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Mini-Review

COVID-19 and Periodontal Disease: The Potential Role of Interluekin-6

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Abstract:

COVID-19 crisis effects people all over the world. Great majority of patients have mild symptoms, while some others experience severe complications or even death. It is indicated that serious symptoms of COVID-19 related to cytokine storm. Many of these components are common with cytokine expression profile of the periodontal disease. Interluekine-6, as a pro-inflammatory cytokine, have a great impact on aggravation of COVID-19 and progression of destruction in periodontal disease. Improving oral health and early detection of periodontal disease in patients would decrease adverse outcomes of COVID-19.

***Keywords:** COVID-19, Cytokine Storm, Interluekine-6, Periodontal Disease*

Introduction

Covid-19 or SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2), as commonly labeled, emerged in December 2019 from Wuhan, China (1, 2). It has rapidly spread across the world and affected more than 110 million cases and more than 200 countries and territories.

As a member of the β coronavirus family, SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus (3). It is considered as the seventh coronavirus capable of developing human infection, four of which; i.e., 229E, NL63, OC43, and HKU1 have merely triggered a simple cold (4), whereas the three others namely SARS-CoV, MERS-CoV, and SARS-CoV-2, may give rise to life-threatening symptoms and even death (5).

Although most of the cases reported so far have been home-stayed with mild symptoms and did not require any hospital care, there have been few severely infected patients with acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome, most probably leading to death (6). As reported by the WHO press conference (January, 2020), Covid-19 was estimated to reach a case fatality rate of approximately 2%.

On the other hand, periodontal disease is a chronic inflammatory disorder resulting in progressive loss of the tooth supporting structures. It is widely spread globally as it affects more than 50% of the adult population and severe periodontitis known as the sixth most prevalent condition in the world (7).

This work proposes to evaluate the common cytokine pathway, especially Il-6 between severe COVID-19 and chronic periodontitis.

Hypothesis

All the evidences showed that there is a common cytokine pathway between periodontal disease and severe COVID-19 which account for a positive relationship between them. Among all cytokine, IL-6 play a major role both in severity of periodontal disease and aggravation of COVID-19.

Evaluation of the hypothesis

Pathophysiology of the severe acute respiratory syndrome coronavirus

The manner Covid-19 behaves has been attributed to a myriad of pathophysiological mechanisms (8). However, a large number of experimental studies and clinical trials safely arrived at the conclusion that pathogenesis of severe cases of Covid-19 had been significantly associated with "cytokine storm"(6, 9-11).

Once being exposed to the virus, the cells of immune system become activated by both innate and antigen-specific adaptive immune responses (12); this has a major part in stimulating the environment of cytokines, the key regulators of immunological and inflammatory responses. Among all cytokines, interleuking-6 (IL-6) is a cytokine operating as a major pro-inflammatory mediator that induces the acute phase response (13).

IL-6 may be the product of almost all stromal and immune system cells (like B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells) as well as a number of non-lymphocytes (such as fibroblast and endothelial cells)(14). IL-6 expression is manly activated by IL-1beta and tumor necrosis factor (TNF alfa), yet it can be secreted as a response to dozens of other factors Toll like receptors (TLRs), prostaglandins, adipokines, stress response and other cytokines, to name but a few(15). As the infectious inflammation begins, the secretion of IL-6 is stimulated by monocytes and macrophages triggered by the TLRs (16).

What give the role IL-6 play a high level of significance are the pleiotropic effects, inducing the host defense system to battle infections and tissue injuries (17-19). However, exaggerated, excessive synthesis of IL-6 when it comes to the fight against SARS-CoV-2, ends to an acute severe systemic inflammatory response of "cytokine storm" that in return severely injures the tissue, leads to multi-organ failure and unfavorable prognosis of severe lung diseases (20-23). This prolonging IL-6 secretion, referred to as 'second wave' activation can be initiated as a response to the loss of "front line" antiviral defiance mechanism and the serum viral RNA load in the patients with critical conditions (17, 24). As IL-6 grows in level, it further aggravates the disease and related to high case fatality in COVID-19, regardless of age and gender (17, 25-27). Thus, studies have indicated IL-6 as an important predictor of severe COVID-19(28, 29).

Pathophysiology of the periodontal disease

A periodontal disease is a chronic inflammatory disease which might result in progressive bone loss and attachment loss. The mechanism underlying this destructive disease involves tissue damage both directly and indirectly. The former is due to plaque bacterial products, while the latter (with more critical consequences) stems from a host inflammatory and immune response, involving the interaction between cells, extracellular matrix and circulating cytokines (30).

Cytokines like interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF)-alpha take central roles in developing inflammatory responses in the periodontium (31, 32). As a multifunctional cytokine, IL-6 is considered to be a potential stimulator of many biologic processes such as antibody (and autoantibody) production, activation of T cells, B cell differentiation, increase in acute-phase proteins, hematopoiesis, induction of angiogenesis, vascular permeability, and osteoclast differentiation (33, 34). When activated, IL-6 shows a double-edged behavior in inflammation with both anti-inflammatory (e.g., downregulation of neutrophil recruitment and pro-inflammatory cytokine expression) and pro-inflammatory effects (e.g., induction of acute-phase reactants by the liver) in chronic diseases (35).

Studies indicate that IL-6 is crucial in developing local and systemic inflammation as it modulates the responses to periopathogns (19). Excessive IL-6 responses (beside the release of active-phase reactants) are likely to trigger the development of a chronic inflammatory lesion that simply causes attachment and bone loss. This could be explained by the fact that IL-6 places tissue degradation effects on the connective tissue and bone, mediated by metalloproteinases (MMP) and osteoclasts, activation of T cells, and amplification of the inflammatory cascade (36).

GCF from sites with periodontal diseases were reported to contain Il-6. As suggested, the more was the IL-6 concentration in GCF, the more severe was periodontal disease (37). Similarly, IL-6 was higher in concentration in a gingival tissue with inflamed sites (38). IL-6 also advances bone resorption both on its own and synergistically with other cytokines' presence (IL-1) (39).

Conclusion

The studies have revealed that periodontal disease may be considered as a predisposing factor for severe COVI-19(40-42). Once well-perceived, this association shows how important it is to take oral hygiene measures as well as the regular follow-ups in order to decrease the bacterial load and subsequently control periodontal diseases. Notably, periodontal diseases are painless and often underestimated by the patient, calling for regular professional recalls.

Besides, the presence of systemic conditions (e.g., diabetes, cardiovascular diseases or hypertension) have been implicated as risk factors in periodontal disease (43). These systemic conditions also considered a great risk to COVID-19 complications (44). Such conditions, therefore, must be meticulously attended so that the hyper-inflammation could be identified and treated as soon as it starts to develop and lead to fatal COVID-19.

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