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REVISIÓN

The mouth, oral health, and infection with SARS-CoV-2: An underestimated topic

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Abstract

With the present review, we propose recognizing and analyzing some fundamental aspects recently reported in the literature, which relate the oral cavity to SARS CoV-2 infection.

A literature search was performed in Pubmed, Scopus, Scielo and the medRivx preprint server. There, articles published during 2019 and 2020 were selected from research associated with oral cavity, COVID 19, SARS-CoV-2, viral diagnosis in saliva and the use of mouth rinses as a possible mechanism to reduce viral load.

A total of 33 articles related to oral cavity; SARS-CoV-2 infection; oral manifestations of COVID 19; symptomatology, saliva diagnosis, and the use of mouth rinses to minimize the risk of infection were selected.

The oral manifestations of COVID 19 were recognized among the findings; also, the potential of the oral cavity as a site of infection and viral dissemination to other organs was evidenced and the role of saliva as a diagnostic tool for SARS-CoV-2.

Knowledge about the oral cavity and the relationship with SARS-CoV-2 is limited, making necessary a better understanding the oral manifestations during COVID-19, symptoms and possible complications in the mouth. The need for the establishment of infection prevention strategies during dental practice is identified.

Key words: SARS-CoV-2; mouth; COVID 19; oral manifestations; saliva; mouthwash

La boca, la salud oral y la infección con SARS.CoV-2: Un tema desestimado

Resumen

La presente revisión se propuso reconocer y analizar algunos aspectos fundamentales reportados recientemente en la literatura, que relacionan la cavidad bucal con la infección por SARS-CoV-2.

Se realizó una búsqueda bibliográfica en Pubmed, Scopus, Scielo y el servidor de preimpresión medRivx. Posteriormente, los artículos publicados durante 2019 y 2020 fueron seleccionados de una búsqueda asociada a la cavidad oral, COVID 19, SARS-CoV-2, diagnóstico viral en saliva y uso de enjuagues bucales como posible mecanismo para reducir la carga viral.

Se seleccionó un total de 33 artículos relacionados con la cavidad bucal; infección por SARS-CoV-2; manifestaciones orales de COVID 19; sintomatología, diagnóstico en saliva y uso de enjuagues bucales para minimizar el riesgo de infección.

Las manifestaciones orales de COVID 19 fueron reconocidas entre los hallazgos; además, se evidenció el potencial de la cavidad bucal como sitio de infección y diseminación viral a otros órganos y el papel de la saliva como herramienta de diagnóstico para el SARS-CoV-2.

El conocimiento sobre la cavidad bucal y la relación con el SARS-CoV-2 es limitado, por lo que es necesario profundizar en las manifestaciones bucales durante la COVID-19, síntomas y posibles complicaciones en la boca. Se identificó la necesidad de establecer estrategias de prevención de la infección durante la práctica odontológica.

Palabras clave: SARS-CoV-2, boca, COVID 19, manifestaciones orales, saliva, enjuague bucal.

Introduction

One year after detecting the first cases of pneumonia putatively attributed to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), much has been learned about the pathogenesis of the corresponding disease (i.e., coronavirus disease 2019 [COVID-19]). However, little is known about the oral manifestations of COVID-19, and the oral tissues involved in viral infection and transmission. This can, in part, be attributed to the restrictions placed on dentists to examine hospitalized patients, and the difficulties in examining infected individuals with mild symptoms and those who are asymptomatic. Nevertheless, the oral cavity has not been given sufficient attention in the context of COVID-19.

Since the 2003 SARS-CoV outbreak, it was determined that this coronavirus could replicate in cells of the salivary gland duct(s). However, due to rapid infection control, research has not progressed further[1]. SARS-CoV-2 is transmitted by droplets or aerosols produced by speaking, coughing, or

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sneezing[2,3]. Additionally, there is evidence supporting SARS-CoV-2 replication in the oral mucosa and salivary gland cells; however, research investigating the relationships between the oral mucosa, oral cavity, and the infection remains incipient.

