REVIEW

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ORAL CLINICAL MANIFESTATIONS IN PATIENTS WITH COVID-19: A REVIEW

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Abstract. *One of the latest newly isolated diseases is COVID-19. COVID-19 is a highly contagious viral disease caused by SARS-CoV-2, a virus that belongs to the Coronaviridae family, Beta-coronavirus genus. To achieve the main purpose, a search was conducted in various databases (PubMed, Google Scholar, ResearchGate) and Internet sites with scientific information by keywords: COVID-19, oral manifestations, oral pathology, orale Manifestationen, Läsionen der Mundschleimland, Geschmacksstörungen, Geruchsstörungen. The collected scientific information is systematized according to 4 main criteria: etiology, pathogenesis, oral manifestations, ways to improve the condition in the oral cavity, preventive measures.*

Key words: *COVID-19, oral manifestation, strategies*

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INTRODUCTION

Viral diseases remain a persistent concern for the human population, posing a significant threat to public health. One of the more recent viral diseases to emerge is COVID-19, an exceptionally contagious viral infection caused by SARS-CoV-2, a member of the Coronaviridae family within the Beta-coronavirus genus [1]. In December 2019, a series of disease cases were identified and confirmed in Wuhan, China. Subsequently, on March 11, 2020, the World Health Organization (WHO) classified COVID-19 as a pandemic [2]. According to the latest data from the WHO, there have been 761,402,282 reported cases worldwide, with 6,887,000 resulting in fatalities [3]. The Unified Information Portal of the Ministry of Health in Bulgaria indicates 1,300,490 confirmed cases, out of which 1,259,623 individuals have recovered, while 38,268 have succumbed to the disease [4].

SARS-CoV-2 has been identified as an airborne pathogen, primarily transmitted through close contact with both asymptomatic and symptomatic individuals, via the inhalation of respiratory droplets and aerosols [5]. It exhibits a high level of contagion, with direct or indirect transmission being possible. The virus remains viable in the air for up to 3 hours and can persist on surfaces for approximately 72 hours. The incubation period of the virus ranges from 1 to 14 days [6], after which clinical symptoms of the disease may manifest. Typically, these symptoms involve acute respiratory issues accompanied by fever, myalgia, fatigue, and alterations in the sense of taste and smell. The respiratory system, particularly the lungs, serves

as a major site of infection in COVID-19 patients. However, the oral cavity and salivary glands can also be affected. Possible oral manifestations include oral cavity lesions, aphthous-like ulcers, stomatitis, oral candidiasis, and herpes recurrences. These clinical findings are predominantly observed in immunocompromised patients and the elderly [7]. Notably, the loss of taste and smell is a distinct symptom associated with this viral infection, stemming from the virus's unique pathogenic mechanism of action.

AIM

The aim of this literature review is to examine and analyze the current scientific information available regarding oral clinical manifestations in patients with COVID-19. In order to accomplish this objective, a comprehensive search was conducted in various databases, including PubMed, Google Scholar, and ResearchGate, as well as websites containing scientific information. The search utilized keywords such as "COVID-19," "oral manifestations," "oral pathology," "orale Manifestationen," "Läsionen der Mundschleimland," "Geschmacksstörungen," and "Geruchsstörungen." The survey was conducted between January and March 2023.

The gathered scientific information was organized and categorized according to four main criteria: etiology, pathogenesis, oral manifestations, and strategies to improve oral cavity conditions and implement preventive measures.

Etiology

The *Coronaviridae* family comprises enveloped positive single-stranded RNA viruses. The viral particle is enveloped by a protein capsid and a lipid bilayer known as the envelope [8]. The large RNA genome is associated with the N-protein, forming a helical nucleocapsid. Within the virus particle, a central core and a matrix can be distinguished. The central core contains the single-stranded linear RNA genome, while the matrix is situated between the nucleocapsid and the lipoprotein envelope. The viral outgrowths resemble the appearance of a "solar corona." Coronaviruses possess three groups of proteins: the nucleocapsid protein, the virion envelope glycoprotein antigen, and the matrix protein [9]. The envelope contains three proteins: membrane protein (M), spike protein (S), and envelope protein (E), as well as the nucleocapsid protein [1, 10]. The spike protein (S) plays a crucial role in the attachment to target cells and subsequent infection. It binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell and is then cleaved by the transmembrane protease serine 2, which facilitates virus entry into the cell [11]. The SARS-CoV-2 virus demonstrates a notable affinity for tissues that express ACE receptors. Consequently, these cells serve as prime targets for the virus and exhibit high susceptibility to infection. ACE receptors are abundantly expressed in various regions of the human body, including alveolar epithelial cells in the lungs, esophageal epithelium, enterocytes in the intestines, cholangiocytes in the bile ducts, myocardial cells in the heart, and the mucous membrane of the oral cavity. The substantial presence of ACE receptors in the oral mucosa is a significant factor contributing to the observation of clinical symptoms within the oral cavity [2].

