have also been reported which includes generalized erythema and edema of gingiva, gingival bleeding, necrotic interdental papillae and desquamative gingivitis. They are seen in critically ill patients with neglected oral hygiene. Candidal plaque-like lesions and dry mouth are also observed in association with Covid-19. Both red and white plaques were observed which got located on the dorsum of the tongue and palate. The major symptoms of Covid-19 include halitosis, pain and swelling on the tongue and masticatory muscles, macroglossia, geographical tongue, papillary hyperplasia associated with taste changes and fatigue have also been reported.[4,5]

The Association Between Periodontal Disease And Covid-19

Periodontal Disease (PD) is a multifactorial disease leading to destruction of supporting structures of the tooth.[3] The risk of Covid-19 complications was significantly higher among patients with moderate-to-severe periodontitis compared to those with milder or no periodontitis.[6] The relationship between PD and severe Covid-19 illnesses could be because of shared co-morbidities, genetic and environmental risk factors and also through common chronic inflammatory pathways.[7,8] Alteration of cytokine profiles could be part of the potential mechanism responsible for the association between periodontal disease and Covid-19.[3] Taking oral medical history of PD could be a characteristic feature to identify a risk group to severe Covid-19.

A. Shared co-morbidities and risk factors between PD and Covid-19

Most co-morbidities and risk factors reported in patients with severe Covid-19 also aggravate the development of gum disease. The shared risk factors by PD and Covid-19 are co-morbidities like diabetes mellitus, hypertension and cardiovascular disease, pregnancy, obesity, HIV, cancer, rheumatoid arthritis, liver disease and patient status like age, pernicious habits of smoking, use of drugs/antibiotics for Covid-19 or infections, can reduce immune status of patient and prognosis and increase the mortality. And can aggravate Covid-19 re-infection and treatment outcomes.[9]

Stress

Psychological stress leads to cytokine release and may account for the cytokine storm in few cases of the pandemic. Stress leads to activation of the "stress system" called the hypothalamic–pituitary–adrenal axis (HPA). As a response to stress, the hypothalamus secretes corticotrophin-releasing hormone, which acts on the pituitary gland facilitating the release of adrenocorticotrophic hormone. In turn, adrenocorticotrophic hormone stimulates the adrenal cortex to secrete cortisol in the blood leading to impaired immune defense mechanisms. Release of pro-inflammatory cytokines and neuropeptides may result in numerous neurological manifestations including psychological disorders, anxiety, depression, and post-traumatic stress disorder.[10] Both the central and peripheral nervous system get affected in virus infected patients.[11] The neurological effects of Covid-19 include headache, encephalitis, encephalopathy, myelitis, seizures, stroke, loss of smell and taste and Guillain–Barré syndrome. A recent systematic review concluded that the pandemic has had a significant impact on physical and mental health. Thus, it is advisable to administer psychological interventions as part of Covid-19 treatment.[12]

Research shows that a positive correlation between stress and increased risk of periodontal disease. Stress increases the salivary cortisol levels, which in turn reduces immune responses and upregulates various inflammatory markers, leading to gingivitis and periodontal tissue damage.[13] Periodontal therapy can play a vital role in preventing tissue damage and thereby inhibit the release of inflammatory mediators. Anti-cytokine inhibitors like tocilizumab used in Covid-19 treatment may have anti-depressant effects that could be useful in reversing the psychological symptoms of stress.[14]

Respiratory diseases:

Periodontal disease has been proved to have systemic link. In respiratory diseases, plausible linking mechanisms include: (i) direct aspiration of oral microorganisms into the lungs, (ii) alteration of mucous surfaces within the respiratory tract, favoring adhesion and invasion of pathogens; (iii) hydrolytic enzymes secreted by periodontal pathogens inhibiting innate immune responses by degrading cytokines and other inflammatory mediators released from periodontal tissues, altering the respiratory epithelium and resulting in enhanced adhesion of pathogens.[15]

Scannapieco et al. in his systematic review suggested a significant association between compromised oral hygiene and nosocomial pneumonia.[16] Azarpazhooh et al suggested that antimicrobial oral hygiene measures could minimize the incidence of respiratory disease in elderly adults.[8] Another study by Deepak et al showed positive relationship between periodontal disease and respiratory diseases.[17]

