

Pathological manifestation of Covid-19 in the oral cavity and the role of saliva in the spread of the virus

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Abstract: The COVID-19 pandemic is the current coronavirus infection pandemic caused by the SARS-CoV-2 coronavirus [18]. The outbreak was first reported in Wuhan, China in December 2019 [11] on January 30, 2020. The World Health Organization declared the outbreak a public health emergency of international concern and a pandemic on March 11 [7, 5] As of April 5, 2021, over 132 million cases have been reported worldwide; more than 2.8 million people have died and more than 106.5 million have recovered.

Keywords: COVID-19, virus, oral cavity, saliva, droplets, symptoms

Coronaviruses are enveloped RNA viruses. Two strains—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)—are zoonotic in origin and are known to cause fatal respiratory illnesses, as is CoVID-19. Because coronaviruses are widespread and their genomes recombine, CoVID-19 is another previously unknown coronavirus. It has also been shown that this virus has a higher contagiousness than its predecessors [6, 13, 4]. Early detection of coronavirus and effective prevention of transmission are the main challenges in the fight against the CoVID-19 epidemic.

Introduction The SARS-CoV-2 virus is primarily transmitted through close contact, most commonly through small droplets produced by coughing, sneezing and talking. Transmission can also occur through smaller droplets that are able to remain suspended in the air for longer periods of time. Less often, infection is possible after touching a contaminated surface, and then to the face. An infected person is most contagious during the first three days after the onset of symptoms, although spread is possible before the onset of symptoms and through asymptomatic people.

The WHO has stated that CoVID-19 is spread primarily through droplets of saliva or nasal discharge). The major salivary glands secrete 90% of the saliva and 10% of the saliva is secreted by the minor salivary glands. Saliva pH ranges from 6 to 7.10. Saliva is a complex biological mixture that at the physiological level contains gingival fluid, cells of the desquamated epithelium of the oral cavity and microorganisms. It may also contain blood, respiratory secretions, stomach acid due to reflux, and food debris if abnormal [22].

About 99% of saliva is water; the remaining 1% contains a large group of components involved in digestion, taste balance and remineralization, as well as the destruction of microorganisms [26].

It has been suggested that the oral cavity is an ideal environment for SARS-CoV-2 invasion due to the special proximity that binds the virus to cells with angiotensin converting enzyme (ACE2) receptors, such as the airways, oral mucosa, tongue, and salivary glands [27]

A recent study showed that the angiotensin-converting enzyme 2 (ACE2) receptor is believed to be a functional receptor (lock) for the COVID-19 virus (key). The ACE2 receptor is well known as a key target for blood pressure regulation [19].

Current and other studies have shown that the ACE2 receptor is highly expressed in various organs of the body. The study highlights its manifestation in the nasal and oral mucosa, especially the tongue.

These organs may be at potentially high risk of contracting COVID-19. In this study, two public genome databases were examined and single cell transcriptome analysis was performed to examine and confirm ACE2 receptor expression on oral mucosal tissues; the tongue is larger than buccal and gingival tissues, epithelial cells and lymphocytes [22]. Because high expression of the ACE2 receptor has also been found in the colon, consistent with other reports of GI involvement in COVID-19 infection; fecal-oral transmission is also possible in addition to the oral and respiratory routes.

Since COVID-19 is easier to detect in saliva than nasopharyngeal swabs, the oral cavity is a critical site for learning and preventing COVID-19 infection.

The ACE2 receptor is one of the therapeutic targets under investigation. This is primarily due to the fact that ACE2 is a receptor for the penetration of the virus into target cells. In this connection, there were fears that a higher expression of ACE2 would allow the virus to more actively invade cells and cause deeper and more severe damage to target organs, primarily lung tissue, where this receptor is found in large quantities.

This is especially true for patients with diabetes and associated pathology - hypertension and CVD, which are characterized by hyperactivation of the RAS with an increase in ACE activity and the production of angiotensin II (AT II) - a modulator of vascular and tissue damage, which, along with metabolic disorders and concomitant pro-inflammatory status, is an extremely unfavorable background for a more severe course of a viral infection.

SARS-CoV-2 has been shown to be a neurotropic and mucotropic virus that can affect salivary gland function, taste, smell, and oral mucosal integrity [24].

There are several scientific papers that have explored the oral cavity as the main route of infection for SARS-CoV-2, the implications of the high risk of infection in dental practice, and the possible use of saliva for diagnosis [27]. While transmission of SARS-CoV-2 can occur through activities that involve the oral cavity, such as talking, breathing, coughing, sneezing, and even singing, most attention has been focused on the nose-lung axis of infection.

