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Review

COVID-19 manifestation in the oral cavity – a narrative literature review

Manifestazioni nella cavità orale dell'infezione da COVID-19 – revisione della letteratura

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SUMMARY

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recently discovered coronavirus, which in 2020 led to a global pandemic. Clinical manifestations of COVID-19 are very diverse and symptoms range from mild to severe. Correlated symptoms might also manifest in the oral cavity, which is a potential pathway for viral infection, and therefore might be a potential pathway for SARS-CoV-2. In recent research among patients with SARS-CoV-2 infection, taste and olfactory disorders, dry mouth, drones and inflammation of mouth, bitter taste in mouth, difficulty in swallowing and burning sensations have been reported. There have been cases of oral mucosal lesions in patients diagnosed with COVID-19 disease. Some correlations between periodontitis and severity of COVID-19 disease have also been observed. Oral mucosa, due to occurrence of ACE2 receptors, is highly susceptible to SARS-CoV-2 infection. The occurrence of changes on oral mucosa should increase the alertness of dental practitioners. However, knowledge in this area is still limited and in the field of oral manifestations of COVID-19 more research and patient observations are required.

KEY WORDS: COVID-19, SARS-CoV-2, oral cavity, oral mucosa

RIASSUNTO

I sintomi correlati all'infezione da SARS-CoV-2 si possono manifestare anche nella cavità orale, e potrebbe rivestire un ruolo cruciale nella diagnosi precoce della malattia. Abbiamo condotto una revisione della letteratura, riguardante le manifestazioni nella cavità orale dell'infezione da SARS-CoV-2. La cavità orale rappresenta uno dei punti di ingresso dei patogeni nel corpo umano e pertanto costituisce una potenziale sede di annidamento anche del SARS-CoV-2. ACE2 è il recettore principale che interagisce con la proteina spike del virus, ritrovata nei tessuti della mucosa orale. Sono stati osservati casi di lesioni della mucosa orale in pazienti con diagnosi di infezione da COVID-19. Sono state anche riportate alcune associazioni tra parodontite e gravità della malattia COVID-19. La mucosa orale, a causa della presenza dei recettori ACE2, è altamente suscettibile all'infezione da SARS-CoV-2. Tuttavia, le evidenze in questo settore sono ancora limitate e sono necessarie ulteriori ricerche e osservazione dei pazienti.

PAROLE CHIAVE: *COVID-19, SARS-CoV-2, cavità orale, mucosa orale*

Introduction

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recently discovered coronavirus. COVID-19 emerged in China and spread rapidly around the world, posing a huge threat to the human population, which led to a global pandemic declared in March 2020 by the World Health Organization (WHO) [1]. In Febru-

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ary 2021, COVID-19 was diagnosed in almost 104 million people and contributed to the death of more than 2 million patients, becoming the worst health challenge that our generation has had to face.

Coronaviruses are a diversified class of RNA-viruses with zoonotic origin, characterised by high transmission in humans and respiratory infections. In 2002 and 2012, two highly pathogenic coronaviruses appeared in population, a severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), becoming the cause of deadly respiratory illness [2]. SARS-CoV-2 is significantly different from SARS-CoV and MERS-CoV in both its genome structure and spike protein structures. SARS-CoV-2 has higher affinity to the cellular receptor angiotensin-converting enzyme 2 (ACE2), which results in easier entrance to human cells than SARS-CoV and MERS-CoV, faster spread in humans and higher mortality rate [3,4]. The infectivity of SARS-CoV-2 is strictly correlated with the ability of virus to enter human body cells with ACE2 as the primary receptor interacting with virus spike protein when entering the cell [5].

SARS-CoV-2 is characterised by high level of transmissibility and ability to spread from human to human by aerosol and contact [6]. This virus is viable in air for 3 hours and on plastic and stainless-steel surfaces for 72 hours [7]. The incubation period for the virus varies from 1 to 14 days. After symptoms are observed, a diagnosis can be achieved by real-time PCR (RT-PCR). SARS-CoV-2 can be detected in fluids from throat swabs, secretions of the lower respiratory tract and blood [7,8].

The aim of this review is to summarise current knowledge about the oral manifestations of SARS-CoV-2, which could improve diagnosis of COVID-19.

