COVID-19 in periodontal patients

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Abstract
Periodontitis is a complex multifactorial disease. COVID-19 pandemic prompted researchers to look for a relationship between SARS-CoV 2 infection and periodontal diseases. The SARS-CoV 2 pathomechanism is associated with the ACE2 receptor, which is highly expressed in periodontal patients. The virus causes a cytokine storm which is also seen in periodontitis. Periopathogen proteases can degrade the S protein of the virus, which facilitates its entry into the host cell. In addition, galectin-3, a protein present in periodontitis, is morphologically similar to the S protein of the virus, which may cause the easier attachment of the virus with the host cell more easily and increase the immune response. In patients infected with SARS-CoV 2, oral lesions such as erosions, ulcers, petechiae, acute parotitis and necrotizing gingivitis occur. The aim of the study is to present the latest reports on the possible mechanisms of the influence of periodontal diseases on the infection and course of SARS-CoV 2 infection and to describe cases of changes in the oral cavity in the course of COVID-19.

Keywords: COVID-19, SARS-CoV-2, periodontitis
Introduction
In December 2019, WHO announced the first case of a patient from Wuhan in China infected with SARS-CoV 2. On March 11, 2020, WHO officially announced the COVID-19 pandemic [1, 2]. SARS-CoV 2 comes from the Coronaviridae virus family and may cause diseases of the respiratory, nervous and digestive systems [3]. The range of routes for spreading the virus is wide and includes the droplet route, contact route, confined space aerosol, and urine [4]. In addition, the probability of infection by the fecal-oral route and from mother to child is being investigated [5, 6]. The viral envelope is covered with membrane proteins S (Spike) and envelope proteins (E). It covers the viral RNA and the phosphorylated nucleocapsid (N) protein [7]. The pathomechanism of SARS-CoV 2 is related to the angiotensin converting enzyme receptor 2 (ACE2), which is expressed on the cells of the lung tissue, small intestine, heart, kidney, testes and also in minor amounts in the blood vessels, liver, spleen, colon and muscles [3, 8]. After entering the human body, the receptor binding domain (RBD), derived from the S1 subunit of the S protein, binds to ACE2 receptors on the surface of host cells. Subsequent changes in the structure of the S protein cause the virus to fuse with the cell membrane of the host cell and penetrate it. The virus multiplies and the cell is lysed [1, 3, 9, 10]. Periodontitis is a multifactorial disease that includes both bacterial factors, host factors and environmental factors [11]. Tissue damage occurs mainly through the release of inflammatory mediators associated with overactive host factors [12]. The main bacteria responsible for causing inflammation are Porphyromonas gingivalis, Prevotella intermedia and Fusobacterium nucleatum [13]. The relationship between periodontitis and systemic diseases has been studied over the years. It is assumed that in diseases of the respiratory system a significant role is played by: direct aspiration of pathogenic microorganisms to the respiratory tract, changes in the structure of mucous membranes, promoting adhesion and invasion of pathogens, and inhibition of the innate response by enzymes of periopathogens [14]. Scannapieco et al. found a significant relationship between poor oral hygiene and the incidence of nosocomial pneumonia [15]. On the other hand, Gomes et al. showed a relationship between periodontitis and respiratory diseases: asthma, chronic obstructive pulmonary disease (COPD) and pneumonia [16]. Moreover, it has also been proven that taking action against oral pathogens can minimize the incidence of respiratory diseases in people in intensive care units or in nursing homes [17]. The research conducted so far on the relationship between periodontal diseases and respiratory diseases has led researchers to consider the relationship between periodontal diseases and COVID-19 [18].

Materials and methods
The authors searched PubMed using the searchterms coronavirus, SARS-CoV2, periodontitis, periodontal disease, COVID-19 for studies published from January 2020 to June 2021. We manually searched the references of selected articles for additional relevant articles. We selected articles relevant to a general medicine readership, prioritizing systematic reviews, cases and clinical practice guidelines. The literature contains the latest reports on COVID-19 in periodontal patients. Papers in which the mechanisms and changes in the oral cavity were confirmed with an infection other than SARS-CoV 2 were rejected.

Results and discussion
Influence of periodontal diseases on SARS-CoV infection

The host's immune system plays an important role in the pathogenesis of periodontal diseases [19]. In patients with gingivitis and periodontitis, a significant increase in the number of IL-17 producing cells in periodontal tissues has been demonstrated. Moreover, the same phenomenon was observed in the blood serum of patients [20, 21]. Increased levels of cytokines locally reflect their amount in the peripheral blood of the body [22]. The symptoms of COVID-19 may be associated with elevated levels of IL-1β, IL-2, IL-7, IL-8, IL-10, IL-17, IFN-γ and TNF-α, what is called a "cytokine storm" [23]. Significantly increased amounts of these cytokines have been noticed in patients hospitalized in intensive care units [24]. Many of them stimulate the immune response of Th-17 lymphocytes, which leads to lung tissue damage and pulmonary edema [23]. Takahashi et al. in their study found that Fusobacterium nucleatum induces ACE2 expression in the alveolar epithelium, and also enhances the production of IL-6 and IL-8 in respiratory epithelial cells [25]. The above information may suggest a relationship between periodontal diseases and the severe course of COVID-19 [26].