The present article reviews some fundamental aspects of what has been observed in the oral cavity regarding the new coronavirus (i.e., SARS-CoV-2), and addresses two main lines of investigation: first, the need for qualified training of healthcare providers and deepen knowledge regarding the role of the oral cavity in SARS-CoV-2 infection and transmission; and second, the pathogenesis of COVID-19 in the context of oral manifestations.

Methodology

A literature search of the PubMed (MeSH), Scopus, SciELO and medRvix (Dentistry and Oral Medicine, Epidemiology, Infectious diseases) databases for articles published in English and Spanish from 2019 to date was performed. Search terms included: "SARS-CoV-2" and "mouth diseases"; "SARS-CoV-2" and "oral manifestations"; ""SARS-CoV-2" and "saliva"; and "SARS-CoV-2" and "mouthwashes". 108 duplicate studies were excluded from the articles retrieved. In the first step, two investigators independently reviewed the search results and screened both titles and abstracts, to remove the studies outside the scope of the review and 622 articles were excluded. Then, we obtained the full texts of all potentially eligible studies, which were further examined to exclude those not fulfilling inclusion criteria; in these step 187 citations were removed. Ultimately, 33 studies were included, and the extracted information was organized in a spreadsheet (Excel, Microsoft Corporation, Redmond, WA, USA) to facilitate analysis. A flow diagram of the literature search is presented in Figure 1.

The inclusion criteria set for the selection of articles were study design: prospective/retrospective cohort study, case-control studies, systematic reviews, original articles with experimental studies in human, animal and *in vitro*, case reports and replies to these reports. The exclusion criteria were opinion articles, editorials and articles published in languages other than English or Spanish.

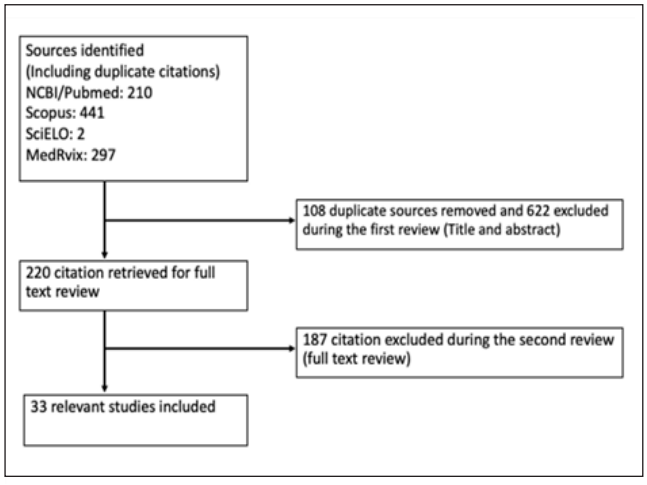

Figure 1. Flowchart of the literature search and included studies.

Results

After identifying the virus and corresponding disease, it was reported that the primary receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2). This membrane ectopeptidase is well expressed in type I and II pneumocytes, enterocytes, cardiac cells, oral epithelial cells, ducts, and acinic salivary gland cells, among other cell types[4-6], which partially explains the pathogenesis of COVID-19.

ACE2 expression has recently been recognized in oral mucosal cells using immunohistochemistry, polymerase chain reaction, and single-cell RNA sequencing techniques[7-10]. In the oral cavity, ACE2 is expressed primarily in epithelial cells of the gingival sulcus, the dorsal surface of the tongue, taste buds, floor of the mouth, ducts, and acinic cells of the minor and major salivary glands[7-10]. The presence of the ACE2 receptor varies according to anatomical location, and expression appears to be increased by inflammatory processes such as periodontal diseases[7-10].

Thus, it has been shown that SARS-CoV-2 infection and replication in the oral cavity appear to occur in independent "niches". Therefore, it is probable that, in addition to its role as the initial entry portal for SARS-CoV-2, the oral epithelia act as a bridge in viral spreading to other locations such as the lower respiratory airways and the gastrointestinal tract. Of significant concern is that the oral cavity mucosa participates in person-to-person transmission[10]. Saliva is the primary vehicle for viral transmission from the oral cavity. There is also evidence that SARS-CoV-2 is found in desquamated epithelial cells; as such, these infected cells may participate in viral dissemination[10].

