THE IMPACT OF THE ASSOCIATION BETWEEN PERIODONTITIS AND CORONAVIRUS DISEASE INFECTION ON ORAL AND SYSTEMIC COMPLICATIONS. REVIEW

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Abstract:
Several risk factors have been associated with severe coronavirus disease and include factors such as advanced age and sex (male) and comorbidities such as obesity and the presence of underlying diseases (eg, hypertension, cardiovascular disease, cerebrovascular disease, chronic kidney disease, and diabetes). These predisposing conditions share several standard features that could explain why they are associated with worse disease outcomes. Persistent and uncontrolled inflammation is a key manifestation of several diseases, such as periodontitis, cardiovascular diseases, neurodegenerative diseases, diabetes, and coronavirus disease infection. The oral cavity is a reservoir for respiratory pathogens, especially among patients with poor oral hygiene and periodontitis, and dysregulated inflammatory and immune response. In fact, periodontal pockets in the elderly have been associated with increased risk of mortality from pneumonia, and periodontitis patients are more likely to develop hospital-acquired, pneumonia than healthy ones are.
Conclusions; Periodontitis shares several common features with coronavirus disease including similarities in comorbidities and effects on systemic inflammation. However, further research would be needed to confirm these hypotheses.
Keywords: *coronavirus disease, periodontitis, systemic inflammation, immune response*

1. Introduction

The objective of this review to evaluate the scientific evidence studying these links and the possible mechanisms behind this association. [1] Coronavirus disease caused the worst global pandemic in recent history with more than 160 million confirmed cases and almost 3.5 million deaths, as of 2021. [2] Coronavirus disease symptoms vary depending on the severity of the disease. Although most coronavirus disease patients are asymptomatic or only suffer a mild disease, a significant group can present signs and symptoms of severe disease, frequently causing serious complications and even death.

Severe symptoms include signs of pneumonia, dyspnea at rest, increased respiratory (above 20 breaths per minute) and heart rates (above 100 beats per minute), loss of appetite, confusion, tightness or pressure in the chest, cyanosis, hypoxia (eg, 93%), and high fever (greater than 38°C). [3-5] However, in some cases the disease can progress into a serious and life-threating condition. This results in a

deterioration of the patient's condition due to damage to vital organs, such as the lungs, heart, nervous system, gastrointestinal tract, and kidneys, as well as an aberrant inflammatory response termed the "cytokine storm" that contributes to coronavirus disease mortality. [6,7] This "cytokine storm" features a hyperactive immune response characterized by increased blood levels of inflammatory mediators such as interferons, interleukins, tumor-necrosis factors, and chemokines, as well as lymphopenia, neutrophilia, alterations of the coagulation cascade, increased levels of markers for organ damage, and increased inflammatory markers. [8-10]. The release of inflammatory mediators involved in the innate immune response is usually essential for the clearance of infectious agents; however, at excessively high levels, such as those seen in the "cytokine storm," these mediators can be harmful and cause severe complications. [9]

Several risk factors have been associated with severe coronavirus disease.

These include factors such as advanced age and sex (male) and comorbidities such as obesity and the presence of underlying diseases (eg, hypertension, cardiovascular disease, cerebrovascular disease, chronic kidney disease, and diabetes). [3,7,10,11]

The latter may suggest that a chronic inflammatory condition, such as periodontitis,

could play a role in the course of coronavirus disease. Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic dental plaque biofilms, characterized by progressive destruction of the tooth-supporting apparatus. [12]

This disease is one of the most common chronic inflammatory noncommunicable

diseases and the sixth-most prevalent condition in the world, affecting about 50% of adults. In its more severe form, periodontitis affects about 11% of the population. [12,13]

Periodontitis not only leads to tooth loss and disability, with the consequent impairment of the patient's quality of life, but it also affects general health. [14-16] Severe periodontitis has been associated with a range of systemic diseases, including diabetes, cardiovascular diseases, and increased mortality. [16] Owing to this increased systemic risk, various investigations have suggested a possible link between periodontitis and increased severity of coronavirus disease disease. [2,17]

2. The Oral Cavity and Coronavirus Disease Infection.

The oral cavity seems to play an important role in coronavirus disease 2019 pathogenicity.

