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“Cytokine Storm”: The Systemic Link between Periodontal Disease and Corona Virus Pandemic



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ABSTRACT

Since last three years the people have been suffering from the pandemic of Covid 19 viral infection across the world. Corona virus, a member of the Coronaviridae family, is related to severe acute respiratory syndrome. This disease is associated with hyper inflammation causing exaggerated immune response, with the excessive levels of pro-inflammatory cytokines and widespread tissue damage. Nasopharyngeal complex, oral cavity and periodontal pockets can harbor the virus. Periodontitis is also a chronic inflammatory condition which can also cause systemic inflammation by release of cytokines. Hence it has been suggested that presence of periodontitis in Covid patients can aggravate the situation by facilitating hyper inflammation and resulting in complications.



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INTRODUCTION:

Since its outbreak in China in December 2019, the entire world had suffered from Corona virus disease in the last three years causing death of millions and millions of people and global lockdown. World Health Organization had declared this as a pandemic (1) in March 11, 2020. The mortality rate of the disease is low (2), but it seriously affected the aged individuals (3) and the patients with comorbidity, with urgent need for hospitalization, ICU admission and ventilation. This is because that any kind of chronic inflammatory disease can cause cytokine storm (4) inside the body causing exaggerated symptoms like respiratory failure, cardiac failure leading to multi organ failure and death. Many researchers have suggested that Periodontitis which is also a chronic inflammatory disease can contribute to the exaggeration of Corona virus infection.

Entry of virus in the oral cavity:

The receptors (5) that are responsible for the entry of virus in oral cavity are the Angiotensin Converting Enzyme receptors II, (6) the Transmembrane protease serine receptors, and the Furin receptors. They are present in taste bud, dorsum of tongue, salivary gland, nasopharynx etc. Thus, the initial symptoms of the disease are loss of taste sensation, xerostomia, anosmia (7), etc. The receptors are also present in different organs of the body, primarily in the lungs, heart, GI systems, which explains the other exaggerated symptoms of the disease like diarrhea, respiratory distress, cardiac failure and even death. The receptors combine with the receptor binding zone of the spike protein of the virus. Virus on entering the cell causes pyrolysis which triggers inflammatory responses.

The cytokines storm: Periodontitis which is a chronic inflammatory disease cause release of cytokines like interleukin, tumor necrosis factor etc. The corona virus disease also causes release of cytokines which leads to exacerbation of the symptoms (8,9). One of the target site of corona virus is respiratory epithelium and exacerbation of symptoms leads to respiratory distress and pneumonia which ultimately leads to cardiac failure (10). Therefore, the virus is also known as SARS COV or the severe acute respiratory syndrome virus.

The cytokine link Pathways:

(i) Inflammasome (Component of innate immune system) is triggered by both the corona virus and periodontal infection. Inflammasome (12) is a group of intracellular multimeric protein complexes that is expressed by myeloid cells which form the first line of host defense

like neutrophils, macrophages, dendritic cells etc. It is stimulated in bacterial, viral infection by (11) specific PAMP (Pathogen associated molecular pattern) or DAMP (Damage associated molecular pattern). NLRP3 (12,21) (a protein encoded by NLRP3 gene) is one of the components of the PRR (Pattern recognition receptors) of the Inflammasome which when gets stimulated and activates caspase 1 enzyme, which triggers the release of pro inflammatory cytokines, particularly interleukins like IL-1B, IL-18 that mediate the inflammation and also induces pro-inflammatory form of cell death called pyroptosis.

(ii)IL-17and TH-17 mediated pathways: Elevated levels of cytokines IL-1, IL-10, IL17 (in Covid 19 (13,14), chronic periodontitis and aggressive periodontitis) stimulates TH-17 innate immune response which leads to Cytokine storm and resultant tissue damage.

(iii)Role of Interleukin-6: Covid infection induces thousand times increase in the release of interleukin-6 (15). Similarly, periodontitis also causes the release Interleukin 6 which in turn causes production of B lymphocytes and myeloid cell differentiation which leads to release of cytokines. So, if both Covid infection and periodontitis coexist, the resultant effect will be cytokine storm (16,17) in the body that ultimately results in tissue damage.

(iv)The neutrophil extracellular trap mechanism is found in several viral and bacterial infection including both covid 19 and chronic periodontitis (18). It causes host cellular damage by autoimmune mechanism. This causes release of cytokines and host tissue damage.

Neutrophils form the first line of defence mechanism of the body (19,20). In addition to phagocytosis, generation of ROS (Reactive oxygen species) they also show formation of Neutrophil extracellular trap, a process referred to as NETosis. In this process nuclear and granular material is disintegrated, chromatin is decondensed, which is later diffused in the cytoplasm. The cytoplasmic membrane ruptures with release of chromatin in extracellular space which entangles virus, bacteria, etc. The chromatin fibres contain DNA and histones like H1, H2B, H3, H4. DNA fibres contain Neutrophil elastase, myeloperoxidase, cathepsin G, proteinase3 which initiates proinflammatory response.

The periodontopathogens particularly the *P. gingivalis* can be found in the epithelial cells of lungs. These periodontopathogens which are present in the gingival sulcus (23) and oral cavity can be aspirated in the lungs through the upper respiratory tract particularly in ventilated patients (22). These periodontopathogens cause damage of the respiratory epithelium facilitating the activity of the corona virus.

DISCUSSION:

Like many other systemic diseases like diabetes, coronary heart disease, respiratory disease, periodontitis is also linked with corona virus disease through cytokine mediated pathways. Research suggests that development of corona virus infection in periodontal patients can lead to exacerbation of symptoms like respiratory distress requiring hospitalisation, assisted ventilation due to development of cytokine storm (24). There is systemic hyper inflammation, dysregulated inflammation leading to engraved situation and even death. Thus, the medical practitioners and the dental surgeons should be aware of the importance of maintaining proper oral hygiene in covid patients especially for the hospitalised patients. If proper brushing and oral prophylaxis is not possible in these patients, care of should be taken with the help of mouth rinse like 0.2 % povidone iodine (25) or 0.12 % chlorhexidine (26).

CONCLUSION:

The current topic is utmost important because we have to understand the fact that uncontrolled release of cytokines and persistence of inflammation can cause life threatening effects. These effects are not only caused at the time of the disease but it has probable long term side effects also. There can be vascular disorders leading to pulmonary embolism, cardiac arrest leading to death, muscle and joint weakness and neurological disorders. These are collectively grouped as Multisystem inflammatory syndrome affecting important organs like heart, kidney and brain. Good oral hygiene and periodontal health should be maintained during and after covid infection in order to preserve good systemic health.

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