Pathogenesis

The pathogenesis of SARS-CoV-2 involves a series of steps, typical of viral infections. These steps include attachment to host cells, entry of virus particles, unmasking of the virus (envelope destruction and genome release), synthesis of viral components, formation of virus particles, and ultimately, the release of the virus from the infected cell to infect new cells [9].

The oral cavity serves as a connection between the external environment and the body, making it a potential route for the virus to enter. The virus can enter cells through two mechanisms: either by binding to peptidases on the host cell membrane (where peptidases act as receptors) or by endocytosis, where the cell engulfs the virus. These mechanisms are described in the scientific article by Drozdzik A. et al. [12].

The primary mechanism of entry involves the viral spike (S) protein on the envelope binding to angiotensin-converting enzyme 2 (ACE2), which is a metallopeptidase located on the cell membrane. The spike protein is cleaved into two subunits, S1 and S2, by a protease originating from the host cell. The S1 subunit dissociates from the rest of the spike protein, while the S2 subunit is cleaved by transmembrane serine protease 2. This cleavage enables fusion with the host cell membrane and subsequent invasion of the cell.

The endosomal pathway occurs when the SARS-CoV-2 spike protein interacts with the ACE2 receptor on host cells, leading to the endocytosis of the virus. Within the endosome, the spike protein is processed by cathepsin L, resulting in the cleavage of S1 and S2 and facilitating the fusion of the viral capsid with the endosomal membrane. This endosomal processing ultimately leads to the release of the viral genome [10].

Following the release of the viral genome into the host cell, a synthesis process ensues, leading to the assembly of virus particles. Mature virus particles then spread throughout the body, infecting other cells in the process.

Oral manifestations in patients with COVID-19

Oral manifestations in patients with COVID-19 have been observed and studied by various researchers. The oral cavity serves as a mirror reflecting the overall health of the body and possesses defense mechanisms against microbial invasion, including the oral mucosa, nonspecific innate immunity, and adaptive acquired immunity. The oral mucosa acts as a physical barrier protecting underlying tissues from microorganisms. The presence of immune cells in the *lamina propria* further supports the immune function of the oral cavity [13, 14].

The oral symptoms associated with COVID-19 can occur either directly as a result of the virus affecting oral structures or as secondary manifestations due to long-term pharmacotherapy. These symptoms are more commonly seen in older individuals and immunocompromised patients, and predisposing factors include poor oral hygiene, opportunistic infections, and stress. Swain S. et al. highlight the importance of thorough oral examinations for early diagnosis and treatment of oral symptoms such as oral ulcerations, gingival bleeding, dry mouth, halitosis, burning sensation, and difficulty swallowing. While some of these symptoms may be associated with systemic diseases, they can also be observed as local manifestations in patients with COVID-19 [7].

Studies by Huang N. et al. and Iranmanesh B. et al. indicate that the tongue, labial mucosa, buccal mucosa, and palate are commonly affected sites for oral manifestations of COVID-19 [5, 14].

Chemosensory disorders, including taste and smell disturbances, are frequently reported in patients with COVID-19. These disorders can manifest as reduced sensation for taste (hypognosia), complete absence of taste (agnosia), or qualitative distortion of taste perceptions (dysgnosia). Gastrointestinal disturbances are also common, occurring in approximately 40% of COVID-19 patients and typically diagnosed between 2 and 14 days after exposure to the virus. The invasion of the virus into taste buds can lead to their damage, resulting in dysgnosia. Figure 5 depicts a depapillated tongue, which is a clinical manifestation described by Genesan A. et al. [16]. Studies suggest that taste and smell alterations can be attributed to direct damage caused by the virus to the corresponding cells, although neurotropism and involvement of the central nervous system with high expression of ACE2 in endothelial cells and neurons have also been proposed. However, the direct effect of the virus on taste and smell cells appears to be a more common mechanism [1, 6, 12, 15, 16, 17, 18].