[18-21] They have been found on the epithelial cells of the tongue, oral mucosa, salivary glands, gingiva, and periodontal pockets at levels comparable to those in the lungs and tonsils.

In addition, severe acute respiratory syndrome coronavirus 2 can be identified in oral fluids and saliva, and its oral viral load has been associated with disease severity. [19]

Some unspecific oral lesions have been associated with coronavirus disease.

These include dry mouth, oral vesiculobullous or pustulous lesions, lip necrosis, fissured or depapillated tongue, or erythematous or hemorrhagic mucosal lesions. [19]

Such lesions are mostly found among patients with systemic conditions that involve

some degree of immunosuppression. [21]

3. Periodontitis and Coronavirus Disease Infection Severity.

Relevant risk factors associated with coronavirus disease severity, including smoking, increased age, obesity, diabetes, hypertension, and cardiovascular disease,[11] are also significantly associated with periodontitis. [13,16]

Hence, it is uncertain whether these factors could just behave as comorbidities or whether there are specific mechanisms and pathological pathways linking periodontitis and increased coronavirus disease severity. [22,23] The association between coronavirus disease 2019 infection and periodontitis has also been investigated in two retrospective studies. [24] Other studies have also suggested a possible effect of coronavirus disease infection on periodontal health. [25]

It has been predicted that an increased prevalence of acute periodontal lesions, particularly necrotizing periodontal disease, could arise in association with coronavirus disease–confirmed cases. [26] However, this hypothesis is yet to be confirmed.

It is well established that translocation of periodontal pathogens to blood (eg, bacteremia) and the associated systemic inflammation are mechanisms contributing to the links between periodontitis and systemic diseases, such as diabetes, cardiovascular diseases, and rheumatoid arthritis. [22,27] However, these mechanisms have not been clearly demonstrated in the association between periodontitis and increased coronavirus disease severity.

4. Mechanisms linking periodontitis with coronavirus disease 2019 pathogenesis

Severe acute respiratory syndrome coronavirus 2 in the periodontal pockets

A study on cadaver biopsies from coronavirus disease–positive patients has reported the presence of the severe acute respiratory syndrome coronavirus 2 within their periodontal tissues. [28] This has led to the hypothesis that periodontal pockets may serve as reservoirs
for severe acute respiratory syndrome coronavirus. [28]

It is well established that periodontal pockets present an ideal environment for harboring biofilms rich in bacterial and viral species that may invade the tissues through the frequently ulcerated pocket epithelium. [29,30]

This pathogenic environment could facilitate the entrance of the severe acute respiratory syndrome coronavirus 2, either directly through this damaged epithelia or indirectly by the upregulation in the expression of angiotensin-converting enzyme 2 receptors induced by some periodontal pathogens, such as *Fusobacterium nucleatum*. [30,31]

Periodontitis as a source of systemic inflammation

Systemic inflammation in periodontitis is characterized by high levels of C-reactive
protein and proinflammatory cytokines (interleukin-1 and IL-6) that have been associated
with initiating or aggravating diseases, such as diabetes and cardiovascular diseases. [14,16]

Periodontitis has also been implicated with the release of neutrophil extracellular traps, an alternative form of cell death secondary to increased levels of mediators, such as interferon-alpha. [32,33] The adverse outcomes of coronavirus disease infections have also been associated with an uncontrolled hyperinflammatory reaction known as the “cytokine storm.”

