

Short Communication

Chronic-periodontitis: could it be a connived-culprit of COVID-19?

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ABSTRACT

Periodontitis is a multi-factorial disease resulting in the disruption of the attachment apparatus. COVID-19 has been alarming to many nations despite consistent efforts. Research has been continuously going on to curb the spread of the disease by gaining knowledge on the insights of the pathology of the disease. The current exploratory research establishes a correlation between periodontitis and COVID-19 and the impact of periodontal health in COVID affected patients. A search was performed using three data bases, PubMed, Scopus and Google Scholar published from 2019 to 2020. The keywords used for the search were COVID-19, and pathogenesis of periodontitis. The results of the search resulted in many reviews, original research, systematic reviews, case reports, etc. The critical selection of the articles especially systematic reviews was given utmost importance. Much less research has been done on the correlation of periodontitis to COVID-19. On the basis of search using the above mentioned keywords, a total of 26 articles were selected out of which only 21 articles were considered for the present exploratory review. The present review provides an insight into the pathogenic aspects of both periodontitis and COVID-19 and helps in establishing an ally which has been minimally explored to date. The pathogenesis of COVID shows a close similarity to periodontitis and henceforth a possible connection of the severity of COVID in patients suffering with chronic periodontitis. Periodontitis presents itself as a risk factor for many systemic diseases, and nevertheless, it has shown a possible similarity in the pathophysiology of COVID-19.

Keywords: Angiotensin converting enzyme receptor, Corona virus, Cytokines, Periodontitis, Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

A conspiring commonality exists between periodontitis and corona virus disease (COVID-19) sharing cytokine pathology. COVID is life threatening with preexisting comorbidities, like diabetes, hypertension, asthma, myocardial dysfunction, etc. Periodontitis plays covertly alongside general risk factors for COVID. Documented literature suggests an inviolable relationship with diabetes and periodontitis.¹ Similarly, COVID-19 also is messing up the mortality rates especially in medically-compromised diabetic-patients. Periodontal medicine deals with the concept of “focal infection theory” relating the disease to cardiovascular conditions.² Scannapieco

suggest periodontal disease as a risk factor for respiratory diseases.³ This potential severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) gains entry into host cells with angiotensin-converting enzyme receptor-2 (ACE-2), distributed greatly in lungs proceeding to respiratory failure at the terminal-stage of the disease. The science of COVID-19 is rapidly evolving, nonetheless the pathophysiology presents with numerous questionable mechanisms. Among them is “cytokine storm” or “macrophage activated syndrome” which is leading to death of patients.⁴ Auto-amplifying cascades of cytokines like interleukines viz. IL-1 β , IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor

(G-CSF), interferon gamma (IFN- γ), tumour necrosis factor alpha (TNF- α), macrophage inflammatory proteins viz. MIP1A and MIP1B, macrophage chemotactic protein-1 (MCP1) and inducible protein-10 (IP10) has been observed in intensive care unit (ICU) admitted patients with severe lung damage.⁵ Periodontitis also manifests due to increase in inflammatory cytokines.⁶ Neutrophil extracellular trap (NET) production is an auto-immune form of cell death common for both COVID and periodontitis.⁷

Maintenance of periodontium is crucial as it is a tranquil risk factor and could accentuate the damage caused by COVID-19. The rationale for the review is that periodontitis with its pathogenic correlation to COVID-19 and that the oral cavity being the main route of transmission of the virus would result in increasing the risk of a periodontitis patient to the SARS-CoV-2 destruction pattern of the body.

METHODS

A literature search has been performed using three different databases, PubMed, Scopus, Google Scholar for articles published from 2019 to 2020. A very minimal research has been done in correlation with the two diseases. Analyses of the articles to be selected was done based on titles and abstracts in the first search. To avoid missing of the data related to the study, articles in the references of the selected articles were further scrutinized. Duplicate articles, cross referenced articles and articles with only abstracts were removed and only full text articles were given the priority for selection and quantitative synthesis was carried out. The keywords for the study were: angiotensin converting enzyme receptor (ACE-2), corona virus, cytokines, periodontitis, and SARS-CoV-2." The inclusion criteria for the selection of the articles such as reviews, original research, systematic reviews and papers only in English language were included with no sample size restrictions whilst exclusion criteria were conference abstracts, case studies, and unpublished data.

RESULTS

A total of fifty-two article abstracts were initially screened. These fifty-two articles were selected through databases to exclude irrelevant articles. A total of twenty-six articles were left. Three studies were rejected as they were case reports. One was unpublished data and one was in a different language other than English. Finally, only twenty-one papers fulfilled the inclusion criteria were included for the writing this systematic review. All the articles selected were written in English. Very limited research was obtained correlating the periodontitis and COVID-19.

DISCUSSION

Minimal exploration relating periodontitis with COVID-19 has been seen in literature to date. In view of the

pathogenesis of periodontitis which clearly has a two-way link with diabetes mellitus, henceforth even diabetic patients are the main culprits of COVID.¹ The play of cytokine storm in severely-ill corona virus disease patients drives to the correlation of this deadly disease with chronic periodontitis which also relies on involvement of cytokines in its pathogenesis. A brief discussion on the three diseases and their interplay is given.

