Systematic Review and Meta-Analysis

Medicine®

OPEN

COVID-19 and its manifestations in the oral cavity

A systematic review

María Verónica Cuevas-Gonzalez, PhD[a], León Francisco Espinosa-Cristóbal, PhD[b], Alejandro Donohue-Cornejo, PhD[b], Karla Lizette Tovar-Carrillo, PhD[b], Rosa Alicia Saucedo-Acuña, PhD[b], Alma Graciela García-Calderón, MEd[b], Dalia Abril Guzmán-Gastelum, MS[b], Juan Carlos Cuevas-Gonzalez, PhD[b,*]

Abstract

Background: SARS-CoV-2 is the virus responsible for coronavirus disease-19 (COVID-19) disease, which has been shown to trigger multiple affectations. One of the first tissue areas to come into contact with the virus is the oral cavity, which develops various alterations. Hence, the objective of this systematic review was to identify the main signs and symptoms of this disease in the oral cavity, and the following research question was established: What are the main oral signs and symptoms in COVID-19-positive persons?

Methods: The electronic databases of PUBMED, SCOPUS, and SCIENCE DIRECT were analyzed, the keywords "ORAL DISEASES," "ORAL MANIFESTACTIONS," and "COVID-19" were used taking into account the following inclusion criteria: studies whose main objective was oral manifestations secondary to the confirmation of COVID-19, plus clinical cases, case series, and retrospective or prospective studies. For the assessment of the risk of bias the JBI Critical Appraisal Checklist for Case Series tool was used.

Results: A total of 18 studies were included, the most common initial signs/symptoms after contagion of SARS-CoV-2 were dysgeusia, dry mouth, and burning mouth, and the main signs/symptoms were the presence of ulcerative lesions, dysgeusia, and Candida albicans infections.

Conclusions: It is very important to detect any alteration in the mucosa in patients with COVID-19 and to provide assertive treatment to avoid complications, and try to maintain adequate oral hygiene throughout the course of the disease to avoid the colonization of opportunistic microorganisms and to avoid complications both orally and systemically.

Abbreviation: ACE2 = receptor angiotensin-converting enzyme 2.

Keywords: COVID-19, oral cavity, systematic review

1. Introduction

Coronaviruses are a family of viruses that were described for the first time in 1960. They are characterized by having a corona-like structure formed by spike proteins. In 2019, a new type of coronavirus, SARS-CoV-2, was discovered, generating the coronavirus disease 2019 (COVID-19), which spread rapidly throughout the world, and is responsible for the current pandemic.[1,2]

SARS-CoV-2 enters cells through the receptor angiotensin-converting enzyme 2 (ACE2). Once contact is established, an enzyme is needed to cut the binding protein S and activate the entry of the virus into the cell. One of the enzymes involved in this process, including transmembrane protease serine protease 2; once inside the cell, it releases the genetic material and begins to replicate it using the host cell's own machinery. One of the main consequences of SARS-CoV-2 infection is the generation of an immune response accompanied by high cytokine production accompanied by a weak interferon response. After the infiltration of macrophages and neutrophils into the affected tissue, the cytokine storm phenomenon follows.[3,4] The above process has been correlated with the severe forms of COVID-19, which is characterized by developing fever, cough, chest pain, dyspnea, and pneumonia (among others), becoming life threatening.[5]

Within the clinical manifestations that are generated after infection by SARS-CoV-2, oral cavity lesions have been

Editor: Hitesh Vij.

All data generated or analyzed during this study are included in this published article and its supplementary information files.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Research Division, National Autonomous University of Mexico, Mexico City, Mexico, [b] Institute of Biomedical Sciences, Autonomous University of Ciudad Juarez, Juarez City, Chihuahua, Mexico.

[*] Correspondence: Juan Carlos Cuevas-Gonzalez, Av. Benjamín Franklin no. 4650, Zona Pronaf Condominio La Plata, 32310 Cd Juárez, Chihuahua, Mexico (e-mail: cuevas_gonzalez@hotmail.com).

