

Is periodontal disease a risk factor for developing severe Covid-19 infection? The potential role of Galectin-3

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Impact statement

There could be a close relationship between periodontal diseases (PDs) severity and Covid-19 infections. This relationship could be caused by Galectin-3-mediated increased immune response and increased viral attachment. Keeping PDs under control and maintaining rigorous oral hygiene during this troubled Covid-19 pandemic period is very important.

Abstract

Patients with older age and pre-existing conditions like cardiovascular disease, hypertension, diabetes, and obesity are in the higher risk group for developing severe Covid-19 infections. The inflammatory pathways that are involved in these conditions are the same pathways that we see in periodontal diseases (PDs). This raises a significant question: Is PD a pre-existing condition that can increase the risk of developing severe Covid-19 infection? Several studies have shown that Galectins play a key role in the homeostasis of immune cells, and recently, a relationship was found between Covid-19 and Galectin-3 (Gal-3). It has been determined that an important area in the spike protein of Coronavirus-19 is almost exactly the same as the morphology of Gal-3, and these spike proteins are critical for the entry of the virus into host cells. We suspect that there is enough evidence to support a close relationship between PDs severity and Covid-19 infections. There is accumulating evidence to suggest a relationship between the severity of PD and the risk of infection with Covid-19, which requires further investigation. This relationship could be caused by Gal-3-mediated increased immune response and increased viral attachment. In this context, we want to emphasize the importance of keeping PD under control by maintaining rigorous oral hygiene during this troubled Covid-19 pandemic period. We would also like to point out the possibility that having PD may be a pre-disposition toward developing a severe Covid-19 infection.

Keywords: Covid-19, Galectin-3, periodontal diseases, acute phase proteins, dentistry, oral hygiene

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In late 2019, an uncertain etiology of lower respiratory infection outbreak happened in Wuhan Province of China. The causative virus was named as 2019 Novel Corona Virus (2019-nCoV), and the disease was called as Corona Virus Disease 2019 (Covid-19). Patients with Covid-19 have a wide range of symptoms including fever, sore throat, nasal congestion, body aches, headache, abdominal pain, diarrhea, cough, and shortness of breath.¹ As studies emerged, two new symptoms were found to be common with Covid-19 infections: anosmia and ageusia.² Most patients with Covid-19 have a milder disease course; however, 20% of the patients develop severe disease with mortality rate of 6% which is mostly associated with older age, systemic diseases, and immunosuppression.¹ These

patients have increased levels of serum pro-inflammatory cytokines and chemokines including IL1- β , IL1RA, IL2, IL7, IL8, IL9, IL10, MCP1, MIP1 α , FGF2, GCSF, GMCSF, IFN γ , IP10, and TNF α that lead to promote disease severity.¹

As expected, health-care professionals are also in higher risk group for contracting this virus. Especially, dental practitioners can get infected easily due to their direct exposure to saliva and blood. For this reason, in many countries, dental offices were closed and dentists have been instructed to provide only emergency treatments for the time being. In order to continue to provide care to their patients, dentists are trying to find ways to adapt their practices to prevent themselves and their patients from SARS-CoV-2 which will continue to be threatening until a

safe and reliable vaccine is developed and distributed. The current research about Covid-19 in dentistry is mainly focused on prevention of the disease. There is no study showing a relationship with oral diseases and Covid-19 infection.²⁻⁴

As SARS-Corona virus-1, the SARS-Corona virus-2 also exhibits affinity toward angiotensin-converting enzyme 2 (ACE-2) receptors which are the important diagnostic biomarkers for the cardiovascular diseases especially myocardial injuries.⁵ This strong relationship between ACE-2 and 2019-nCoV spike protein showed that the people with more ACE-2 expression may be more prone to 2019-nCoV. Studies have also shown the presence of ACE-2 receptors in oral mucosa (tongue, buccal mucosa, and gingival).⁶ Therefore, it is possible that oral diseases could have an important role in terms of being a risk factor for Covid-19, which is transmitted by droplets.

