

# Exploring the correlation between COVID 19 and periodontal disease

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## Abstract

An association of periodontal disease with the severity of COVID 19 disease has been observed during COVID 19 pandemic. This article explores the various hypotheses that link the two conditions, to understand their interrelationship. Targeted research may help elucidate evidence for screening of high-risk groups and identification of therapeutic targets.

**Keywords:** COVID 19, high-risk groups, hypotheses, periodontal disease, therapeutic targets

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## INTRODUCTION

Over the last 2 years of the COVID 19 disease pandemic, an association was noted between periodontitis and COVID 19 disease.<sup>[1]</sup> Understanding the pathologic basis of the association between the two diseases may establish the role of treating periodontitis as part of the standard protocol of management of COVID 19. As both COVID 19 and periodontitis are characterized by chronic inflammation, the discovery of common immune mediators may lead to discovery of therapeutic targets.<sup>[2]</sup> This article is a brief compilation of the various hypotheses relating the two entities, to understand the importance of periodontal health in the management of COVID 19.

## DISCUSSION

Studies have revealed that patients suffering from COVID 19 and periodontal disease are more likely to be hospitalized and require oxygen treatment as compared to those without

coexisting periodontitis.<sup>[3]</sup> Various hypotheses have been proposed to explain the observed correlation between COVID 19 disease and periodontal disease.

### 1. Role of inflammatory Cytokines

A cytokine storm with elevation of various cytokines like IL-1 beta, IL-6, IL-7, TNF alpha, has been reported in COVID 19 and the cytokine level correlates well with disease severity<sup>[4]</sup>

In COVID 19 disease, interstitial pneumonia, attributed to overexpression of IL-6 is associated with higher fatality rates. A meta-analysis by Coomes *et al.*<sup>[5]</sup> suggested that IL-6 levels were 2.9-fold higher levels in patients with COVID-19, who were in critical state as compared to those suffering from mild or moderate illness. Periodontitis, a common oral disease independently elevates IL-6.<sup>[6]</sup> Thus, co-existing periodontitis in COVID 19 patients can contribute to elevated levels of IL-6, with worsening

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outcomes. Marouf *et al.*<sup>[3]</sup> report that 12% of COVID 19 patients with periodontitis experienced severe complications while only 2% of those without periodontitis suffered from severe COVID 19 disease.

### Role of ACE-2 receptors

The binding of SARS CoV-2 to ACE 2 receptors, in the gingival crevice and periodontal pockets, leads to high viral load in the oral cavity ACE 2 expression is increased in diabetics, patients with COPD, asthma and liver disease, which explains the vulnerability of these patients to severe COVID 19.<sup>[7]</sup> These receptors are implicated in various oral manifestations reported in COVID-19 like dysgeusia, oral ulcers, vesicles, blisters, Kawasaki like disease, bleeding from lips, and strawberry tongue.<sup>[3]</sup> Takahashi Y *et al.*<sup>[8]</sup> have shown that aspiration of periodontopathic bacteria increases the expression of ACE 2 receptors in the lungs and bronchi, through bacterial endotoxins and other pathogenic products. Thus, persons with periodontal disease are likely to overexpress ACE 2 receptors in their respiratory mucosa, predisposing them to COVID 19.

### 2. Role of CD-147

The epithelial cells of gingiva and subgingival periodontal pockets express high levels of CD147. Wang *et al.*<sup>[9]</sup> demonstrated that SARS CoV-2 may gain entry into target cells by binding to the CD 147) on cell membranes in addition to the ACE-2 receptors. Thus, pre-existing periodontitis may facilitate the entry of SARS CoV2 through this route.

### 3. Role of Galectin mediated immune response

Galectins, a group of  $\beta$ -galactoside-binding lectins, produced by various immune and epithelial cells have pro or anti-inflammatory action, depending on their localization and the target cell.<sup>[10]</sup> Galectins induce ACE-2 receptors to generate the glycan lattice on the viral and endothelial cell surfaces, which leads to an enhanced inflammatory response and a conformational change in viral structure, facilitating entry of the virus into endothelial cells. Inflammatory diseases like periodontitis, which can lead to increased Gal-3 production may indirectly increase risk of COVID 19 through increased viral entry.<sup>[11]</sup>

A morphological similarity exists between Gal 3 and an important locus of the SARS- CoV-2 spike protein. Thus Gal 3 inhibitors may target this spike protein preventing viral entry into target cells.<sup>[12]</sup> Gal 3 inhibitors cause decreased production of inflammatory cytokines IL-1 and IL-6 and increased expression of the anti-inflammatory cytokines like IL-10.<sup>[13]</sup> Thus Gal-3 inhibitors can serve as a therapeutic target improving outcome of both COVID-19 and periodontitis.

### 4. Role of Neutrophil extracellular traps

Neutrophil extracellular traps (NETs) act as scaffolds that retain microorganisms, that get trapped in the DNA fibers, limiting their spread, and facilitating concentration of antimicrobial agents at that site.<sup>[14]</sup> NETosis is a multiple step process in which NADPH oxidase activates the neutrophils to release reactive oxygen species (ROS), which then acts on the nucleus and causes chromatin de-condensation and cytolysis to release NETs. NETs are associated with the pathophysiology of periodontitis as well as viral diseases like COVID-19. In periodontitis, high levels of Interferon Alpha, the main mediator for NETosis are observed, while, in viral diseases, host evasion mechanisms are responsible for triggering NETosis.<sup>[15]</sup> Further, NETosis induced by viruses results in an extreme systemic response, with increased production of cytokines, chemokines and immune complexes.<sup>[16]</sup> Thus, in COVID 19 patients with periodontitis, the combined resultant increase in NETs leads to severe disease.

### 5. Role of Oral Dysbiosis

Oral dysbiosis, resulting from loss of host-microbial homeostasis, is a known nosocomial complication in long term hospitalized patients and shows an association with periodontitis.<sup>[17]</sup> A metagenomic analysis of severe COVID 19 patients showed presence of periodontitis associated genera *Fusobacterium*, *Veillonella* and *Prevotella*<sup>[18]</sup> Thus hospitalized patients with COVID 19 can develop oral dysbiosis which can predispose to periodontitis, which in turn can negatively impact the severity of SARS CoV2 disease.

As periodontal disease is highly prevalent in the population, it may well be the 'elephant in the room' with respect to management of COVID 19. Understanding the underlying mechanism that connects the two conditions will open up novel research avenues for development of therapeutic targets for COVID 19 [Figure 1]. Recognizing the underlying pathophysiology will help to elucidate the importance of oral health status, particularly periodontal health in reducing disease severity in those infected with SARS CoV2.

### CONCLUSION

The pharmacotherapeutics for COVID 19 have changed several times since the first reported cases, based on the emerging evidence. A better understanding of the mechanism underlying the observed correlation between SARS CoV2 infection and periodontal health, may lead to inclusion of oral care as part of the standard protocol for management of COVID 19. Public health initiatives to screen for periodontal disease may effectively identify