Clinical manifestations of COVID-19

COVID-19 is mainly associated with pneumonia, which in more severe cases can develop into acute respiratory distress syndrome (ARDS). The severity of infection can be assessed based on the results of a biochemical blood test including level of albumin, lactate dehydrogenase, C-reactive protein, lymphocytes and neutrophils [9]. Patients with COVID-19 disease present symptoms such as leukocytosis, leukopenia and lymphopenia, hypoalbuminaemia, an increase of lactate dehydrogenase, aspartate transaminase, alanine aminotransferase, bilirubin and D-dimer [10]. To improve prognosis of COVID-19, patients should be provided with respiratory support at early stages of the disease [11].

Clinical manifestations of COVID-19 are very different and observed symptoms range from mild to severe. The most common symptoms are fever, cough, fatigue, complicated dyspnoea and pneumonia. Other less frequently reported symptoms include headache, haemoptysis, diarrhoea, runny nose and phlegm-producing cough [12]. In the most severe cases, symptoms rapidly progress to acute respiratory distress syndrome, respiratory failure and multiple organ failure, becoming the cause of death [7]. Patients with general comorbidities such as diabetes, cancer, cardiovascular diseases are more susceptible to develop complications of COVID-19 [7,8,13]. Middle-aged and elderly patients with chronic diseases are also more susceptible to respiratory failure and have poorer prognoses [11]. In addition, patients with moderate and severe periodontitis are more susceptible to general health complications of COVID-19 [14]. Although periodontitis is commonly correlated with other chronic inflammatory diseases as diabetes and hypertension, which are known risk factors of severe COVID-19 [15,16], periodontitis has a significant impact on the severity of COVID-19 [14].

The influence of SARS-CoV-2 on the human body remains unknown, although there are also symptoms in the oral cavity, which may play a crucial role in the early diagnosis of COVID-19 [17].

Materials and methods

A literature search for relevant papers in the literature from January 2020 to February 2021 was conducted using PubMed and Scopus databases. We included only studies on the oral manifestations of SARS-CoV-2 infection. Key words included: SARS-CoV-2 infection, SARS-CoV-2 symptoms, SARS-CoV-2 in oral cavity, COVID-19 symptoms, COVID-19 disease, SARS-CoV-2 in saliva, oral cavity, taste impairment, dry mouth, oral mucosa lesions.

ACE2 receptors in oral mucosal tissues and saliva

The infectivity of SARS-CoV-2 is dependent on the ability of the virus to enter human cells and it has been shown that ACE2 is the primary receptor interacting with virus spike protein, which enables cell entry [5]. The oral cavity is one of the entry points to the body and a potential pathway for viral infection, and therefore might be a potential pathway for SARS-CoV-2 [18]. There is also a possibility that oral mucosa might be a potential route of entry for SARS-CoV-2 into human cells [19]. The SARS-CoV-2 cellular entry receptor ACE2 is found in oral mucosal tissues including the tongue and floor of the mouth [20]. However, ACE2-positive cells are also observed in other oral mucosa tissues such as buccal and gingival epithelial cells [21]. The presence of ACE2 receptors in oral tissues suggests that the oral cavity

can be perceived an initial site of entry for SARS-CoV-2 [21]. Another potential reservoir for SARS-CoV-2 in the oral cavity might be gingival sulcus, which is a well-established ecosystem promoting colonisation of microorganisms [22,23]. In both clinically healthy and pathological pockets, other viruses, such as herpes simplex virus and human papilloma virus have been discovered [24,25]. SARS-CoV-2 RNA has also been identified in the ulcerated squamous cell carcinoma of the tongue. This finding could be of some interest as it emphasises the potential risk for pathologists handling samples from asymptomatic patients with unknown SARS-CoV-2 status [26]. Therefore, according to the study by Chen et al. SARS-CoV-2 can be detected in saliva. This might be correlated to the presence of ACE2 receptors and their tissue distribution [27]. In research by Liu et al., it was shown that salivary gland epithelial cells are characterised by high expression of ACE2 receptors [28]. It should be mentioned that ACE2 expression is higher in minor salivary glands than in lungs, which might lead to the possibility that salivary glands might be an important site for SARS-CoV-2. It has also been observed that the possibility of SARS-CoV-2 nucleic acids in saliva is higher among patients with more progressed infection [27]. Furthermore, dysfunction of salivary glands in late stage of COVID-19 infection was observed [27]. According to Xu et al., contaminated saliva secreted by infected salivary glands are probably a potential reservoir for SARS-CoV-2 and might be the main reason for the spread of COVID-19 through asymptomatic infection [18].