Periopathogens present in the oral cavity increase the expression of the ACE2 receptor, which promotes SARS-CoV 2 infection [27]. According to studies, most healthy people aspire to the respiratory tract during sleep, and an even greater percentage occurs in the elderly [28, 29]. It has been shown that periodontal bacteria can be observed in bronchoalveolar lavage [30]. In recent studies, periopathogens have been detected in bronchoalveolar lavage fluid of COVID-19 patients [31]. Aspirated periopathogens by pathogenic agents increase ACE2 expression in bronchi and lungs, which may contribute to an increased risk of SARS-CoV 2 infection [32].

During SARS-CoV infection, the virus's S protein is degraded by proteases, which promotes fusion with the host cell [33]. Such proteases include furin and TMPRSS2. Despite their presence in the oral cavity, periodontal proteases may also contribute to cleavage of S protein, which promotes SARS-CoV 2 infection [32, 34]. Higher levels of acute phase proteins, in particular C-reactive protein, have been observed in patients with periodontitis [35]. One of the proinflammatory proteins is galectin-3, which is one of the factors responsible for T-cell inflammation [36]. Galectin-3 has been shown to be present in immune cells, epithelial and endothelial cells [37]. Kara et al. described a positive relationship between the high level of galectin-3 and the advancement of the depth of the periodontal pocket, which allows treating this biomarker as an acute phase factor in periodontal pockets [38]. Caniglia et al. demonstrated a relationship between SARS-CoV 2 and the aforementioned galectin-3. Virus's S protein, especially important at the time of virus entry into the cell, has been shown to be morphologically very similar to galectin-3 [39]. The N-terminal domain of the S protein (S1-NTD) strongly interacts with a molecule commonly found in cells - GM1 ganglioside [40]. Moreover, it was observed that galectins bind GM1 ganglioside with high affinity. It can be assumed that inhibition of galectin-3 may lead to disruption of virus-cell association, and thus reduce its activity. In patients infected with SARS-CoV 2, galectin-3 inhibitors reduce the amount of proinflammatory cytokines secreted, and decrease the levels of TNF-α and IL-6 [39, 41]. The relationship between periodontal disease and COVID-19 may be due to galectin-3-induced increased immune response as well
as increased viral-cell association caused by this acute-phase protein [38].

**Oral changes in COVID-19**

SARS-CoV 2 has been detected in the saliva of infected patients, and it has been found that the saliva RT-PCR test may be even more sensitive than the nasopharyngeal secretion test [42]. In addition, ACE2 receptors have been demonstrated to exist in the oral mucosa, particularly on the back of the tongue [43]. Eruptions in the course of COVID-19 include: erosions, ulcers, blisters, spots, papules, vesicles, pustules or hemorrhagic crusts. Moreover, a crimped or smoothed tongue, ecchymosis, erythema and halitosis are observed [42]. The most common affected sites include: the hard palate, the dorsal surface of the tongue, and the mucosa of the lips [44].

The most common changes observed are ulcerative changes. Most studies refer to single ulcers [45-47], but mention also of multiple and minor lesions [48, 49] Ciccarese et al. reported the case of a 19-year-old woman who presented with multiple erosions, ulcers, and scabs. on the lips and bruises on the gums and the palate [50]. There have also been reports of macular or macula-vesicular lesions on the oral mucosa in patients with COVID-19 accompanied by erythematous changes [50-52].

Capaccio et al. reported a case of a 26-year-old patient with SARS-CoV 2 infection who had a painful swelling of the left parotid gland without purulent exudate. Serological tests for antibodies to paramyxovirus and cytomegalovirus were negative. It was the first symptom of COVID-19, it was followed by fever, myalgia, and disturbed sense of smell and taste [53].

Lechien et al. also reported three cases of COVID-19 patients who developed acute parotitis without purulent discharge, and MRI confirmed interstitial lymphadenitis [55]. A similar case of a 21-year-old woman with unilateral painful swelling of the parotid gland in the course of COVID-19 was reported by Fischer et al. [55].

Patel et al. presented the case of a 35-year-old woman who presented with severe pain and bleeding gums and halitosis. The patient developed a fever 3 days earlier. Intraoral examination revealed necrotic interdental papillae and bleeding from gingival gaps without detecting loss of connective tissue attachment. Necrotizing gingivitis was diagnosed. [56]

**Conclusion**

In recent years, the relationship between periodontal diseases and systemic diseases has been intensively studied. Following the COVID-19 pandemic, many researchers began looking for links between SARS-CoV 2 infection and oral disease. The presented literature describes possible mechanisms of an increased risk of SARS-CoV 2 entry into the body and a more severe course of COVID-19 in patients with periodontitis. Moreover, numerous changes on the mucosa have been observed in those infected with the coronavirus. Their presence often precedes systemic symptoms, and knowledge may be useful in the early diagnosis of infection. More than a year has passed since the beginning of the pandemic, and there is still no long-term research. The described cases may lead to the search for potential relationships between periodontal diseases and COVID-19. In order to better understand the possible mechanisms, more research is needed.
References