How to cite this article: Cuevas-Gonzalez MV, Espinosa-Cristóbal LF, Donohue-Cornejo A, Tovar-Carrillo KL, Saucedo-Acuña RA, García-Calderón AG, Guzmán-Gastelum DA, Cuevas-Gonzalez JC. COVID-19 and its manifestations in the oral cavity: a systematic review. Medicine 2021;100:51(e28327).

Received: 8 July 2021 / Received in final form: 27 November 2021 / Accepted: 29 November 2021

http://dx.doi.org/10.1097/MD.0000000000028327

described; therefore, the objective of this systematic review is to identify the main alterations in oral cavity derived from COVID-19. The development of this project was based on the PRISMA criteria; 3 different databases were analyzed in which clinical cases, case series reports, or cross-sectional studies were identified, which aimed to describe the oral characteristics of patients with COVID-19.

2. Methods

2.1. Research question

What are the main oral signs and symptoms in COVID-19-positive persons?

3. Registration and protocol

The study was registered in PROSPERO (No. CRD42021262650).

3.1. Selection criteria

3.1.1. Inclusion.

- Studies whose main objective was the study of oral manifestations posterior to the confirmation of COVID-19.
- Clinical cases, case series, retrospective, or prospective studies.

3.1.2. Exclusion.

- Review-type studies or systematic reviews.
- Studies whose methodology does not mention positivity to COVID-19 in the study subjects or does not clearly mention how to perform the intraoral examination.
- Studies that were based on surveys, due to the absence of an examination to corroborate the oral manifestations.

3.2. Search strategy

The search was carried out in the electronic databases of PUBMED, SCOPUS, and SCIENCEDIRECT. The following keywords were used: "ORAL DISEASES," "ORAL MANIFESTATIONS," and "COVID-19." The Boolean operators "OR" and "AND" were used, and the strategy was carried out both individually and jointly. The search strategy was limited to texts in Spanish and English, excluding literature reviews and systematic reviews; due to the importance of the topic, no time limit was established for the search; the last was March 2020.

All the studies that met the established criteria were placed in a bibliographic manager (Mendely) for further analysis.

3.3. Study selection

For the selection of the studies, a first filtering was carried out on the title and abstract, identifying the presence of the keywords used in the search strategy. Selected studies were placed in a bibliographic manager (Mendeley) to identify duplicate studies. Lastly, the full texts were reviewed to finally identify the studies that met the previously established selection criteria. The selection of the studies was carried out independently by 2 examiners (C-GJC and CGMV); in case of discrepancy a third evaluator participated (D-CA).

3.4. Data extraction

Information such as author, country, type of study, number of subjects included in the study, mean age, initial oral signs/symptoms after the first days of infection, and main signs/symptoms related to COVID-19 were collected from the selected studies.

To determine the initial oral signs/symptoms, we based on the initial description of the symptoms within the first 14 days of the disease. To determine the most frequent signs or symptoms of the case series report studies, the data reported with the greatest frequency were taken into account (Supplementary material, http://links.lww.com/MD/G542).

3.5. Risk of bias

The JBI Critical Appraisal Checklist for Case Series tool was used to determine the risk of bias. It consists of 10 questions focused on the description of the patient, his/her evaluation, the interventions carried out, and the report of adverse effects, according to the evidence provided. Each question was scored as yes, no, or unclear.[6] For the observational studies, the tool STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was used. The evaluation of the studies was carried out independently by 2 examiners (C-GJC and CGMV); in case of discrepancy a third evaluator participated (D-CA).

3.6. Data analysis

The data were examined with descriptive analysis; for quantitative variables (e.g., age and number of patients) measures of central tendency were reported as mean, standard deviation, minimum and maximum values; for qualitative variables (e.g., severity of COVID-19, need for hospitalization, or oral signs and symptoms) frequencies were reported. The data were placed in a database and statistics were made based measures of central tendency. Descriptive statistics of the data were performed using the SPSS V.22 program.