Consequently, the infectious and inflammatory links between respiratory illness like COPD and asthma and periodontitis could also represent potential factors related with exacerbation of coronavirus disease 2019 (Covid-19) respiratory distress.[3]

It was suggested that patients with Covid-19 with COPD have an increased risk of aggravation and patients with pre-existing COPD have a 4-fold increased risk to develop severe Covid-19 illness. It was explained that the increased risk could partly be because COPD

patients exhibit increased expression of ACE-2 in airways. Increased expression of ACE-2 and TMPRSS2 in asthmatic patients could indicate increased susceptibility for SARS-CoV-2 infection and Covid-19 morbidity.[9]

Superinfections:

It has also been suggested that bacterial and fungal superinfections may be widespread in severe cases of Covid-19 and these infections could supersede the original viral infection. Bacterial agents like Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Enterobacter species, Staphylococci, Escherichia coli and Enterococcus species were documented to cause bacterimia and ventilator associated pneumonia (VAP) in Covid-19 patients. The most common fungal agents to cause VAP/ secondary pneumonia and urinary tract infections are Mucorale species, Aspergillus flavus, Aspergillus fumigatus, Candida albicans, and Candida glabrata.[18,19] It was found that 50% of patient mortality occurred from secondary bacterial infections rather than from viral infection. Patients with comorbidities such as diabetes, hypertension, COPD, cardiovascular and cerebrovascular disease were at increased risk of post-viral complications and death from Covid-19.[3]

B. Periodontopathogens, ACE inhibitors and periodontal pockets as viral reservoirs

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.[20] Also, it was suggested that periodontopathic bacteria might enhance SARS CoV-2 virulence by cleaving its S glycoproteins.[6] The ACE2 expression in the minor salivary glands is higher compared with the lungs. Thus, the salivary glands could act as a potential reservoir for SARS-CoV-2.[3] To et al. reported that live virus could be cultivated using saliva samples from patients infected with Covid-19.[21] ACE2 is expressed at various sites like nasopharyngeal region, the oral epithelial cells of the tongue, buccal mucosa, gingival tissues, periodontal pockets, and gingival crevices. Oral epithelial cells show higher expression of ACE2 and transmembrane protease serin 2 (TMPRSS2) Trypsin like proteases such as TMPRSS2 are required to activate the SARS-CoV-2 S-protein to bind host cells.[22,23] Though these proteases were expressed in the oral cavity, periodontal pathogens can also produce such proteases that may help in activating the S-protein which would further increase the SARS-CoV-2 infectivity.[20]

The oral cavity including the periodontal pockets could act as a viral reservoir.[6] Periodontal pockets prove to be favourable environments for replication of pathogenic viruses like human herpes simplex virus and human papillomavirus.[24] The virus may get into the systemic circulation from periodontal pockets via GCF and then mix with saliva, or may enter the systemic circulation via periodontal capillaries. Periodontium associated viruses can also infect the immune cells that continuously infiltrate the periodontal pocket.[25]

In a recent study, Gupta et al assessed the presence of SARS-CoV-2 in GCF samples of Covid-19 patients. Virus got detected only in asymptomatic carriers and patients with mild symptoms, whereas individuals with compromised oral hygiene had elevated levels of inflammatory exudate. The authors concluded that periodontal pockets may play a role to aid in virus replication. As the viral load in GCF increases, the virus gains entry via saliva to the systemic circulation. Therefore, GCF may represent a potential mode of transmission.[26]

Drugs administered to treat the SARS-CoV-2 virus, lack of oral hygiene, and other co-morbidities may produce dysbiosis of the oral microorganisms triggering periodontal disease. It has been shown that patients with severe Covid-19 manifestations have reported the emergence of microorganisms which are associated with periodontal disease. Researchers suggest that the virus recognizes the ACE-2 receptors not only in the nasopharynx but in oral mucosa too. The entry of the virus can disrupt the immune system including the oral microbiota of the host triggering a dysbiosis leading to superinfection.[9]