COVID-19 disease oral manifestations

The most frequently observed oral manifestations among patients with SARS-CoV-2 infection are taste and olfactory disorders, dry mouth, drones and inflammation of mouth, bitter taste in mouth, difficulty in swallowing and burning sensations in mouth (Tab. I).

In research by Chen et al., there was a questionnaire on the oral health status of patients with infection by SARS-CoV-2. The study included 108 patients, 52 males and 56 females. Oral manifestations of COVID-19 included loss of taste, dry mouth, dryness and inflammation of mouth. Loss of taste was reported in 47.2% cases (36.5% in males, 57.1% in females), dry mouth among 46.3% cases (46.2% in males, 46.4% in females) and dryness and inflammation of mouth among 11.1% of patients (13.5% in males, 8.9% in females). This study demonstrated that patients infected by SARS-CoV-2 generally present symptoms related to the oral cavity like loss of taste and dry mouth, which might be included in diagnostic criteria of COVID-19 [27].

In a multicentre case series by Qiu et al., olfactory and/or taste dysfunction were reported among patients with COVID-19. This study included 349 patients and in 41% of cases such symptoms were present. 10% of patients presented only olfactory or gustatory symptoms and 19% of patients presented olfactory and/or gustatory symptoms prior to any other COVID-19 symptoms. This study also suggested that loss of smell and taste among patients might be a screening criteria that is useful in early identifications of COVID-19 [29].

In a cross-sectional study on 59 patients hospitalised for COVID-19, cases of olfactory and taste disorders were observed, 33.9% of patients reported at least one taste or olfactory disorder and 18.6% reported both taste and olfactory disorder, 20.3% of patients observed those symptoms before hospitalisation and in 13.5% the symptoms appeared during hospitalisation. Smell and taste disorders were reported more often by females (52.6%) than males (25%) [30].

In an observational study by Sinjari et al. on a group of 20 SARS-CoV-2 positive hospitalised patients, oral manifestations such as dry mouth, taste disorders, burning sensations and difficulty in swallowing were observed. 30% of patients in this study developed xerostomia during hospitalisation, 25% of patients reported impaired taste, 15% burning sensation of the mouth and 20% difficulty in swallowing. It should be stressed that burning sensations were reported only by female patients. Considering sex and age of patients, no significant results were observed [31].

Although taste disorder in the most common oral mani-

Table I. Mostly commonly reported COVID-19 oral manifestations.

Author	Number of patients	Type of study	COVID-19 oral manifestations
Chen et al. (2020) [27]	108	Clinical study	Loss of taste, dry mouth, dryness and inflammation of mouth
Qiu et al. (2020) [29]	394	Multicentre case series	Olfactory and taste disorders
Giacomelli et al. (2020) [30]	59	Cross-sectional study	Olfactory and taste disorders
Sinjari et al. (2020) [31]	20	Observational study	Dry mouth, taste disorders, burning sensations, difficulty in swallowing
Luo et al. (2020) [32]	60	Cross-sectional study	Dry mouth, bitter taste in mouth

festation, other SARS-CoV-2 conditions related to oral cavity have also been observed. In research by Luo et al., symptoms in 60 hospitalised patients with COVID-19 were analysed. A large variety of conditions were included, including SARS-CoV-2 oral manifestations. 29% of patients reported dry mouth and 13% experienced bitter taste in the mouth [32].

Taste disorder observed as an early symptom of COVID-19 before other symptoms may support the hypothesis that oral cavity mucosa might be an initial site of infection by SARS-CoV-2, especially taking into consideration the fact that taste receptors are widely distributed in tongue, where 96% of the oral ACE2-positive cells are observed [20,21].

It has been shown that ACE2-positive salivary gland epithelial cells are early targets of other coronaviruses, and that salivary gland functions may be affected at an early stage of the infection [28]. This might be a possible explanation for a dry mouth symptom reported by patients undergoing SARS-CoV-2, although this hypothesis requires further research [21].