Xerostomia, or dry mouth, is often observed as a symptom of COVID-19 due to the abundance of ACE2 receptors in the salivary glands, tongue, and oral mucosa. The degenerative properties of the virus can lead to the destruction of acinar cells, which are responsible for saliva production. The disrupted structure of these cells impairs the effective formation of saliva. Xerostomia can cause burning sensation in the mouth, difficulty swallowing, and an increased risk of developing tooth decay due to the insufficient amount of saliva that hampers effective cleaning of tooth surfaces. Infection of acinar cells in the salivary glands triggers a local inflammatory reaction, resulting in salivary gland dysfunction and xerostomia as a clinical consequence [1, 7, 12, 15, 17].

Aphthous-like lesions are another oral manifestation seen in patients with COVID-19. These lesions appear as multiple shallow ulcers with erythematous halos and yellow-white pseudomembranes on both keratinized and non-keratinized mucosa. Non-necrotic aphthous-like lesions are more commonly observed in younger patients with mild infection, while necrotic aphthous-like lesions with hemorrhagic crusts are more frequently seen in older patients, immunosuppressed individuals, and those with severe systemic infections. These lesions typically heal within approximately 10 days [14, 17, 19, 20].

Herpetiform lesions have also been described in scientific studies. They manifest as numerous painful, unilateral round ulcers with a yellowish-gray appearance and an erythematous border on both keratinized and non-keratinized mucosa. The presence of these lesions often precedes systemic symptoms. Clinically, a wide range of oral ulcerations has been observed, ranging from lesions resembling aphthous stomatitis to generalized ulcerations with necrosis. Some of these oral lesions exhibit a herpetiform pattern resembling herpes infection, although they test negative for herpes simplex virus. Immunosuppression and stress associated with COVID-19 are considered possible reasons for the occurrence of secondary herpetic gingivostomatitis. Acute COVID-19 infection, combined with inadequate therapeutic measures, may contribute to adverse oral health outcomes [13-15].

Ulcerative/erosive lesions manifest as painful lesions with irregular borders on the tongue, hard palate, and oral mucosa. Various factors have been suggested as causes for the development of these lesions, including the use of drugs (often non-steroidal anti-inflammatory drugs), vasculitis, or thrombotic vasculopathy secondary to COVID-19 [21-25].

The presence of **white and red spots or plaques** on the back of the tongue, gingiva, and palate has been reported in several scientific papers. **Candidiasis**, caused by *Candida albicans*, can occur as a secondary effect of COVID-19 due to factors such as prolonged antibiotic therapy, deterioration of general condition, and decline in oral hygiene. *Candida albicans* is a normal part of the human microbiome and does not cause harm in individuals with a healthy immune system. However, when the immune system is compromised, it can lead to infections of the skin and mucous membranes. Bacterial and fungal co-infections are considered secondary effects of COVID-19 rather than direct damage caused by SARS-CoV-2. Patients with oral candidiasis often experience local discomfort, taste disturbances, burning sensation in the oral cavity, glossodynia, and dysphagia [7, 14, 16].

The oral mucosa, which is covered with a multi-layered squamous epithelium, contains multiple sections that are potentially susceptible to SARS-CoV-2 infection due to the presence of ACE receptors. This makes the oral cavity prone to infection and possible transmission of the virus to the respiratory system and gastrointestinal tract. The colonization of the oral mucosa by SARS-CoV-2 has been demonstrated in studies [5, 12, 26].

Enanthema, the presence of rashes or lesions on mucous membranes, can develop in various viral diseases, including COVID-19. Different types of enanthema have been reported, such as aphthous ulcers, Koplik spots, Nagayama spots, petechiae, papulovesicular or maculopapular lesions, white or red spots, and swelling of the gums and lips [14].

