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REVIEW ARTICLE

Association of periodontitis and COVID-19 – a narrative review

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Abstract

Introduction and Objective. Periodontitis is a multifactorial inflammatory disease triggered by the dysbiosis of subgingival microbial biofilm and fuelled by host immune response. Periodontal inflammation may affect other systems and organs. Systemic inflammation is also a main characteristic of severe forms of Corona-Virus-Disease-2019 (COVID-19). Some genetic/environmental factors in periodontitis patients might implicate the course of COVID-19, thus, the aim of the study was to analyse the association of periodontitis with COVID-19 complications.

Review Methods. Literature available on 13 August 2022 was searched by using the *PubMed, Web of Science* and *Google Scholar* databases. Articles were selected that contained the key words: COVID-19, SARS-CoV-2, periodontitis, oral manifestation.

Brief description of the state of knowledge. From the initial serach, 26 articles were retrieved for final analysis. Available data have shown that periodontitis may be a predisposing factor for the development of severe COVID-19. Periodontitis was associated with increased rates of hospitalization, assisted ventilation and death due to COVID-19 complications. Similar inflammatory pathways are activated in COVID-19 and periodontitis, and periodontal pathogens may contribute to a more severe course of COVID-19.

Summary. Since some evidence confirms a relationship between periodontitis and severity of COVID-19, it is essential to maintain periodontal health and good oral hygiene as an important measure for the prevention and management of COVID-19 and its complications.

Key words

COVID-19, periodontitis, host response, SARS-COV-2

INTRODUCTION AND OBJECTIVE

COVID-19 (Corona-Virus-Disease-2019) is a severe acute respiratory infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 infects host cells via the surface glycoproteins that mediate host cell attachment and invasion by specific binding to angiotensin-converting enzyme 2 (ACE-2) [1]. ACE2 is expressed in many organs and tissues, and most prominently expressed in the respiratory epithelium, endothelium, gastrointestinal tract, renal system, cardiac muscle cells, and in the oral and nasal mucosa – in particular the salivary glands and tongue. COVID-19 in animal studies have shown that increased expression of ACE2 increased the severity of SARS-CoV-2 infection [2, 3]. Once the cells are infected, it induces activation of an inflammatory cascade, known as the proinflammatory storm. Thus, the consequence of SARS-CoV-2 infection can be damaging to multiple organs and tissues, resulting in subsequent multi-organ failure. The course of the disease can be described by two or three main stages (Tab. 1) [2, 4].

Periodontitis is a common, chronic, multifactorial infectious and inflammatory disease that is related to many chronic systemic diseases [5, 6]. It is estimated that periodontitis affects about 42% of people over 30 years of age and 60% of people over 65, while advanced periodontitis (i.e. Stages 3 and 4 periodontitis) affects about 11% of the adult population worldwide [1]. Tissue destruction in periodontitis is primarily associated with host hyperresponsiveness and the release of pro-inflammatory mediators, and the pathomechanisms of periodontitis has several common features with some systemic diseases, e.g. diabetes mellitus type 2 [7]). Moreover, several risk factors common for periodontitis and COVID-19 have been identified [1].

Table 1. COVID-19 stages [5]

Stage 1	Stage 2	Stage 3
• usually asymptomatic • activation of the innate immune response upon recognition of the virus (mainly through pathogen-associated molecular patterns (PAMPs)) • low levels of IFN-γ	• lower intensity of symptoms • activation of the adaptive immune response, producing specific antibodies and T lymphocytes that limit inflammatory reactions • release of DAMPs, exacerbating the inflammatory response	• cytokine storm, along with hypercoagulability • multi-organ dysfunction • shock

The importance of oral health in association with COVID-19 is underscored in the literature; therefore, the aim of this review was to investigate whether periodontitis increases the risk of the severe form of COVID-19 and to,investigate the mechanisms underlying this relationship.