Diagnosing SARS-CoV-2/COVID-19 from saliva samples has attracted much interest due to the possibility of using this bodily fluid to confirm infection in a minimally invasive manner; moreover, several studies have shown that it is feasible. Detection from saliva yields results comparable to those obtained using nasopharyngeal swab methods[11-14]. It is well known that saliva sample collection involves less risk, both to the operator and the patient, is easily and safely transported, and does not require highly trained personnel, thus resulting in cost reductions[15].

Regarding oral manifestations, published case reports have mainly described erythematous, vesicular, and ulcerative lesions, together with vascular lesions. A thorough review published by Galván-Casas *et al.*[16] regarding dermatological and oral cavity manifestations of COVID-19, mainly described enanthema, characterized by the appearance of erythematous small dots or spots on the hard and soft palates, lesions traditionally associated with childhood viral infections. Among individuals with COVID-19, these lesions appear a few days after infection and are accompanied by odynophagia[16].

Vesicular and ulcerative lesions are superficial and mostly only a few millimeters in diameter. They are, however, often painful, multiple, and have been described as varicelliform eruptions of the skin, similar to the lesions produced in oral herpes simplex virus (HSV) 1 and 2 infections[17-21]. In some cases, the appearance of these lesions may be the first manifestation of SARS-CoV-2 infection or concomitant systemic manifestation(s). Frequently, the evolution of COVID-19 complications may be accompanied by the development of oral lesions[16,17].

The pathogenesis of these vesicular and ulcerative lesions in the oral mucosa of patients infected with SARS-CoV-2 appears to be similar to that observed in HSV infections, which are cytopathic, causing loss of epithelial tissue integrity, leading to the formation of intraepithelial vesicles and loss of epithelial coverage progressing to ulcer formation. Although there is no direct evidence of the consequences of infection in cells of the oral cavity, it is known that SARS-CoV-2 induces a cytopathic effect on airway epithelial cultures with loss of intercellular adhesion and syncytia formation[22].

Considering that this particular coronavirus replicates in the epithelial cells of the oral cavity, this could explain the oral manifestations described to date. The few reported cases have shown that oral mucosal lesions can be aggravated by secondary lesions appearing as a decrease in salivary secretion, and the anti-inflammatory and immunosuppressive therapies that patients with COVID-19 undergo. Additionally, there is a fact that appears not to have been considered—namely, the risk for additional infection or inflammatory processes in patients using oral-tracheal ventilation devices that impair oral hygiene, leading to endogenous microbiota alteration (dysbiosis) and overgrowth of periodontopathogenic bacteria, or any of the typical members of the oral microbiota such as *Candida* species; for example, oral pseudomembranous or erythematous candidiasis have been described [23-24].

Severe caries or periodontal diseases sequelae are more serious in those patients who overcome COVID-19[25]. This problem has local implications in the mouth and wider systemic consequences due to the dissemination of infectious agents to the lower airways, complicating pneumonia, and contributing to the elevation of systemic markers, such as C-reactive protein and pro-inflammatory cytokines[26-28]. Therefore, studies investigating possible two-way relationships between this local inflammatory process and COVID-19 are warranted.

The systematic review[29] about oral manifestations of SARS-CoV-2 infection on 10.228 patients, found a prevalence of 45% for taste alterations. The most frequent was dysgeusia (38%), followed by hypogeusia (35%) and ageusia (24%) showing a positive association (OR=12.68), mainly with mild and moderate forms of COVID 19 disease. These symptoms could be due to direct infection of taste bud cells, although nerve alteration(s) should not be ruled out, such as those described for anosmia during COVID-19.

Other reported symptoms include burning mouth sensation and xerostomia (subjective manifestations of oral dryness). These manifestations could be attributed to a decrease in salivary secretion and indirectly to salivary gland ducts and acini infection; however, more evidence is required[29]. On the other hand, in severe hospitalized patients the lack of oral food intake and lack of hygiene can decrease salivary secretion stimuli contributing to additional manifestations.

