Oral manifestations associated with SARS-COV-2: A literature review

Manifestaciones orales asociadas a SARS-COV-2: Revisión de la literatura

Manifestações orais associadas ao SARS-COV-2: Revisão da literatura

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Abstract

Objective: Identify the main oral manifestations associated with COVID19 and describe their location in the oral cavity.
Methods: The literature search was conducted in PubMed, Medline, LILACS, LIVIVO, Web of Science, and SciELO. The following words were searched for: *oral mucosa, oral mucosa lesion, oral manifestations, COVID-19*, and *SARS-CoV-2*. Duplicate articles were eliminated, and the pieces were shortlisted. Finally, inclusion and exclusion criteria were applied.
Results: This study included 47 articles. The main oral manifestations in patients with COVID-19 are taste disorders, xerostomia, ulcers, vesicles, and others located in different areas of the oral mucosa.
Conclusions More studies are needed to determine the potential oral etiopathogenesis of SARS-CoV-2. Moreover, dentists play a significant role in the multidisciplinary and telemedicine team.

Keywords: COVID-19, oral manifestation, oral mucosa.

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Resumen

Objetivo: Identificar las principales manifestaciones y describir su ubicación en la cavidad oral en pacientes COVID-19.

Métodos: Se utilizaron las bases de datos PubMed, Medline, LILACS, LIVIVO, Web of Science y SciELO; utilizando los términos de búsqueda *oral mucosa, oral mucosa lesion, oral manifestations, COVID-19* y *SARS-CoV-2.* Se eliminaron duplicados, luego se realizó preselección de artículos, y finalmente se aplicaron los criterios de inclusión y exclusión.

Resultados: Se seleccionaron 47 publicaciones, encontrando manifestaciones orales en pacientes COVID-19 tales como alteración en gusto, xerostomía, úlceras, vesículas, entre otras; ubicándose en diferentes áreas de la mucosa oral.

Conclusiones: Se necesitan más estudios para vislumbrar la posible etiopatogenia a nivel oral del SARS-CoV-2. Además, se destaca el rol del odontólogo en el equipo multidisciplinario y en la teleconsulta.

Palabras clave: COVID-19, manifestación oral, mucosa oral.

Resumo

Objetivo: Identificar as principais manifestações e descobrir sua ubiquação na cavidade oral em pacientes com COVID-19.

Método: Foram utilizadas as bases de dados PubMed, Medline, LILACS, LIVIVO, Web of Science e SciELO; utilizando os termos de pesquisa oral mucosa, oral mucosa lesion, oral manifestations, COVID-19 e SARS-CoV-2. Duplicadas foram removidas, depois uma pré-seleção de artigos foi feita, e finalmente os critérios de inclusão e exclusão foram aplicados.

Resultados: Foram selecionadas 47 publicações, encontrando manifestações orais em pacientes com COVID-19, tais como alterações no paladar, xerostomia, ulcerações, vesículas, entre outros; localizando-as em diferentes áreas da mucosa oral.

Conclusão: São precisos mais estudos pra vislumbrar a possível etiopatogenia a nível oral do SARS-CoV-2. Ademais, destaca-se o role do odontólogo na equipe multidisciplinar e na tele consulta.

Palavras-chave: COVID-19, Manifestação oral, mucosa oral.

Introduction

The new infectious disease Coronavirus 2019 (COVID-19), whose etiology is Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2), has had a massive impact worldwide given its transmission rate, the resulting severe respiratory disorders, and the number of deaths globally. All this significantly compromises people's quality of life.[1] Since it originated in Wuhan, China, the disease has reached a high infectivity rate. Projections estimate 47 million cases worldwide and a mortality rate ranging from 3% to 12%. Over one million people have died.[1-3]

The specific origin of the pandemic is not fully understood. Although it is unclear how humans acquired the disease, it is estimated that it involved an animal. Bats are the main wild beings that are reservoirs for this type of virus. A viral jump occurred between this animal and a human being in Wuhan, China, in November 2019.[2,4]