Kawasaki-like disease, referred to as Kawa-COVID, has been observed in some patients with oral manifestations such as glossitis, cheilitis, erythema, and a swollen tongue (referred to as strawberry tongue) [27]. The onset of oral or cutaneous manifestations in Kawasaki-like disease is delayed compared to respiratory or gastrointestinal symptoms due to a delayed hyperactivation response. The release of acute inflammatory mediators in response to the direct impact of the virus on the skin and oral mucosa is believed to be the cause, rather than direct effects of the virus itself [7, 14].

It has been suggested that the gingival sulcus, which is an established ecosystem in the oral cavity, could potentially serve as a reservoir for SARS-CoV-2. The presence of increased levels of pro-inflammatory cytokines in inflamed gingiva in COVID-19, such as IL-1β and TNF-α, may indicate local inflammatory conditions. The impaired immune function caused by SARS-CoV-2 infection can promote the expansion of periodontal pathogens in periodontal pockets, leading to the development of acute periodontal conditions. Periodontal diseases, including periodontitis, are inflammatory pathologies that can result in the progressive destruction of the periodontium. The immune defense of the host against pathogens is the main cause of periodontal disorders. Periodontal bacteria also have the potential to enter the bloodstream and spread systemically, contributing to disease in remote organs. Transient bacteremia can occur during activities such as tooth brushing, chewing, flossing, and certain dental procedures [6, 7, 13].

Patients with COVID-19 may experience symptoms such as **halitosis** (bad breath), **submandibular lymphadenopathy** (enlarged lymph nodes under the jaw), and **various oral lesions**. Oral lesions can include diffuse erythematous lesions, painful swollen gingiva (gums), necrosis of the interpapillary areas, and the presence of papules, spots, and plaques on the mucous membranes of the lips, tongue, hard palate, and oropharynx. Immunosuppression and stress associated with COVID-19 infection can contribute to the development of a secondary type of herpetic gingivostomatitis [28-30]. Some COVID-19-positive patients may also develop blisters on the mucous membranes of the lips, desquamative gingivitis, and skin rashes. The presence of ulcers, vesicles, and petechiae on the mucous membranes of the tongue, palate, lips, gums, and cheeks has also been observed in COVID-19 patients, although it is not yet clear whether these symptoms are directly caused by SARS-CoV-2 infection or are a result of immune dysfunction or superinfection with other microorganisms [7, 8].

Based on the scientific information gathered, we can draw the following conclusions:

1. The causative agent of COVID-19, SARS-CoV-2, primarily affects the respiratory system but can also affect the oral cavity as an entry point for the virus.
2. Chemosensory disturbances (loss of taste and smell) and xerostomia (dry mouth) are the most commonly reported oral symptoms associated with COVID-19.
3. Oral symptoms observed in COVID-19 patients can be a direct result of the viral action on oral structures or may occur as secondary manifestations due to long-term pharmacotherapy, such as corticosteroids or antibiotics.
4. Oral manifestations of COVID-19 are more likely to occur in immunocompromised patients, those with poor oral hygiene practices, and individuals with harmful habits (e.g., smoking, excessive alcohol consumption).

5. Prevention measures, including the use of local antiseptics and regular dental check-ups, can help limit oral manifestations associated with COVID-19.

It's important to note that these conclusions are based on the available scientific literature, and further research is still needed to fully understand the oral manifestations and their implications in COVID-19.

Strategies to improve the condition of the oral cavity, preventive measures

To improve the condition of the oral cavity and implement preventive measures in the context of COVID-19, the following steps can be taken [1]:

1. Patient triage: Organize the work schedule in a way that allows sufficient time between patient visits for disinfection, ventilation, and preparation of the dental office. Avoid crowding in the waiting room by managing appointments effectively.
2. Infection control and hygiene practices: Strictly adhere to infection control protocols, including proper hand hygiene, use of personal protective equipment (PPE) such as masks, gloves, and face shields, and regular disinfection of surfaces and instruments. Follow the guidelines provided by relevant health authorities.
3. Aerosol management: Implement measures to reduce aerosol generation during dental procedures, such as using high-volume evacuation systems, rubber dams, and pre-procedural rinses with antimicrobial solutions. Consider the use of alternative techniques or technologies that minimize aerosol production.
4. Environmental measures: Ensure proper ventilation in the dental office to improve air circulation and reduce the concentration of airborne particles. Use air purifiers or filtration systems if necessary.
5. Patient education: Provide patients with information about preventive measures, such as maintaining good oral hygiene practices, including regular brushing and flossing, and the use of mouthwashes with antimicrobial properties. Encourage patients to report any oral symptoms or changes in their oral health.
6. Vaccination: Encourage both dental healthcare professionals and patients to get vaccinated against COVID-19 as per the recommendations of health authorities. Vaccination plays a crucial role in preventing severe disease and reducing transmission.
7. Regular dental check-ups: Encourage patients to maintain regular dental visits for preventive care and early detection of oral health issues. Dentists can identify and address any oral manifestations or symptoms associated with COVID-19 during these visits.