The presence of oral mucosa cells with high ACE2 receptor distribution might lead to inflammatory reactions in such organs and tissues as tongue and salivary glands [21]. According to Dziedzic et al., SARS-CoV-2 infection is the reason for diversified oral cavity disorders caused by both susceptible oral tissues and impairment of the immune system. Oral ulcerations, gingivitis, recurrent oral herpes simplex virus infections, opportunistic fungal infections and xerostomia caused by a decreased salivary flow have been observed among patients with COVID-19 [33]. Rarely reported oral manifestations are presented in Table II.

According to Carreras-Presaset et al., oral vesiculobullous lesions among patients with COVID-19 have also been reported. There were symptoms such as pain of palate, pain of tongue and many small ulcers on the palate with unilateral affection. Blisters on the internal lip mucosa and desquamative gingivitis has been observed. Patients presented ulcers or blisters, which commonly appear in other viral infections, such as hand, foot, and mouth disease and herpetic gingivostomatitis [34].

Soares et al. have also reported the occurrence of oral manifestations in a 42-year-old male diagnosed with COVID-19 [35]. Intramural examination revealed the ulcerated lesion and multiple reddish macules of different sizes scattered along the hard palate, tongue and lips. Petechia-like and small vesicobullous lesions on skin were also observed. After 3 weeks observation, lesions on both the oral mucosa and skin subsided [35].

Oral mucosa lesions have also been diagnosed in a 19-year-old SARS-CoV-2 positive patient [36]. Intraoral examination revealed erosions, ulcerations and blood crusts on the inner surface of the lips and palatal and gingival petechiae. Skin lesions were also observed. Both mucosal and skin lesions disappeared after 10 days [36].

In a case report by Amorim Dos Santos et al., oral mucosa changes in a patient with COVID-19 were observed. Oral manifestation included a persistent white plaque on the tongue dorsum refractory to antifungal therapy and multiple ulcers in the tongue dorsum resembling herpetic oral lesions [37].

In a report by Patel et al., necrotising periodontal disease was observed in a 35-year-old female suspicious for COVID-19. The patient presented with fever, submandibular lymphadenopathy and halitosis. Oral manifestations of the disease like painful, diffuse erythematous and edematous gingiva with necrosis of papillary areas were also observed. The oral lesions recovered after 5 days were diagnosed as necrotising periodontal disease due to bacterial coinfections along with COVID-19 [38].

The diverse impact of COVID-19 on oral health, including both subjective symptoms reported by patients and oral mucosa lesions undoubtedly require a proper dental care. Patients recovering from COVID-19, especially if hospitalised, should be provided with special oral health monitoring to ensure their full recovery [33].

The changes observed on the oral mucosa related to COVID-19 are not pathognomonic, and their treatment is symptomatic and does not differ from the treatment of oral mucosa lesions resulting from other diseases or disorders. Treatment includes the use of drugs that accelerate healing and painkillers, a gentle diet, maintain proper oral hygiene and saliva substitutes in case of dry mouth symptoms [34-39].

Table II. Rarely reported COVID-19 oral manifestations.

Author	Type of study	COVID-19 oral manifestations
Carreras-Presaset et al. (2021) [34]	Case report	Pain of palate, pain of tongue, small ulcers on the palate, blisters, desquamative gingivitis
Soares et al. (2020) [35]	Case report	Ulcerated lesion and reddish macules on the hard palate, tongue and lips
Ciccarese et al. (2020) [36]	Case report	Erosions, ulcerations and blood crusts on lips; palatal and gingival petechiae
Amorim Dos Santos et al. (2020) [37]	Case report	Persistent white plaque and multiple ulcers on the tongue dorsum
Patel et al. (2020) [38]	Case report	Necrotising periodontal disease

COVID-19 has become the subject of research by many specialists from various fields of medicine, who, depending on the clinical situation, attempt to develop appropriate standards of management. This applies to treating the symptoms of SARS-CoV-2 infection as well as encouraging proper treatment of patients with chronic diseases in a new pandemic reality [40-42].

Conclusions

Oral mucosa, due to the presence of ACE2 receptors, is highly susceptible to COVID-19 infection. Symptoms of COVID-19 related to the oral cavity such as taste impairment, dry mouth and burning mouth syndrome may appear in patients with SARS-CoV-2 infection, becoming crucial for identification of the disease. The occurrence of oral mucosa lesions related to SARS-CoV-2 infection should increase alertness among dental practitioners. However, knowledge in this area is still limited. More research and patient observations are required in the field of oral manifestations of COVID-19.

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