4. Results

4.1. Search strategy

According to the proposed strategy, 185 studies were identified in 3 bibliographic databases. In the first filter made by title and abstract, 45 possible candidate studies were identified for inclusion. When reviewing the full text, 27 studies were eliminated because they did not fulfill the established criteria, leaving 18 studies that met the previously established selection criteria (PRISMA flow chart).

4.2. Data description

Of the total of selected studies, the mean age was 47.7 years (minimum 9 and maximum 69 years). Of the 18 studies selected, 8 reported hospitalization of study subjects, and 10 mentioned the development of mild to moderate COVID-19. The most common initial sign/symptom after SARS-COV-2 infection was dysgeusia, and the main sign/symptom 14 days after SARS-COV-2 infection was the development of ulcerative lesions in 7 studies, dysgeusia in 4 studies, and *Candida albicans* in 3 studies (Table 1).

Table 1

Descriptive statistics of the data, the age, and the total number of individuals identified in the selected studies are described.

Variable	Media (standard deviation)	Min–Max
Age	44.7 (197)	9–69
Total of persons in all studies	Total	
756	1–128	
N * (%)		
Hospitalization		
Yes	8	44.4
No	8	44.4
No data	2	11.2
COVID-19 severity		
Mild–moderate	10	55.6
Severe–moderate	6	33.3
No data	2	11.1
Initial sign/symptom		
Dysgeusia	4	22.2
Dry mouth	1	5.6
Burning mouth	3	16.7
Main sign/symptom		
Ulcers	7	38.9
Candidiasis	3	16.7
Leukoplakia	1	5.6
Thrombi formation	1	5.6
Dysgeusia	4	22.2
Erythema	1	5.6
Herpes	1	5.6
Papillitis	1	5.6
Pain	1	5.6

The main signs and symptoms were reported according to the number of studies.
*The frequency was based in studies number.

4.3. Risk of bias

The risk of bias was analyzed with the JBI Critical Appraisal Checklist for Case Series tool. Of the 10 items it contains, we decided to eliminate the one related to statistical analysis because it did not apply to the types of studies analyzed. Overall, the risk of bias was low (Table 2).

5. Discussion

COVID-19 is a disease that has affected a large proportion of the population worldwide. People infected with SARS-CoV-2 may develop mild illness characterized by fever, fatigue, myalgia, and a dry cough. However, 14% will develop signs and symptoms that lead to the need for hospitalization with oxygen supplementation, and 5% will require intensive care.[7] On the other hand, between 20% and 75% of the general population infected are asymptomatic[8]; therefore, the diagnosis and control of the disease becomes complex.

The oral cavity is one of the main entry routes for SARS-CoV-2, because transmission can be directed through fomites, droplets of saliva (generated when speaking, coughing, or sneezing). It has been proposed that the oral cavity may constitute a virus reservoir; the gingival sulcus is a well-established niche where inflammatory enzymes and molecules accumulate and promote the colonization of microorganisms. Therefore, there is speculation that it may act as a reservoir for SARS-CoV-2.[9] Therefore, oral cavity mucosa is one of the first tissues to be in contact with the virus and can suffer some alterations.

We were able to identify those patients in the early stages of COVID-19 (less than 14 days after infection) develop symptoms that include mainly alteration in flavor perceptions, or dysgeusia and a burning mouth; as the disease progressed, the patients presented mainly ulcerative lesions or *Candida albicans*.[10–12]

These data coincide with studies made by other research centers that mention that dysgeusia is the most common symptom with an 80% presence among subjects infected with SARS-CoV-2, as well as the presence of ulcerative lesions in 65% of the population, which are located mainly on the tongue, palate, lip, and cheek, followed by *C albicans* in 22.7% of cases.

Table 2

Risk of bias from clinical case studies and observational studies.