The main infection routes of SARSCoV2 in humans are saliva droplets expelled when talking[1,2,5-9] or sneezing within a distance of two meters or when in contact with exposed surfaces.[2,6-9] Fifty percent of transmissions occur through exposure to asymptomatic people.[2] It is important to note that patients can transmit the infection up to two weeks after recovering from the disease.[4]

Current research shows that the SARSCoV2 virus invades human cells through the angiotensin-converting enzyme 2 (ACE2) receptor.[1,7,9-23] In this way, cells with ACE2 receptor distribution can become hosts to the virus and cause an inflammatory response in adjacent organs and tissues, including the oral cavity.[1, 7,8,10,12,14, 16-19,21-28]

This literature review aims to identify the main oral manifestations in patients with COVID19 and to describe their location in the oral cavity.

Materials and methods

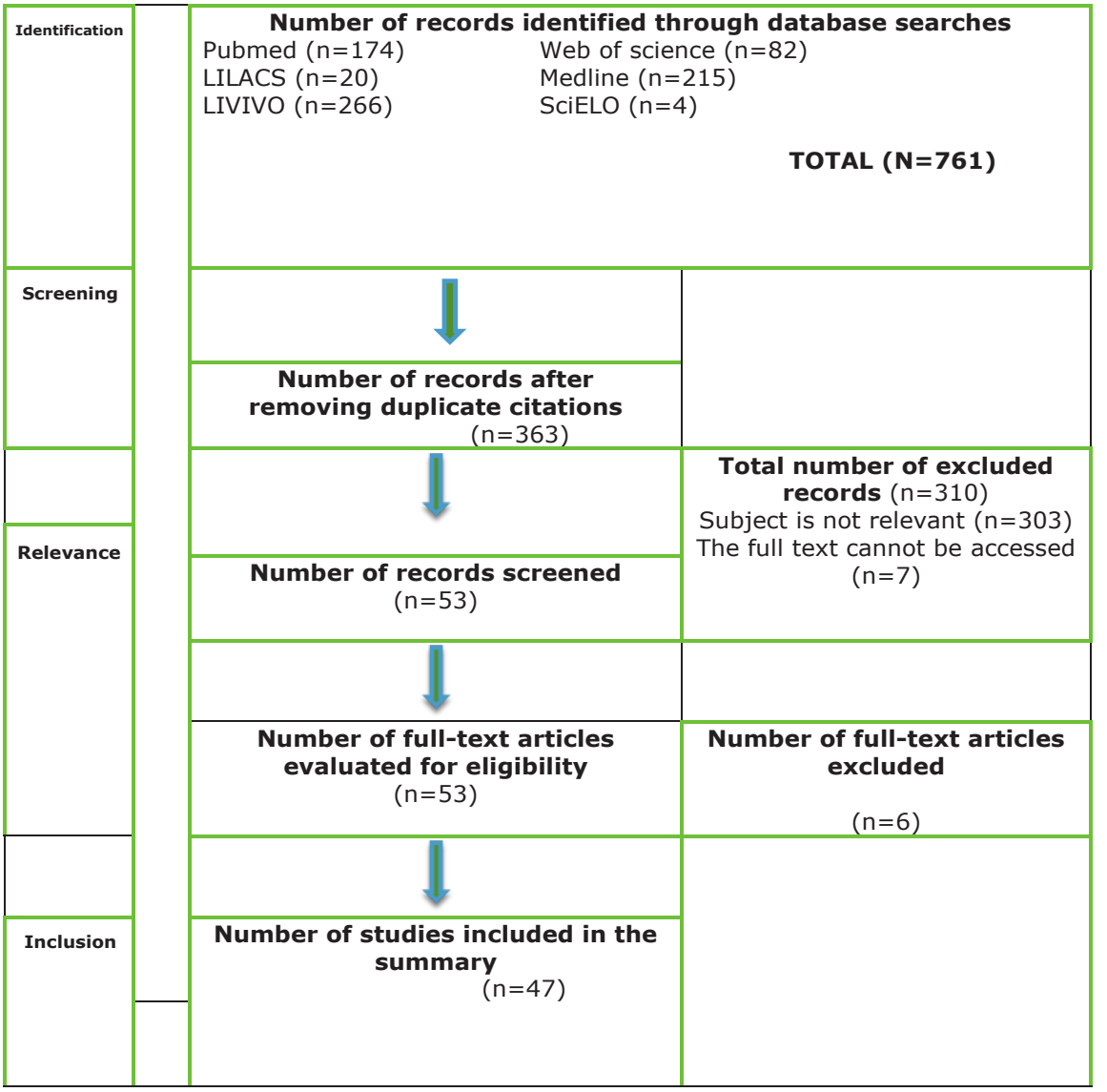
This literature review included the following stages: selecting the topic, defining the objectives, stating the inclusion and exclusion criteria, developing a work plan for the literature search, selecting, and retrieving the studies that meet the criteria, collecting data to analyze and summarize the results, and finally, drawing conclusions.