Oral manifestations such as loss of taste, dry mouth, and oral lesions are evident in about half of COVID-19 cases, although it remains unknown whether SARS-CoV-2 can directly infect and replicate in oral tissues such as salivary glands (SG) or mucous membrane. This is very important because, if these are sites of early infection, they may play an important role in the transmission of the virus to the lungs or gastrointestinal tract via saliva, as has been suggested in other microbial diseases such as pneumonia and inflammatory bowel disease.

An increase in atypical clinical manifestations during SARS-CoV-2 infection has been reported, including dermatological and oral manifestations. The pathogenesis of skin lesions in COVID-19 is not well known, but some hypotheses have been formulated. For example, the presence of viral particles in dermal blood vessels can cause lymphocytic vasculitis due to the production of cytokines, i.e. interleukin-1 (IL-1), interferon gamma (IFN- γ), and tumor necrosis factor alpha (TNF- α) by CD4+ T helper lymphocytes and migration of eosinophils, CD8+ cytotoxic T cells, B cells, and natural killer (NK) cells.

Another possible explanation for skin disorders associated with SARS-CoV-2 is the formation and accumulation of microthromboses, which can reduce blood flow to the skin microvessel, and the presence of deoxygenated blood in the venous plexuses can further contribute to the occurrence of these skin diseases. Moreover, the deposition of complement components C5b-9 and C4d in low-inflammatory thrombogenic vasculopathy and their co-localization with COVID-19 glycoproteins was shown by Magro et al. It is reasonable to assume that the skin lesion is caused by a combination of these mechanisms rather than by one.

Taste disturbances were the most common oral symptom in patients with COVID-19, likely due to a local inflammatory response caused by rhinitis triggers that may interfere with normal taste bud function. In addition, damage to the oral mucosa has been described during SARS-CoV-2 infection. Since the first description of oral lesions in SARS-CoV-2 patients reported by Martín Carreras-Presas et al. [28], several more recent studies have also reported oral mucosal lesions in COVID-19 such as ulcers, aphthae and macules. The clinical significance of oral mucosal involvement during SARS-CoV-2 infection remains controversial.

As previously reported by Xu H [36], high expression of ACE2 on oral epithelial cells, especially the tongue, suggests that the oral cavity may be an anatomic site particularly susceptible to SARS-CoV-2 infection. Therefore, as suggested by Brandão et al. [8], the interaction between SARS-CoV-2 and ACE2 can impair the function of oral keratinocytes, leading to painful oral ulcers. In addition, oral mucosal lesions during COVID-19 may be justified by a variable inflammatory response that can cause vascular inflammation, as seen in cutaneous manifestations.

The most recent publications on oral mucosal lesions in patients affected by COVID-19 support an association with organic lesions and/or complications of thrombocytopenia, anticoagulant therapy,

disseminated intravascular coagulation, and systemic inflammation. According to Cruz Tapia et al., clinical manifestations and histological findings suggest the possibility that the oral cavity presents with primary or secondary changes in vascular hematologic injury associated with COVID-19.

However, as reported by Martín Carreras-Presas et al. [28] and Hedou et al. [21], ulcers or vesico-vesicular lesions may occur as with other viral infections. It is highly documented that high levels of fatigue and stress can increase the risk of HSV [21] reactivation.

Moreover, oral injury can also be a manifestation of an immunosuppressive state and microbiome dysbiosis caused by viral infection. According to Bezerra et al. [7], it is reasonable to speculate that deregulation of systemic immunity by COVID-19 may cause a longer lasting immune imbalance that may predispose to these late secondary oral lesions. In addition, according to de Sousa et al. [14], most patients developed oral mucosal injury during hospitalization, supporting the hypothesis of coinfections, immunosuppression, and adverse reactions to COVID-19 medications.

Oral signs and symptoms are taste disorder, non-specific oral ulcers, desquamative gingivitis, petechial, and coinfections such as candidiasis [1].

From our review, it follows that the pathomorphological changes of COVID-19 in the oral cavity are very diverse and the prevalence of clinical manifestations has not yet been well studied. Many studies describe the role of oral fluid in the spread of the virus, which is one of the first factors in human infection. Moreover, people with dental problems are at risk for contracting coronavirus infection. Therefore, the study of oral fluid and oral changes in the oral cavity with COVID-19 is considered very relevant.

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