JBI critical appraisal checklist for case series

Autor	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Quality
Brandão TB	*	*	*	*	*	*	*	*	*	High
Corchuelo J	*	*	*	*	*	*	*	*	*	High
Amorim Dos Santos J	*	*	*	*	*	*	*	*	*	High
Cruz Tapia RO	*	*	*	*	*	*	*	*	*	High
Sinadinos A	*	*	*	*	*	*	*	*	*	High
Martín Carreras-Presas C	*	*	*	*	*	*	*	*	*	High
Kitakawa D	*	*	*	*	*	*	*	*	*	High
Riad A	*	*	*	*	*	*	*	*	*	High
Riad A	*	*	*	*	*	*	*	*	*	High
Díaz Rodríguez M	*	*	*	*	*	*	*	*	*	High

STROBE (strengthening the reporting of observational studies in epidemiology

Autor	Abstract	Introduction	Methods	Results	Discussion	Quality
Fantozzi PJ	*	*	*	*	*	High
Gherlone EF	*	*	*	*	*	High
Halepas S	*	*	*	*	*	High
Nuño González A	*	*	*	*	*	High
Biadsee A	*	*	*	*	*	High
Bruna Sinjari	*	*	*	*	*	High
Favia G	*	*	*	*	*	High
Fidan	*	*	*	*	*	High

Dysgeusia is a term used to identify all kinds of taste disturbances, including ageusia or hypogeusia. Various mechanisms have been described that could explain the etiology of taste loss during COVID-19; neurotropism is one possible explanation for the alteration of taste and smell. This damage could occur through the central nervous system, which has high expression of ACE2 in endothelial cells and neurons, or by crossing the olfactory epithelium directly through the cribriform plate to reach the central nervous system.[13] In contrast, in a study by Sakaguchi et al[14] the authors identified that in fungiform, taste buds of the stratified squamous epithelium of the tongue, and taste cells were positive for ACE2, transmembrane protease serine protease 2, which could be the main explanation for the loss of taste perception.

The presence of ulcerative lesions is caused by different etiologies such as infections, immunosuppression states, trauma, or neoplasms.[15] According to our observations, ulcerative lesions occurred mainly in moderate to severe COVID-19; among the studies reviewed, the presence of ulcers was related to herpes.[16] This virus has the characteristic that after the first infection it remains inactive in the trigeminal ganglion or ganglion of gasser.[17] Reactivation will depend largely on immunosuppression periods, so it is not surprising that in the face of SARS-CoV-2 infection, the patient suffers a recurrence of the herpes virus, generating painful ulcerative lesions—a fact that can be correlated with the sensation of burning mouth identified as a symptom in the early stages of COVID-19.

Patients with severe COVID-19 develop acute respiratory distress syndrome, which is treated with oxygen supplementation, and the patient is placed in a supine position. It has been reported that one of the main side effects of this treatment is the appearance of pressure ulcers in areas of friction from the oxygenation equipment when in contact with mucous membranes and skin. This main affects subjects older than 60 years and with a body mass index greater than 28.5 kg/m^2.[18] Additionally, due to the cytokine storm, interleucin 6, and tumor necrosis factor alpha are not only associated with the chronic stages of inflammation but also with the development of pressure ulcers.[19] In summary, patients with COVID-19 who develop ulcers develop due to state of immunosuppression inherent to the disease, as a side effect of oxygen supplementation treatment, or as a consequence of the cytokine storm.

Finally, the second most common lesion that we identified was *C albicans*. Since it is part of the human microbiome, it does not damage the host in an immunocompetent state; however, during immune system disturbances, it can cause infections of the superficial skin and mucous membranes, and even systemic infections.[20] Therefore, we consider this injury to be a secondary effect of COVID-19 and not an injury directly related to SARS-CoV-2.