REVIEW METHODS

The literature available on 13 August 2022 was searched by using the *PubMed, Web of Science* and *Google Scholar* databases. Articles were selected using the following

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key words: COVID-19, SARS-CoV-2, periodontitis, oral manifestation. Review articles and studies based on self-reported oral health were excluded from further analysis. From the initial search, a total of 26 articles was retrieved for final analysis. After reviewing and collecting pertinent data, the knowledge acquired was compiled and systematized.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Correlation between the oral cavity, respiratory system and COVID-19. Periodontal status in the COVID-19 patients was analysed in 7 studies in a total of 2,643 individuals (Tab. 2). In a study based on the University of Florida patients' registry, periodontitis was not associated with COVID-19 status (OR 1.1; 95% CI 0.3- 4.2); however, after adjusting for smoking, patients with periodontitis were 4.7 times more likely to have COVID-19 than patients without periodontitis [8]. In the study based on the national electronic medical records of 568 patients with COVID-19, periodontitis was shown to be associated with COVID-19 complications, such as admission to an intensive care unit (OR = 8.81, 95% CI 1.00–77.7), the need for assisted ventilation (OR = 4.57, 95% CI 1.19–17.4) and death (OR = 8.81, 95% CI 1.00–77.7). Additionally, a significantly higher white blood cell count, levels of D-dimer and reactive protein C were demonstrated in the group of patients with COVID-19 and periodontitis, compared to those with COVID-19 alone [1]. In another case-control study, significant associations of mean plaque scores ≥ 1 (OR 7.01; 95% CI 1.83 to 26.94), gingivitis (OR, 17.65; 95% CI, 5.95 to 52.37), mean CAL ≥ 2 mm (OR, 8.46; 95% CI, 3.47 to 20.63), and severe periodontitis (OR, 11.75; 95% CI, 3.89 to 35.49) with COVID-19 were found [9].

Another observational study demonstrated that periodontitis posed a similar risk for COVID-19 complications as well as diabetes and hypertension, as periodontitis patients were 3 times more likely to have COVID-19 complications compared to non-periodontitis patients (p = 0.025), while diabetes and hypertension patients were 3.5 times more likely to have COVID-19 complications [10].

Association between periodontitis severity and COVID-19 has also been demonstrated in retrospective studies. In patients with COVID-19 greater alveolar bone loss was found compared to controls (0.641 ± 0.613 mm vs 0.260 ± 0.631 mm; p < 0.01.), and increased number of missing teeth (OR 2.1871; 1.146–4.174) was significantly associated with hospitalization [11]. Gupta et al. (2022) demonstrated that the incidence of hospital admissions and assisted ventilation increased with the advancement of periodontitis. The need for assisted ventilation was the highest in with patients with periodontitis stages 3 and 4. Approximately 10% of patients died from COVID-19, all of whom were characterized by advanced periodontitis [12]. Similarly, Kaur et al. (2022) showed that the severe form of periodontitis was associated with moderate-to-severe COVID-19 infection that required hospitalization, and in this cohort, elevated levels of lymphocytes, WBCs, and CRP were detected [13].

A recent meta-analysis of epidemiological studies demonstrated a non-statistically significant tendency for an increased risk of SARS-CoV-2 infection in subjects with periodontitis (OR 1.69; 95% CI, 0.91–3.13, P = 0.09). However, it was found that periodontitis may worsen clinical COVID-19, since periodontitis subjects were more likely to