The search was conducted from 9 October to 30 December 2020 in PubMed, Medline, LILACS, LIVIVO, Web of Science, and SciELO. The search terms defined for the database search were: *oral mucosa, oral mucosa lesion, oral manifestations, COVID-19,* and *SARS-CoV-2*, with boolean operators OR and AND. Results: ((COVID-19) OR (SARS-CoV-2)) AND (mucosa oral)), ((COVID-19) OR (SARS-CoV-2)) AND (oral mucosa lesion)) and ((COVID-19) OR (SARS-CoV-2)) AND (oral manifestations)). The title and abstract were read to determine relevance. Then, the full texts were read to determine if they met the inclusion and exclusion criteria.

The inclusion criteria covered articles published within the last two years that contain the search terms in Spanish and English.

The following articles were excluded: studies conducted on animals, focused on treating patients infected with the SARSCoV2 virus, COVID19 patients without oral manifestations, and those related to prevention and/or biosafety measures that did not meet our objectives.

Figure 1. Flowchart of the article search, review, and selection process



Development

Duplicate articles were discarded and studies that met the inclusion and exclusion criteria were selected. The final selection included 47 articles: 9 case reports, 1 case report with narrative literature review, 2 systematic reviews, 3 critical reviews, 9 narrative reviews, 4 observational studies, and 19 letters to the editor. In addition, information from one article and two websites was included in the introduction.

The cases reported in the literature describe heterogeneous lesions between patients and even in the same patient.[10-13] What varies is the presentation, location, and size.[5,10,12,29] Oral manifestations have appeared in healthy COVID-19 patients with no relevant medical history,[1,5,12,13,18,30-33] and in patients with underlying conditions.[1,7,10,12,13,16,18,23,27-30,33-41]

The manifestations that are mentioned more frequently are taste disorders and ulcers, while the least mentioned are pustules, glossitis, and geographic tongue. The main manifestations found are described below (Table 1):