Oral hygiene is an aspect that should not be left aside, and it is of great importance to encourage the patient to reinforce hygiene techniques. Recent studies have shown that patients with poor oral hygiene increase the severity of COVID-19 symptoms. In contrast, in patients who maintained good oral hygiene, the symptoms of COVID-19 decreased significantly ($P < .001$).[21] By maintaining adequate oral hygiene, the overpopulation of microorganisms considered opportunistic, and the appearance of infections type *C albicans,* are avoided.[22–35]

6. Limitations

One of the main limitations of the study is the lack of follow-up of the patients evaluated, both prior to the SARS-COV-2 infection to discriminate between conditions or lesions already present, and the lack of follow-up after SARS-COV-2 infection to establish the recovery time of the patients, so we propose to conduct studies that include a longer observation time of the patients.

7. Conclusions

COVID-19 is a disease that has multiple side effects. In the in oral cavity, the main symptom directly related to SARS-CoV-2 is dysgeusia, which appears from the first days of infection. The development of ulcers and *C albicans* are alterations that are related to moderate to severe COVID-19, which are the product of the treatment used for severe cases of the disease. It is important to discriminate between lesions or alterations that actually develop from SARS-CoV-2 and the alterations that the patient already had. It is of great importance to detect any alteration in the mucosa in patients with COVID-19 and to provide assertive treatment to avoid complications, and try to maintain adequate oral hygiene throughout the course of the disease to avoid the colonization of opportunistic microorganisms, and to avoid complications both oral and systemic.

Acknowledgments

The authors appreciate the support provided by the CONACYT through its scholarship (number: 326127; CVU 537149) to Maria Veronica Cuevas Gonzalez during her Doctoral studies in the Maestría y Doctorado de Ciencias Médicas, Odontológicas y de la Salud, UNAM.

Author contributions

Conceptualization: Maria Veronica Cuevas-Gonzalez, Dalia Abril Guzmán-Gastelum.
Data curation: Rosa Alicia Saucedo Acuña.
Formal analysis: Leon Francisco Espinosa-Cristobal.
Investigation: Alma Graciela García-Calderón.
Methodology: Alejandro Donohue-Cornejo.
Writing – original draft: Karla Lizette Tovar Carrillo, Juan Carlos Cuevas-Gonzalez.

References

[1] Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: the status and perspectives in delivery points of view. Adv Drug Deliv Rev 2021; 170:1–25.
[2] Liu X, Liu C, Liu G, Luo W, Xia N. COVID-19: progress in diagnostics, therapy and vaccination. Theranostics 2020;10:7821–35.
[3] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021;19:141–54.
[4] Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021;93:250–6.
[5] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–93.
[6] Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P MP. Chapter 7: Systematic reviews of etiology and risk. Aromataris E, Munn Z (Editors) JBI Man Evid Synth JBI, 2020. 2020.
[7] Herrera D, Serrano J, Roldán S, Sanz M. Is the oral cavity relevant in SARS-CoV-2 pandemic? Clin Oral Investig 2020;24:2925–30.
[8] Yanes-Lane M, Winters N, Fregonese F, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: a systematic review and meta-analysis. PLoS One 2020;15:e0241536.