C. Cytokine storm and inflammatory mediators of PD in Covid-19

Most SARS-CoV-2-infected individuals remain asymptomatic although a few develop mild to moderate symptoms. Very few (Less than 5%) individuals develop serious symptoms like acute respiratory distress syndrome (ARDS) and multiple organ failure requiring ICU support. Viral replication in host cells leads to activation of the NLRP3 inflammasome. This results in release of pro-inflammatory cytokines. This inflammatory response is further upregulated by the release of damage associated molecular patterns (DAMPs) following cell death. Hyper-responsive hosts present with exaggerated cytokine release, referred to as a cytokine storm or cytokine release syndrome.[27,28] In the early stages of viral infection, the virus penetrates into the epithelial layer leading to activation of innate immune responses. On entering the tissues, it infects the macrophages, dendritic cells and neutrophils and further enhances viral spread. The virus activates adaptive immune responses which results in enhanced cytokine release and leading to differentiation of naive T cells. Increased vascular permeability also plays a vital role in the cytokine storm, permitting the infiltration of effector cells and thereby intensifying proinflammatory cytokine release.[29]

Hypercytokinemia, a common consequence of this pandemic causes acute lung injury, followed by ARDS as its severe form, in a large proportion of patients affected. Local inflammation can spread to the systemic circulation leading to sepsis, thrombocytopenia, leukopenia, and hyperthermia. Elevated cytokine production increases the systemic levels of C-reactive protein (CRP), haptoglobin, fibrinogen, serum amyloid A, and α1-antitrypsin. This leads to enhanced vascular permeability, altered coagulation mechanisms and improved complement activation. Cytokine production can induce increased proliferation of monocytes/macrophages and excessive apoptosis of lymphocytes, leading to immunodeficiency.

Studies have shown that serum pro-inflammatory cytokine levels in patients infected with SARS-CoV-2 were also elevated, especially IFN-γ, IFN-γ-induced protein 10, IL-1β, IL-6, IL-12, and monocyte chemoattractant protein (MCP-1).[3]

Sahni et al suggested that the strong Th17 response in severe periodontitis may exacerbate the cytokine storm in Covid-19.[30] It exhibits itself as elevated serum levels of IL-1 beta, IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, GM-CSF, G-CSF, IFN-gamma, TNF alpha, MIP1A, MIP1B, MCP1 and IP10. Patients exhibiting with an exaggerated form of symptoms necessitating ICU admission further show even greater levels of IL-2, IL-7, IL-10, IP-10, G-CSF, MIP1A, MCP1 and TNF alpha. Elevated Th17 pathway responses have also been observed in patients of SARS-CoV and MERS-CoV. Th17 type of inflammatory response is involved in the manifestation of the cytokine storm and adverse outcomes leading to pulmonary oedema and tissue damage in lung infections including that caused by SARS-CoV-2.[31] All these hypothetical pathways could also foresee an increased incidence of periodontal lesions, especially necrotizing periodontal

disease (NPD) during this pandemic times.[32]

Two possible mechanisms which could explain the association between periodontitis and the Covid-19 disease are: (1) the direct contact of virus with the periodontal tissues, also due to the high expression of ACEII and CD147and/or (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.[31,33]

Marouf et al in his study showed that fatal Covid-19 outcomes were significantly related with elevated blood concentrations of D-dimer, WBC and CRP, and lower concentrations of lymphocytes.[6] Patients admitted to the ICU and those requiring assisted ventilation presented with high blood levels of CRP and D-dimer. These results are in accordance with previous studies reporting elevated inflammatory indicators in deceased Covid-19 patients.[34] Interestingly, here the Covid-19 cases with periodontitis also had significantly higher WBC and CRP serum levels than those without periodontitis, which may indicate a possible link of this association through systemic inflammation. Successful treatment of periodontal disease has been shown to improve serum markers of systemic inflammation (CRP, IL-6) as well as systemic metabolic control.[35,36]

Periodontitis and poor oral hygiene disrupt the symbiotic relationships between oral microorganisms and can enhance the pro-inflammatory cytokine release. Bacteria in dysbiotic biofilms further promote cytokine release; these cytokines in GCF mix with saliva. Upon aspiration, it may induce inflammation or infection within the lungs. Interbacterial exchange between the lungs and the oral cavity potentially increases the risk of respiratory infections.[3]

