Periodontal Connections to the Coronavirus Disease 2019: An Unexplored Novel Path?

The first reported case of novel coronavirus disease 2019 (COVID-19) was on 31st December 2019 in Wuhan, China. The World Health Organization officially declared COVID-19 as a pandemic on 13th March.[1] The disease is caused by a novel coronavirus from the human airway epithelial cells called 2019-nCoV.[2] Like the receptor of the severe acute respiratory syndrome-CoV virus, the angiotensin-converting enzyme II (ACE-2) is likely the cell receptor of 2019-nCoV. The ACE-2 expressed on the oral mucosa and had been heavily enriched in the tongue epithelial cells. These outcomes clarified the primary reason that there is a potentially substantial COVID-19 infectious susceptibility risk for oral cavity as ACE-2 plays a vital part in the cellular entry. Therefore, ACE-2-expressing cells can act as target cells and are predisposed to 2019-nCoV infection and brought up a proof for the future prevention procedure in dental practice and daily life.[2] As gingiva comprises an integral part of masticatory mucosa, it may also possess a good number of ACE-2 receptors, which can predispose to infection with 2019-nCoV.

Cytokines are water-soluble, low molecular weight, glycoprotein biomarkers secreted by the non-haematopoietic and haematopoietic cells in during infection. Biomarkers induced during inflammatory responses have been related to the onset or progression of tissue insult.[3] Pro-inflammatory biomarkers demonstrate pleiotropic effect and target particular cells by controlling their activation, proliferation and function in the periodontal tissues.[4] Then, elevated levels of pro-inflammatory biomarkers such as tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6 and IL-8 may lead to the destruction of periodontal tissues.[5] Patients infected with 2019-nCoV have also exhibited raised levels of pro-inflammatory cytokines and chemokines. The increased levels of IL-1β, interferon (IFN)-γ, CXCL10 and CCL2 strongly indicated towards the activation of T-helper-1 (Th1) cell function. More fundamentally, the '*Cytokine Storm'* emerged as the main factor for more severe clinical course. This concept derived from the observation that COVID-19 patients necessitating the intensive care unit (ICU) admission showed raised concentrations of CXCL10, CCL2 and TNF-α than patients with less severe infection and not requiring ICU admission.

Further complicating the issue, it should be emphasised that in patients with COVID-19 infection, there is also increased secretion of Th2-immune-oriented cytokine (IL-4 and IL-10), which suppress inflammation. Taken together, these data clearly indicate that, in 2019-nCoV infection, acute respiratory distress syndrome (ARDS) is the ultimate consequence of a cytokine storm. Here, the release by immune effector cells of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1 β, IL-6, IL-12, IL-18, IL-33 and TNF-α), transforming growth factor-β and chemokines (CXCL8-10, CCL2-3 and CCL5) triggers and sustains the unusual systemic inflammatory response. The cytokine storm is readily followed by the immune system 'attacking' the body, which in turn will lead to ARDS as well as multiple organ failure, the result being death. The effects of a combination of many immune-active molecules result both cytokine storm and the consequent ARDS.[6] Few pro-inflammatory mediators found in severe periodontal and COVID-19 disease are similar such as IL-1 β, IL-6 and TNF-α. We can suggest that patients with severe form of periodontal diseases can display severe symptoms of COVID-19 if they get infected with it, since they already have increased blood levels of pro-inflammatory mediators or cytokines. Further, we are of the opinion that treating the patients with severe forms of periodontitis (with advanced destruction and bone loss) is important and might be essential because that will reduce the circulating pro-inflammatory mediators or cytokines, which were also seen in cytokine storm in severe forms of COVID-19. For this reason, more research should be directed towards this, as good oral hygiene and stable periodontal state could decrease the incidence of severity of COVID-19 symptoms.

Gingival crevicular fluid (GCF) is defined as inflammatory exudate and an altered tissue transudate in a normal healthy condition. Originally, they originate from the gingival plexus of blood vessels in the gingival corium and are subjacent to the epithelium of the dental–gingival space. GCF is used to detect periodontal diseases such as gingivitis, periodontitis (chronic and aggressive) and drug presence in the periodontal pockets via the systematic pathway and is widely used for proteomic analysis.[7] Moreover, the analysis of the GCF also provides a non-invasive diagnostic method. GCF can be collected by various techniques, but most studies use the absorption technique by employing paper strips or points.[8] GCF samples have been studied to isolate and assess herpes simplex virus, Epstein–Barr virus and human cytomegalovirus earlier.[9] Therefore, assessing the presence of the 2019-nCoV in the GCF will be yet another convenient, non-invasive method to isolate the virus and additionally to confirm the pathway of entry into the oral cavity.

Finally, we can highlight following based on the brief discussion

1. The presence of ACE-2 receptors should be more investigated in the gingiva

2. Therefore, identifying patients with severe form of periodontal disease and treating them is essential, as it may be helpful in the reduction of the circulating inflammatory mediators, decreasing the severity of COVID-19 cases
3. Periodontal pockets can act as potential reservoir for 2019-nCoV; however, further studies are required to draw a conclusion
4. GCF can be a novel, non-invasive and more accessible tool in detecting the 2019-nCoV presence.

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Conflicts of interest

There are no conflicts of interest.

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