Periodontal diseases (PDs) are inflammatory diseases and they are highly prevalent among children and adults worldwide. PDs are often caused by a long-term accumulation of microbial dental plaque, which cause acute or chronic inflammation of the dental supportive tissues.⁷ Several studies demonstrated increased numbers of cytokine and chemokine producing cells in gingival tissues of patients with periodontitis and gingivitis as compared with healthy controls. Interestingly, elevated levels of these cytokines were also found in the serum of these patients.⁸ PD acts within the same chronic inflammatory model seen in other diseases such as cardiovascular disease, diabetes, obesity, aging, and hypertension, and several studies have suggested the existence of a bidirectional link between periodontal health and these pathologies.^{8,9} This supports that there is a strong relationship between PDs and systemic health.

Proteins with an increase or decrease in serum levels during systemic inflammation are called acute phase proteins (APPs).⁹ It has been suggested that inflammation in PD affects the level of positive APPs especially C-reactive protein.¹⁰ In recent studies, it has been shown that Galectins also play a key role in the homeostasis of immune cells.¹¹ Galectin-3 (Gal-3), a member of β -galactoside binding proteins, is expressed in many tissue, immune cells, epithelial cells, endothelial cells, and sensory neurons.¹² Gal-3 is very important in many biological functions including fibrosis, cell growth, inflammation, transformation, angiogenesis, pre-mRNA addition, differentiation, apoptosis, and host defense.¹³ Gal-3 in the cytoplasm membrane and extracellular environment modulates intercellular and cell-matrix relationships. Gal-3 is a proinflammatory protein and is also involved in T-cell-mediated inflammation.¹⁴

In a recent study, a relationship was found between coronavirus (CoV-19) and Gal-3. It has been determined that an important area in the spike protein of CoV-19 is almost exactly the same as the morphology of Gal-3, and these spike proteins are critical for the entry of the virus into host cells.¹⁵ Another study found structural similarities of SARS-COV2.¹⁶ S1-NTD leads a strong interaction with GM1 ganglioside, a molecule commonly found on cell surfaces. These data strongly support the linkage model for SARS-

CoV2 to stabilize viral adhesion.¹⁷ It was also shown that Galectins bind GM1 ganglioside with high affinity. So, it is possible that inhibition of Gal-3 can disrupt the attachment of the SARS-Cov2 and decrease the virus activity.

It has also been reported that Gal-3 is an animal lectin involved in the disease process of various inflammatory conditions from Atherosclerosis to Asthma.¹⁵ Gal-3 inhibition causes decreased production of interleukin (IL)-1 and IL-6 while also causes increased levels of IL-10.¹⁸ In SARS-COV2 patients, Gal-3 inhibitors causes in reducing the incidence of cytokine release syndrome by suppressing the release of pro-inflammatory cytokines. Additionally, it has been shown that Gal-3 levels were increased in virally infected cells and these inhibitors may bind in highly affected regions of the body.¹⁹ Inhibitors of the Gal-3 molecule reduce both IL-6 and TNF- α levels in vitro and show in vivo anti-inflammatory effects.¹⁵

Recently, we completed two different PhD thesis studies which are the first studies investigating Gal-3 levels in PDs, regarding the biomarker levels, Hs-CRP, and Gal-3 associated with the severity of the PDs (gingivitis and periodontitis). These studies revealed a positive correlation between these biomarkers and clinical periodontal parameters. It was concluded that increased levels of Gal-3 is associated with the severity of the PDs and can be used as a positive acute phase reactant in PDs.

We suspect that there is enough evidence to support a close relationship between periodontitis severity and Covid-19 infections. This relationship could be caused by Gal-3-mediated increased immune response and increased viral attachment. There is a strong relationship between PDs and systemic other diseases. Furthermore, the systemic situation and comorbidities are common risk factors in severe Covid-19 patients. In this context, we want to emphasize the importance of keeping PD under control and the importance of maintaining rigorous oral hygiene during this troubled Covid-19 pandemic period. We would also point out the possibility of PD presence as a predisposition to the negative consequences associated with Covid-19. Nevertheless, more studies are required to elucidate the association between PDs and Covid-19, why in some patients, Covid-19 causes more severe symptoms.

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