This condition involves increased serum levels of interleukin-2, 6, 7, 8, and 10, tumor necrosis factor-alpha, granulocyte colony-stimulating factor, interferon-gamma inducible protein 10 (IP-10), monocyte chemoattractant protein 1, macrophage inflammatory protein 1-alpha, galectin- 3, and C-reactive protein, with concomitant significantly lower numbers of T-lymphocytes. [34] This inflammasome, which has been shown to increase the serum and salivary of periodontitis patients, may play a significant role in the coronavirus disease cytokine storm and has been shown to aggregate in the lungs, resulting in fatal pneumonia. [35]

Severe coronavirus disease References Periodontitis References Associated comorbidities

Hypertension, obesity, age, sex, diabetes, cardiovascular diseases, smoking, chronic pulmonary disease, coronary artery disease, chronic renal disease, cancer, atherosclerotic diseases [3,7,10,36,37]. Hypertension, obesity, age, diabetes, cerebrovascular disease, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, hypertension, atherosclerotic disease [13-16,22,27,38]

Elevated inflammatory biomarkers

Interleukin-1, 1beta, 1RA, 2, 6, 7, 8, 9, 10, C-reactive protein, galectin-3 prostaglandin E2, interferon-gamma inducible protein 10, monocyte chemotactic protein-1, macrophage inflammatory protein-1alpha, fibroblast growth factor-2, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, interferon-gamma, tumor necrosis factor-alpha, C3 and C5, and NOD-like receptor family pyrin domain-containing 3 inflammasome, ferritin [8,6,9-11,18, 35,39-41]

Matrix metalloproteinases Lactate dehydrogenase Alanine aminotransferase Troponin I Procalcitonin Aspartate aminotransferase [8,42,18]. In this study, coronavirus disease patients with periodontists had significantly higher blood levels of inflammatory markers, such as C-reactive protein, than coronavirus disease patients without periodontitis did. [40] Systemic inflammation has also been related to alterations in the sleep-wake cycles of the Considering the importance of the dysregulation of the inflammatory response in coronavirus disease complications, modulation of the immune system has been explored as a therapeutic approach to prevent the cytokine storm. These types of drugs can reduce the levels of C-reactive protein and IL-6 levels, improve lung function, and resolve acute respiratory distress syndrome in coronavirus disease patients. [41]

Periodontitis as a source of direct aspiration of bacterial pathogens to the lungs in coronavirus disease patients

Another possible association between periodontitis and coronavirus disease severity may involve the well-established connection between the oral microbiome and respiratory diseases. [42] The oral cavity is a reservoir for respiratory pathogens,74 especially among patients with poor oral hygiene and periodontitis, and dysregulated inflammatory and immune response. [2] In fact, periodontal pockets in the elderly have been associated with increased risk of mortality from pneumonia, and periodontitis patients are more likely to develop hospital-acquired, pneumonia than healthy ones are. [43,44] Oral opportunistic pathogens, such as *Capnocytophaga* and *Veillonella*, have been found in the bronchoalveolar fluid of coronavirus disease patients. [2]

5. Health Implications of The Association Between Coronavirus Virus Disease and Periodontitis

Prevention of periodontitis is achieved by daily self-performed oral hygiene and quarterly or biannual professional removal of the microbial biofilm. [45]

Periodontal care could also help prevent coronavirus disease complications indirectly by managing associated comorbidities, such as diabetes and systemic inflammation.

Thus, given the ability of periodontal therapy in reducing systemic inflammation and improving glycemic control in type 2 diabetic subjects, [46-48] it has been hypothesized that periodontal care could help prevent coronavirus disease

complications, although future research would be needed to test this possibility.

Oral hygiene has a well-established relationship with infectious respiratory diseases; oral care, particularly periodontal treatments, can help prevent the onset of pneumonia and influenza and the exacerbation of chronic obstructive pulmonary disease. [45]

Indeed, there are suggestions that periodontal care could help in prevention of coronavirus disease complications, but currently there is no evidence on the possible impact of periodontal treatment in coronavirus disease complications. [49,50]

6. Conclusions

Periodontitis shares several common features with coronavirus disease including similarities in comorbidities and effects on systemic inflammation. Indeed, some early studies have identified a possible association between the presence of periodontitis and the risk of coronavirus disease infection and complications.

These associations could stem from a priming effect on systemic inflammation, although the presence of periodontal bacterial in the lungs could also be playing a role. In this context, preventive oral hygiene measurements and periodontal care could play a role in preventing coronavirus disease infections and complications.

However, further research would be needed to confirm these hypotheses.

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