Table 1: Oral manifestations reported in patients with COVID-19

Oral manifestation	Type of publication	References
Taste disorders	5 case reports 2 systematic reviews 7 narrative reviews 2 critical reviews 10 letters to the editor 3 observational studies 1 case report with narrative literature review	30 references (1,6-12,14,16-19,21-24,26,29,30,33,36,38,40-46)
Burning sensation	1 case report 3 narrative reviews 3 letters to the editor 2 observational studies 1 case report with narrative literature review	10 references (6,8,12,18,27,36,39,41,44,47)
Xerostomia	2 case reports 5 narrative reviews 1 critical review 2 letters to the editor 2 observational studies	12 references (5,6,8-10,16-18,24,29,36,47)
Halitosis	3 narrative reviews 2 letters to the editor	5 references (16,17,25,27,48)
Erythema	4 case reports 1 narrative review 1 systematic review 3 critical reviews 4 letters to the editor 1 observational study 1 clinical case with narrative literature review	15 references (1,9-13,19,20,27,28,30,31,41,46,49)
Petechias	2 case reports 4 narrative reviews 1 systematic review 2 critical reviews 3 letters to the editor 1 clinical case with narrative literature review	13 references (1,5,9,11,13,15,17,18,20,26,27,31,41)
Macules	2 case reports 1 narrative review 1 systematic review 2 critical reviews 3 letters to the editor 1 observational study 1 clinical case with narrative literature review	11 references (10-13,17,19,20,26,29,41,47)
Bulla/blisters	3 case reports 5 narrative reviews 1 systematic review 3 critical reviews 3 letters to the editor 1 observational study 1 clinical case with narrative literature review	17 references (8,9,11,12,15-20,23,26,28,30,37,41,49)

Oral manifestation	Type of publication	References
Pustules	1 case report 1 narrative review 2 letters to the editor	4 references (13,27,31,32)
Ulcers	6 case reports 6 narrative reviews 1 systematic review 3 critical reviews 11 letters to the editor 2 observational studies 1 clinical case with narrative literature review	30 references (1,5,6,8-13,15-20,23,25-30,33-35,38,41,44-46)
Desquamative gingivitis	2 case reports 3 narrative reviews 1 systematic review 2 critical reviews 1 letter to the editor	9 references (9,11,12,15,18,19,25,27,30)
Salivary gland infection	3 narrative reviews 2 critical reviews 2 letters to the editor 1 clinical case with narrative literature review	8 references (8,19-21,24,28,41,45)
Geographic tongue	2 letters to the editor	2 references (6,44)
Glossitis	3 narrative reviews 1 critical review 2 letters to the editor	6 references (9,16,17,27,39.44)
Candida coinfection	2 case reports 1 narrative review 1 systematic review 2 letters to the editor 1 observational study 1 clinical case with narrative literature review	8 references (5,6,10,11,17,39,41,46)
Herpetiform lesions	4 case reports 3 narrative reviews 1 systematic review 1 critical review 3 letters to the editor 1 observational study 1 clinical case with narrative literature review	14 references (1,9-11,14,17,18,26,27,30,33,41,42,46)

The location of lesions is unspecific, but they appear mainly on the palate, tongue (mainly on the dorsum), and also lip (inners side and semi mucosa). Lesions are also reported in the oral mucosa, gingiva, and oropharynx (Table 2).

Table 2: Localization of oral manifestations reported in patients with COVID-19.

Localization	Type of publication	References
Palate	3 case reports 4 narrative reviews 1 systematic review 2 critical reviews 10 letters to the editor 1 observational study 1 clinical case with narrative literature review	22 references (1,6,9,11-13,15,17,18,20,23,26-31,35,38,39,41,43)
Tongue	5 case reports 2 narrative reviews 1 systematic review 2 critical reviews 11 letters to the editor 2 observational studies 1 clinical case with narrative literature review	24 references (1,5,6,9-12,17,20,23,26-29,32,33,35,38,39,41,44-46,49)
Lip	6 case reports 4 narrative reviews 1 systematic review 2 critical reviews 7 letters to the editor 2 observational studies 1 clinical case with narrative literature review	23 references (1,5,6,9,11,13,15,17,18,20,23,26-30,34,37,38,41,42,46,49)
Oral mucosa	2 case reports 2 narrative reviews 1 systematic review 1 critical review 3 letters to the editor 1 observational study	10 references (1,9,11,15,27,28,29,37,46.49)
Gum	1 case report 3 narrative reviews 1 systematic review 1 critical review 5 letters to the editor 1 clinical case with narrative literature review	12 references (5,6,9,11,13,15,18,26-28,41,48)
Oropharynx	2 case reports 2 narrative reviews 1 systematic review 2 letters to the editor 1 observational study	8 references (5,10,11,13,18,23,27,31)