Vascular lesions have, to a lesser extent, also been reported. These can appear as spots or nodules with dark red or purple coloration mainly on the palate. Endothelial injury and coagulation disorders with severe consequences have been well described in COVID-19[30]. Endothelial cells express ACE2 and are susceptible to SARS-CoV-2 infection, thus leading to cell dysfunction, apoptosis, and perivascular inflammatory responses. Therefore, endothelial alterations may explain the appearance of vascular lesions in the oral cavity[31].

Table 1 shows a summary of the main primary and secondary manifestations of SARS-CoV-2 infection in the oral cavity.

Table 1. Oral Primary and Secondary Manifestations of SARS-CoV-2 infection.

Primary oral manifestations Covid 19			
Type of lesions	Signs	Symptoms	Ref.
Erythematous	Enanthema: small dots or spots on the hard and soft palates	Odynophagia	16
Vesicular and ulcerative	Superficial and mostly a few millimeters in diameter. Varicelliform aspect, like the oral herpes simplex virus (HSV) 1 and 2 infections	Very painful, short duration	17-21
Vascular	Spots or nodules with dark red or purple coloration, mainly on the palate	Asymptomatic	30
Secondary oral manifestations Covid 19			
Decreased salivary flow	Opportunistic infections: Candidiasis. Dysbiosis, periodontitis, caries	Mild pain, burning sensation	23-25
Taste alterations	None	Dysgeusia, hypogeusia, ageusia	29

What about the use of oral rinses?

Another topic that has been extensively discussed in recent months is the use of oral rinses, mainly as part of protocols for dental care before consultation, as a mechanism to reduce or control the viral load of SARS-CoV-2. However, it would not be the only scenario in which rinses can be used because they are also recommended in the care of hospitalized patients.

For example, we recommend for pediatric transplant patients at the *Hospital Pediátrico La Misericordia in Bogotá*, an oral hygiene care protocol including brushing, flossing, and rinsing with bicarbonate water and benzydamine hydrochloride, four times per day. The teeth and oral mucosa of hospitalized patients should be cleaned with gauze moistened with bicarbonate water, followed by benzydamine hydrochloride. If lesions appear, chlorhexidine can be added[32].

In patients hospitalized with COVID-19, it would be ideal to clean tooth surfaces and the oral mucosa at least once daily with antiseptic rinses that have demonstrated activity against caries and periodontitis involving bacteria or *Candida* species. During the pandemic, office dental care protocols recommend a rinse before starting any intervention. The most recommended include 1% hydrogen peroxide, 0.2% iodopovidone, or 0.22% chlorhexidine[33]. There is *in vitro* evidence supporting the viricidal effect of these mouth rinses on SARS-CoV-2; however, *in vivo* evidence supporting these antiseptic effects remains inconclusive[34-37]. The in vitro effects of cetylpyridinium chloride on the new coronavirus have been recently reported, but further evidence is needed[38].

Although clinical evidence supporting the effects of these mouthwashes on SARS-CoV-2 remains very scarce and controversial, it is always advisable to reduce the microbial load in the oral cavity, especially in patients with systemic complications or comorbidities who cannot maintain biofilm mechanical control or cannot clean by themselves[39].

In conclusion, the dentist's role is important for diagnosing and treating oral lesions observed in SARS-CoV-2-positive patients, promoting oral hygiene in infected patients, and applying measures to maintain oral health, mainly in hospitalized patients. Given the similarity in the clinical appearance of the lesions produced by HSV 1 and 2 with those observed in COVID-19 patients, it is crucial to make a correct differential diagnosis to establish the appropriate treatment.

Similarly, dental professionals must continue to implement protocols published by dental and infectious disease associations and actively participate in the appropriate education of patients and the community regarding the correct implementation of protective measures and contribute to the evaluation of the utility of mouthwashes in preventing virus transmission during the pandemic.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this review work.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this article.

Conflict of interest. The authors declare that the revision was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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