[9] Xiang Z, Koo H, Chen Q, Zhou X, Liu Y, Simon-Soro A. Potential implications of SARS-CoV-2 oral infection in the host microbiota. J Oral Microbiol 2021;13:1853451.
[10] Brandão TB, Gueiros LA, Melo TS, et al. Oral lesions in patients with SARS-CoV-2 infection: could the oral cavity be a target organ? Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e45–51.
[11] Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis 2021;27:710–2.
[12] Díaz Rodríguez M, Jimenez Romera A, Villarroel M. Oral manifestations associated with COVID-19. Oral Dis 2020;Epub ahead of print.
[13] Mahmoud MM, Abuohashish HM, Khairy DA, Bugshan AS, Khan AM, Moothedath MM. Pathogenesis of dysgeusia in COVID-19 patients: a scoping review. Eur Rev Med Pharmacol Sci 2021;25:1114–34.
[14] Sakaguchi W, Kubota N, Shimizu T, et al. Existence of SARS-CoV-2 entry molecules in the oral cavity. Int J Mol Sci 2020;21:6000.
[15] Fitzpatrick SG, Cohen DM, Clark AN. Ulcerated lesions of the oral mucosa: clinical and histologic review. Head Neck Pathol 2019;13:91–102.
[16] Kitakawa D, Oliveira FE, Neves De Castro P, Carvalho LFCS. Short report - Herpes simplex lesion in the lip semimucosa in a COVID-19 patient. Eur Rev Med Pharmacol Sci 2020;24:9151–3.
[17] Asai D, Nakashima H. Pathogenic viruses commonly present in the oral cavity and relevant antiviral compounds derived from natural products. Medicines (Basel) 2018;5:120.
[18] Sleiwah A, Nair G, Mughal M, Lancaster K, Ahmad I. Perioral pressure ulcers in patients with COVID-19 requiring invasive mechanical ventilation. Eur J Plast Surg 2020;43:727–32.
[19] Gefen A, Ousey K. CoviD-19: pressure ulcers, pain and the cytokine storm. J Wound Care 2020;29:540–2.
[20] Moser D, Biere K, Han B, et al. COVID-19 impairs immune response to candida albicans. Front Immunol 2021;12:640644.
[21] Kamel AHM, Basuoni A, Salem ZA, AbuBakr N. The impact of oral health status on COVID-19 severity, recovery period and C-reactive protein values. Br Dent J 2021;24:1–7.
[22] Corchuelo J, Ulloa FC. Oral manifestations in a patient with a history of asymptomatic COVID-19: case report. Int J Infect Dis 2020;100:154–7.
[23] Amorim dos Santos J, Normando AGC, Carvalho da Silva RL, et al. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? Int J Infect Dis 2020;97:326–8.
[24] Fantozzi PJ, Pampena E, Di Vanna D, et al. Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. Am J Otolaryngol 2020;41:102721.
[25] Cruz Tapia RO, Peraza Labrador AJ, Guimaraes DM, Matos Valdez LH. Oral mucosal lesions in patients with SARS-CoV-2 infection. Report of four cases. Are they a true sign of COVID-19 disease? Spec Care Dent 2020;40:555–60.
[26] Gherlone EFF, Polizzi E, Tetè G, et al. Frequent and persistent salivary gland ectasia and oral disease after COVID-19. J Dent Res 2021;100:464–71.
[27] Halepas S, Lee KC, Myers A, Yoon RK, Chung W, Peters SM. Oral manifestations of COVID-19 related multi-system inflammatory syndrome in children: a review of 47 pediatric patients. J Am Dent Assoc 2020;152:202–8.
[28] Sinadinos A, Shelswell J. Oral ulceration and blistering in patients with COVID-19. Evid Based Dent 2020;21:49.
[29] Riad A, Gomaa E, Hockova B, Klugar M. Oral candidiasis of COVID-19 patients: case report and review of evidence. J Cosmet Dermatol 2021;20:1580–4.
[30] Nuño González A, Magaletsky K, Martín Carrillo P, et al. Are oral mucosal changes a sign of COVID-19? a cross-sectional study at a field hospital. Actas Dermosifiliogr 2021;112: 640–4.
[31] Riad A, Kassem I, Hockova B, Badrah M, Klugar M. Tongue ulcers associated with SARS-CoV-2 infection: a case series. Oral Dis 2020; Online ahead of print.
[32] Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z. Olfactory and oral manifestations of COVID-19: sex-related symptoms —a potential pathway to early diagnosis. Otolaryngol Head Neck Surg 2020;163:722–8.
[33] Sinjari B, D'Ardes D, Santilli M, et al. SARS-CoV-2 and oral manifestation: an observational, human study. J Clin Med 2020;9: 3218.
[34] Favia G, Tempesta A, Barile G, et al. Covid-19 symptomatic patients with oral lesions: clinical and histopathological study on 123 cases of the university hospital policlinic of bari with a purpose of a new classification. J Clin Med 2021;10:757.
[35] Fidan V, Koyuncu H, Akin O. Oral lesions in Covid 19 positive patients. Am J Otolaryngol 2021;42:102905.