Gupta et al in his study indicated that Neutrophil Extracellular Trap production is involved in the pathogenesis of both these diseases.[37] High neutrophil counts and lower lymphocyte counts have been seen in patients with severe forms of the disease compared to mild forms. Increased neutrophil counts are usually associated with bacterial infections but more rarely observed in viral infections.[3]

CONTROL OF CYTOKINE LEVELS BY EFFECTIVE MAINTENANCE OF PERIODONTAL HEALTH

Pre-procedural use of mouthwash and nasal spray by patients with confirmed or suspected Covid-19 as well as healthcare workers pre- and post-treatment have proved to minimize the risk of disease transmission.[38]

It has been shown that povidone iodine gargling solutions were effective against SARS-CoV and MERS-CoV, but the effectiveness of pre-procedural rinses against SARS-CoV-2 remains unclear and needs further investigations.[39] Oral rinses prove to be effective in altering the viral lipid envelope so that it helps to reduce the disease transmission and viral load. It has been recommended by the American Dental Association that usage of 0.2% to 0.5% povidone solutions or 1% hydrogen peroxide helps to reduce the viral transmission. In hospitalized patients, oral hygiene measures to reduce the plaque build-up can minimize the bacterial load, prevent aspiration of oral pathogens, and minimize the risk of pneumonia or respiratory illness.[3]

Larvin et al reported that a higher risk of mortality was recorded in Covid-19 individuals with bleeding gums and concluded that mortality risk was higher in patients with periodontal disease. So it was most important to assess oral health status in patients with Covid-19 to prevent adverse outcomes.[40]

The throat is a crucial site for viral replication during the initial stages of infection. It was observed in studies that during the first week of infection, oropharyngeal swabs of patients infected with SARS-CoV-2 had high concentrations of viral RNAs, indicating active replication that reached the peak values around day 4 post-infection.[41]

Upon viral infection and replication, ACE2 (primary receptor for SARS-CoV-2) expression is downregulated, resulting in an acute inflammatory response. ACE2 helps in balancing the cytokine levels; higher levels of ACE2 downregulate the proinflammatory cytokines. However, higher levels of ACE2 help the entry of SARS-CoV-2 virus into the oral cavity. The ACE2-SARS-CoV-2 complex reduces ACE2 expression on the cell surface and this results in enhanced production of cytokines. Administration of ACE inhibitors may increase the ACE2 levels and increase the anti-inflammatory response. Combinations of periodontal therapy and ACE inhibitors may reduce the progression of periodontal disease and may minimize the risk of adverse Covid-19 outcomes.[3]

Recent studies indicate that the periodontal pocket epithelium may be a focal point of infection for SARS-CoV-2 and thus periodontal therapy would help to minimize the systemic spread of viral pathogens. Thus, non-surgical periodontal therapy along with treatment using anti-cytokine inhibitors may have beneficial effects in patients with SARS-CoV-2 infection. Treatment with the IL-6 antagonist Tocilizumab during the initial stages of Covid-19 has shown beneficial effects. Early detection and treatment of periodontal disease, as well as identification of hyper-responsive individuals through cytokine profiling, may prove to be useful in selection of appropriate anti-cytokine drugs. Though promising outcomes have been reported following treatment of patients with Covid-19 with immunomodulators, further clinical trials are needed to understand the efficacy and safety of these drugs according to disease stage and severity.[3,25,26,42]

Conclusion

Current evidences suggest that increased production of pro-inflammatory cytokines is the important cause of the adverse events related to Covid-19. Periodontal disease could further increase the cytokine release via altered microflora, expression of multiple viral receptors, bacterial superinfection, and aspiration of periodontal microorganisms. Though SARS-CoV-2 infects cells only through ACE2 receptors, the mechanisms through which virions bring about the deleterious effects in the central nervous system remain unclear. The association between Covid-19, stress and periodontitis could be influenced by altered cytokine responses following viral replication. More clinical trials evaluating periodontal status in patients with Covid-19 are needed to assess the clear mechanisms. As compromised oral hygiene could exaggerate SARS-CoV-2 infection, it is essential to maintain good oral hygiene and periodontal health to preserve overall health.

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