Table 2. Association between periodontal status and COVID-19

Author	No. of COVID-19 participants	Main results
Katz 2020 [8]	7	• Periodontal disease (PD) was not correlated with Covid-19 status, but after adjusting for cigarette smoking, patients with PD were 4.7 times more likely to have COVID-19 than patients without PD.
Marouf 2021 [1]	568	• Periodontitis was associated with COVID-19 complications, such as admission to an intensive care unit, need for assisted ventilation, and death. • White blood cells, D-dimer and C-reactive protein levels were significantly higher in COVID-19 patients with periodontitis.
Kaur 2022 [13]	116	• The chances of COVID-19 infection may increase with periodontitis. • Lymphocyte, WBC and CRP levels were increased in patients with moderate and severe COVID-19, compared to those with a milder form of the disease. • Severe periodontal disease was related to moderate-to-severe COVID-19 infection that required hospitalization.
Anand 2022 [9]	79	• Participants with COVID-19 had significantly higher mean values for plaque scores, number of missing teeth, gingival bleeding scores, PD, REC and CAL. • The mean percentages of interproximal sites with PD ≥ 4–5 mm, CAL ≥ 3–6 mm was significantly higher in the COVID-19 group than in the control group. • Percentages of subjects with mean plaque score ≥ 1, gingivitis, mean CAL ≥ 2 mm and severe periodontitis was significantly higher in the COVID-19 group.
Said 2022 [10]	1 325	• COVID-19 complication were more frequent in patients with stages 2–4 periodontitis. • Untreated periodontitis was associated with a significant risk of need for mechanical ventilation, while for treated periodontitis this risk was not significant.
Wadhwa 2022 [11]	387	• COVID-19 patients had greater alveolar bone loss compared to controls. • Patients with COVID-19 had fewer missing teeth. • COVID-19 patients requiring hospitalization had a greater alveolar crest height loss, and a greater number of missing teeth than non-hospitalized COVID-19 patients.
Gupta 2022 [12]	82	• Greater periodontitis severity was associated with a higher risk of needing assisted ventilation, hospital admission, COVID-19-associated pneumonia, and death. Patients with greater periodontitis severity ended-up in intensive care units, as opposed to patients with healthy periodontium. • Patients with bleeding gums on probing were significantly more likely to require assisted ventilation, be admitted to the hospital and become ill with COVID-19. • Probing depth, gingival recession and CAL, and higher severity of periodontitis were significantly associated with all COVID-19 complications. • Patients who died had a significantly higher mean probing depth, gingival recession and CAL, compared to those who survived.
Baima 2022 [14]	meta-analysis	• A meta-analysis of epidemiological studies showed only a non-statistically significant trend toward an increased risk of SARS-CoV-2 infection in patients with periodontitis. • Periodontitis was associated with a 4-fold increased likelihood of hospitalization, a 6-fold requirement for assisted ventilation, and more than 7-fold likelihood of death from COVID-19 complications.

experience a more severe course of COVID-19. Specifically, periodontitis was associated with a 4-fold increase in the odds of hospitalization (OR = 4.72; 95% CI, 1.11–20.03; p = 0.04), 6-fold increase in requiring assisted ventilation (OR = 6.24; 95% CI, 2.78–14.02; p = 0.00), and a more than 7-fold increase in deaths due to COVID-19 complications (OR = 7.51; 95% CI, 2.16–26.10; p = 0.00) [14].

Shared mechanisms of immune response in periodontitis and COVID-19. Current evidence suggests that the association between periodontitis and COVID-19 could be explained through the direct role of aspirated periodontal bacteria in worsening pneumonia, as well as through the indirect effect of periodontitis in inducing systemic inflammation that may exacerbate the reaction to SARS-CoV2 infection [15].

Oral opportunistic pathogens, such as *Capnocytophaga* and *Veillonella*, have been found in the bronchoalveolar fluid of COVID-19 patients [16]. It has also been proposed that in older individuals, translocated gram-negative periodontal bacteria may cause LPS-induced dysfunction and facilitate SARS-CoV 2 replication in lung cells [17]. It is widely accepted that bacterial superinfection may be widespread in severe cases of COVID-19. Bacterial infections may dominate the primary viral infection or even be the cause of death [18–20].

Overproduction of pro-inflammatory mediators, both locally and systemically, is another mechanism shared by periodontitis and COVID-19. Once a host response is triggered by an infectious stimulus, the extent of inflammatory response seems to be related to genetic/epigenetic factors rather than the type of infection. Virgos cytokine release in the host is often referred to as a 'cytokine storm'. A cytokine storm induced by SARS-CoV-2 infection appears to be the main cause of severe COVID-19. Likewise, the same mechanism plays a key role in the progression of periodontitis, and cytokine/chemokine profiles are shared in periodontitis and COVID-19, e.g. interferon (IFN)-γ, interleukin (IL)-1β, IL-6, IL-12, IL-17 and monocyte chemoattractant protein (MCP)-1 [21]. The literature also reports elevated serum levels of IL-7, IL-10, IL-17, IL-2, IL-8, IL-9, granulocyte macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), IFN-gamma, tumour mencorisi factor (TNF) alpha, macrophage inflammatory protein (MIP)1A, MIP1B, MCP1, and interferon gamma-induced protein (IP)10 [21–23].