Discussion

Although oral mucosa lesions have been reported in patients infected with SARS-COV-2 virus, it is believed that the cause is not the virus itself, but that the lesions would be secondary to the drugs[5,7,9-11,15,17,18,21,26,28,30,32,36,39,41,43,50] administered for the treatment, or due to the compromise and deterioration of the immune system,[1,6,9-12,15-17,26,27,33,34,36,38,41,45,50] which also enables opportunistic infections.[5,6,9-11,15-18,25-28,33,36,39,41,42,45,48,50] The most commonly reported conditions are *Candida albicans* coinfections[5,6,10,11,17,39,41] and/or other viruses.

[1,9,10,16,17,27,33,41-43,45,46,50] Despite these assumptions, some of the studies reviewed theorize about SARS-CoV-2's vascular and thrombotic effect on the oral mucosa.[6,9,12,15,17,23,27,29,34] Similarly, oral mucosa lesions could be triggered by factors such as stress.[5,8,18,22,25,26,32,37]

We must emphasize the importance of the ACE2 receptor, which is distributed in the cell membrane of various organs and tissues, such as the respiratory tract, the nervous system, the digestive system, and the skeletal muscle.[1,9,13,23,24,27] In the oral cavity, they appear in the oral[1,7,8,12,16-19,21-27] and gingival [7,14,21,23,24] mucosa epithelial cells. There is a strong presence in tongue epithelial cells [1,7-11,14,15,17,18,21,24,25,27,33,36] and salivary glands.[1,9-12,16-20,24,27,36] Due to this high expression,[8,9,11,14,15,18,19,21,22,24,25,27,33], the tongue is described as a susceptible organ.[14,19,25,33] Some authors say that salivary glands[6,8,10,21,24,36] and periodontal pockets[9,18,25,36,44] could act as virus reservoirs.

These ACE2 receptor would be the main SARSCoV2 receptors, causing cells that distribute this receptor to trigger inflammatory reactions in the associated organs and tissues.[1,9,10,13] Therefore, several authors state that this interaction in the tongue could explain taste disorders in patients with COVID19.[1,8-11,15-19,22,24] It has also been said that the interaction between the virus and this receptor alters the function of oral keratinocytes and the epithelial lining of the salivary gland ducts after infection.[1] Additionally, saliva and nasal secretion could have high viral loads involved in these oral alterations.[9,12]

Multiple authors agree on the need for additional studies and thorough resear ch[1,5,9-16,23,24,26,28-31,34-36,42,43,50] to determine the pathogenic mechanisms of SARS-CoV-2 on oral tissues and thus determine whether oral mucosal lesions are directly or indirectly related to COVID19 progression.[1]

Conclusion

Oral manifestations in COVID-19 patients have been reported in multiple sites of the oral cavity and are highly heterogeneous. The subject is so new that the prevalence of these manifestations is still unknown since the cases reported are few compared to the number of infected patients. Additionally, most cases lack complementary tests, such as biopsies or hematology tests, which help identify the real etiological agent. All this leaves unanswered questions about the possible etiopathogenesis or factors that might influence the development of these lesions. Therefore, it is necessary to conduct further research.

Finally, it is essential to recognize that dentists are crucial members of the health and telemedicine teams. Dentists should perform a careful oral examination to diagnose, treat, and control the pain caused by the lesions described.

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The authors declare no conflict of interest

Authorship contribution
1. Conception and design of study
2. Acquisition of data
3. Data analysis
4. Discussion of results
5. Drafting of the manuscript
6. Approval of the final version of the manuscript.

NSG has contributed in 1, 2, 3, 4, 5 and 6.
TNT has contributed in 3, 4, 5 and 6.
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