It's important to stay updated with the guidelines provided by local health authorities and dental associations, as recommendations may vary based on the evolving understanding of the virus and its transmission.

Indeed, dental procedures that involve water-air cooling can generate aerosols containing saliva, bacteria, viruses, and blood, which can contribute to the spread of SARS-CoV-2. To mitigate this risk, the use of personal protective equipment (PPE) is crucial. Dentists should wear work equipment, masks, hats, protective glasses, helmets, and gloves to minimize exposure to aerosols and ensure their own safety.

Hand hygiene is of utmost importance and should be performed before starting work and after each patient. The World Health Organization (WHO) recommends the use of alcohol-based hand sanitizers containing 60-70% ethanol, as it effectively inactivates bacteria and viruses, including SARS-CoV-2.

Maintaining good oral hygiene is also essential in preventing the severity of COVID-19 symptoms. Patients should be encouraged to strengthen their oral hygiene habits. Recent studies have shown that patients with poor oral hygiene experience more severe symptoms of COVID-19, while those with good oral hygiene exhibit reduced symptoms [31].

According to studies conducted by Cascella M. et al., the treatment of the disease depends on the severity of the clinical symptoms. Clinically, the disease proceeds in two phases - early and late phase. During the early phase, increased virus replication is observed. According to studies, the application of antiviral drugs is most effective in this period of the disease. The later phase of the disease is defined by a hyperinflammatory state caused by the release of cytokines. At this stage, anti-inflammatory drugs such as corticosteroids, immunomodulatory therapies, or a combination of these may be more effective than antiviral therapies [10].

The use of oral antiseptics has been reported to help eliminate SARS-CoV-2 from the oral cavity. Povidone-iodine, hydrogen peroxide, and chlorhexidine are three commonly recommended oral antiseptics against SARS-CoV-2. These agents have been shown to reduce the viral load in saliva for a period of 2-3 hours after rinsing the mouth [12]. Therefore, it is advisable to use antiseptics, especially before examining or treating the oral cavity. It is important to note that common ingredients in toothpastes and mouthwashes can also affect the interaction between

the spike protein and the ACE2 receptor, potentially influencing viral transmission.

Additionally, it is recommended to regularly change toothbrushes and disinfect them. Immersing the brush head in a diluted hypochlorite solution for approximately 30 minutes followed by rinsing with water and allowing it to dry, can be an effective method of disinfection [29].

These preventive measures, including proper use of PPE, hand hygiene, good oral hygiene practices [12, 17, 29, 30] and the use of oral antiseptics, contribute to reducing the risk of SARS-CoV-2 transmission in the dental setting. It is important to stay updated with guidelines from local health authorities and dental associations for the latest recommendations [31-35].

Conclusions

The oral cavity can serve as an entry point for the SARS-CoV-2 virus, leading to characteristic clinical manifestations in COVID-19 patients. Dysgeusia, or taste disturbances, is a common early symptom observed in infected individuals. Co-infection with Candida albicans can occur as a result of the treatments used for severe cases of COVID-19. It is important for patients presenting with such symptoms to undergo oral cavity examination. Factors such as poor oral hygiene, stress, and opportunistic infections can contribute to a more severe course of the disease. Dentists play a crucial role in the diagnosis, treatment, and prevention of infection spread by implementing appropriate treatment protocols, utilizing modern disinfectants and antiseptics, and organizing the treatment process accordingly. By understanding the relationship between COVID-19 and the oral cavity, dental professionals can contribute to comprehensive patient care and help prevent the transmission of the virus. It is essential to stay updated with the latest research and guidelines from health authorities to ensure the best possible management of oral manifestations associated with COVID-19.

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