An association between increased levels of IL-6 and COVID-19 has been demonstrated. The expression of IL-6 is known to be a strong predictor of critical illness and mortality among the patients with COVID-19. IL-6 inflammatory response via gingival fibroblasts can lead to increased cathepsin L expression which favours coronavirus adhesion. Moreover, aspiration of periodontopathogens, such as *F. nucleatum,* could induce IL-6 production by alveolar epithelial cells as well as bronchial and pharyngeal epithelial cells, which in turn could worsen the severity of viral pneumonia [1, 24]. Therefore, the concept of the use of an IL-6 antagonist (tocilizumab) for pharmacotherapy in patients infected with SARS-CoV-2 supplemented with the use of topical antiseptics (e.g. chlorhexidine) is recommended. Preliminary studies of early COVID-19 treated with tocilizumab showed promising results [24].

Activation of Th17-related inflammatory response and IL-17 is another common mechanism for COVID-19 and periodontitis. It has been demonstrated that non-surgical periodontal treatment resulted in a decrease in IL-17 levels, both in gingival crevicular fluid (locally) and systemically in patients with periodontitis [1, 12].

Another proposed immunological link between periodontitis and COVID-19 is through galectin 3 (Gal-3), a proinflammatory protein that has been involved in the disease procession of various inflammatory conditions [1, 23]. Galectins are a family of β-galactoside-binding lectins and its expression in tissues is developmentally regulated. Galectin-3 is widely expressed in human tissues. The multiple localization of galectin-3, i.e. in the cytoplasm, in the nucleus, on the cell surface and in biological fluids, contributes to its diverse functions. It is involved in cell differentiation, inflammation, fibrogenesis and host defence, in the pathogenesis of cardiovascular remodelling, as well as in various autoimmune and inflammatory processes [25]. Gal-3 has a morphology almost identical to the SARS-CoV-2 virus spike protein that plays a major role in virus entry into host cells. Inhibition of Gal-3 was shown to reduce IL-6 production which may be used as a therapeutic target. Human saliva contains exosome-derived Gal-3 vesicles, which by increasing the phagocytic activity of neutrophils and stimulating cytokine production may be involved in local immune defence in periodontal tissues [1].

It has been speculated that periodontopathogens, through the production of proteases, may help activate protein S and further increase the infectivity of COVID-19. It is probable that aspiration of periodontal bacteria may exacerbate COVID-19 by inducing the expression of ACE2, the receptor for SARS-CoV-2, and inflammatory cytokines in the lower respiratory tract. Periodontal bacteria may increase the virulence of SARS-CoV-2 by cleaving its S-glycoproteins and, at the same time, periodontal pockets may act as a reservoir for the virus [1].

Additionally, it has been shown that SARS-CoV-2 can be detected in the salivary glands, mainly the minor salivary glands, where the virus can replicate, survive, and then spread throughout the body and to other individuals. Moreover, the saliva of asymptomatic individuals contain SARS-CoV-2 that could be spread via droplets, and the amount of viral burden in saliva correlated with the presence of viral symptoms. The presence of replicating SARS-CoV-2 in oral tissues supports the idea that the oral cavity may serve as a reservoir for the virus, with the virus's potential to bind to ACE2 receptors in the oral cavity for entry into the host. Thus, optimal oral hygiene and professional plaque control could potentially decrease the microbial load in the oral cavity [2, 18].

The inter-correlation between periodontitis and COVID-19 suggests that maintaining good oral hygiene, i.e. bacterial plaque control, is essential. Reduction of bacterial exchange between the oral cavity and lungs, could reduce the risk of pulmonary complications. Periodontal treatment may also play an important role in inhibiting the release of inflammatory mediators. In fact, it was demonstrated that local antimicrobials used to prove oral hygiene in nursing home and intensive care unit patients, reduced the incidence of respiratory illnesses [26].

SUMMARY

While the data supporting the link between periodontitis and COVID-19 are not fully conclusive, there is a biological plausibility for the mechanisms that bind these diseases together. Periodontitis, along with other systemic disease, should be considered a risk factor for severe COVID-19. Therefore, it seems optimal to implement the prevention of periodontal disease in COVID-19 risk groups. An oral health maintenance strategy should specifically address the risk groups, such as the elderly, diabetics, and those with cardiovascular diseases and periodontitis. Appropriately early identification and treatment of patients with periodontitis could be beneficial in the prevention of severe COVID-19.

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