Pathology of COVID-19

The world has been witnessing never before sequences of health disaster after 1918 Spanish flu pandemic. COVID-19 started off in late December 2019 as a cluster of pneumonia cases in Wuhan Hubei province of China and then travelled across the globe affecting millions with considerable numbers of deaths. On 11 February 2020, WHO named it as COVID-19 for corona virus disease as started in 2019, in its situation report.⁸

The pandemic is still shivering mankind ruining economies of many developing countries. Corona virus is made up of structural proteins and nonstructural proteins. Structural proteins include spike protein (S), envelope protein (E), matrix protein (M) and nucleocapsid protein (N). Spike protein plays a pivotal role in the pathogenesis of the virus.⁹

Corona virus with its "trimeric congregation on its cell surface", gains entry into target cell with the help of its spike protein. Spike protein is made up of S1 and S2 domains.¹⁰ A receptor binding domain (RBD) on S1 is exposed and attaches to a receptor like ACE-2 resulting in conformational changes. Now, S2 promotes in syncytium by membrane fusion of virus and host along with release of proteases resulting in ingress of viral genome into host cell and succeeded by replication of viral genome and formation of numerous virions. This whole process of Spike protein is further aggravated by release of transmembrane protease serine-2 (TMPRSS-2). ACE-2 receptors which are present through-out the body are mainly present in lungs, making lung as a highly susceptible organ for COVID and significant counts of morbidity is through pulmonary failure.¹¹ As with any foreign agent, the initial stimulus for the virus is stimulation of immune cells and release of pro-inflammatory cytokines like CL8, CXCL10, C3a, C5a IL-1 β , IL-6, IL-8, TNF- α , and IFN- γ causing damage in the lower respiratory tract. Cytokine storm which is the auto-amplifying cascades of inflammatory cytokines suppress the host innate and adaptive immune response thereby causing pulmonary fibrosis.^{12,13}

Depletion of T-cell subsets and exhaustion of CD-8 lymphocytes increase lung damage. Apoptosis of epithelial and endothelial cells has been observed with vascular damage and intravascular coagulation leading to alveolar damage, pulmonary edema, pleural effusion and focal hemorrhages. Multi-organ failure along with severe lung damage is the main reasons for death of patients.^{14,15}

Pathology of periodontitis

Periodontal disease presents itself as loss of alveolar bone being the important entity ultimately leading to loss of tooth. However, the entire phenomenon pertaining to the pathogenesis results due to a disturbance in host equilibrium progressing to disease. Understanding the role of host response plays a crucial role in periodontitis. Cytokine pathology presents an overwhelming response towards destruction of periodontal attachment apparatus along with destruction of alveolar bone. Evidence from research in non-primate humans suggest an invasive role of IL-1 and TNF- α on alveolar bone which when treated with their corresponding inhibitors showed a decrease in resorption of alveolar bone and progression of attachment loss.¹⁶ Prostaglandin E2 (PGE-2) plays a critical role in periodontal bone loss. IL-6 and IFN- γ also are associated with bone loss.¹⁷ Henceforth, disturbance in host immune equilibrium with release of excessive chemokines, cytokines thus stimulating release of pro inflammatory molecules aggravating self-destruction is the key for pathology behind periodontal disease. Lymphocytes are the most important immune cells which are responsible for the release of inflammatory cytokines like IL-1, IL-6, IL-11 etc. Bone resorptive factors like receptor activator of nuclear kappa b ligand (RANKL) bind with RANK promoting osteoclastogenesis. Osteoprotegerin (OPG) in turn binds with RANKL as a protective action on bone. Coupling of bone which is essential for maintenance of bone homeostasis with formation of new bone by stimulating osteoblasts is disturbed. Uncoupling of bone results with predominance of osteoclasts. Adaptive immune response by CD4⁺T lymphocytes and pro-inflammatory cytokines show a crucial role in attachment and bone loss.⁶

Association of COVID-19 and periodontitis

The dreadful flu-like disease devastating the mankind is the COVID-19 which is thought to spread through droplets either by coughing and sneezing. ACE-2 receptors are present throughout the body and are mostly concentrated in the lungs. Salivary glands also are supposed to carry ACE-2 receptors as numerous as lungs and henceforth saliva also lodges SARS-CoV-2.¹⁸ Periodontal pocket lodges numerous micro-organisms and is in continuous contact with the flow of saliva.^{19,20} The result could be SARS-CoV-2 in close proximity to the pocket epithelium. Epithelial gaps and stimulation of immune response could begin in response to the virus like any foreign agent. The cytokine pathology happens to be common not denying the fact of the exaggerated immune responses for both the diseases. Release of pro-inflammatory cytokines and innate and adaptive immune pathologies point out to be associated with both the diseases. The severity of COVID-19 mortalities is more especially in medically compromised people. Diabetes, hypertension, lung pathology, etc. are known risk factors for COVID-19. Periodontitis association with diabetes mellitus has been authenticated along with its association of cardiovascular

and respiratory diseases.²¹ Thus; chronic periodontitis also presents itself as a silent risk factor for COVID-19 disease which has to be yet elucidated with confirmatory evidence based research.

CONCLUSION

Amid the shivering pandemic and its consequences with yet to develop treatment modalities, every speck of data and thoughts play a decisive role. Considering the familiar immune responses and risk factors associated with both the diseases, Periodontitis role as a risk factor for COVID-19 should not be denied. Oral health is as important as general health and henceforth oral awareness programmes should be encouraged along with many other precautions like face masks, hand washing, maintaining social distance etc. Significance of tooth brushing and periodontal maintenance also adds on to the containment of this contagion.

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