


CHAPTER 19

Changes in the stomatognathic system in face of COVID-19 - an integrative review

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ABSTRACT

The oral cavity is closely related to SARS-CoV-2 due to the high concentration of angiotensin-converting enzyme 2 receptors. In addition, the infection and its associated therapies contribute to the manifestation of oral changes in different cases.

The purpose of this research was to conduct a review regarding the possible changes that SARS-CoV-2 causes in the stomatognathic system. The methodology used was an integrative literature review, guided by the research question developed by the PICO strategy.

The results showed that the main oral changes associated with COVID-19 are disorders of taste and smell, followed by dry mouth or hyposalivation and ulcerations. Several oral manifestations have been observed, however, there is not enough evidence to determine a causal relationship with infection or SARS-CoV-2. It is important that health professionals are aware of dysgeusia and hyposmia as the first sign of COVID-19.

Keywords: Coronavirus infections, Mouth, Dentistry, Public health.

1 INTRODUCTION

A new coronavirus was first detected in late 2019 and quickly became a global outbreak, being named SARS-CoV-2 (LIU; KUO; SHIH, 2020). Declared a pandemic by the World Health Organization (WHO) in March 2020, the infection has had 51,848,261 confirmed cases and 1,280,868 deaths, and is present in 220 countries/territories (WHO, 2020). Patients present with a wide range of symptoms: fever, cough, shortness of breath, sore throat, nasal congestion, myalgia, headache, abdominal pain, diarrhea, and others (HUANG, et al. 2020), and as research regarding COVID-19 has advanced, gustatory and olfactory disturbances have been found to be common (PASSARELLI, et al. 2020).

The routes of transmission of SARS-CoV-2 involve direct transmission - coughing, sneezing and partridges - or contact with oral, nasal and ocular mucosa (MOURA; MOURA; PEREIRA; MARINHO, 2020) and it has also been found that the viruses can be transmitted in an interpersonal manner through contact, direct or indirect, with fluids such as saliva (DE CAMPOS TUNÃS et al., 2020).

The oral cavity has an intimate relationship with SARS-CoV-2 due to the high concentration of angiotensin-converting enzyme (ACE2) receptors in its organs and tissues. The virus expresses proteins on its outer surface that facilitate its binding to host cells via ECA2 (DIAS, et al., 2020) and therefore organs

and tissues that express high amounts of ECA2 can be targeted by SARS-CoV-2 and develop an inflammatory response associated with the viral presence (XU, et al., 2020). The ACE2 receptor can be found in other organs such as small intestine, testicles, adipose tissue, in the thyroid, kidneys, myocardium, among several others; it can also be seen in the salivary glands, having an average expression level of 1.8 pTPM (protein-coding transcripts per million) - it is the tenth organ with the highest concentration of ACE2, with a higher expression level, even, than the lung (WANG, et al, 2020). Research on receptors in the oral cavity has shown that there is expression of ACE2 in the oral mucosa and that there is a higher concentration in epithelial cells of the tongue (XU, et al, 2020).

There is still no drug therapy considered, by scientific evidence, effective against COVID-19 and, those with potential have been associated with several side effects (NCBI, 2020). Thus, SARS-CoV-2 infection and its associated therapies may contribute to different outcomes related to the oral cavity (AMORIM, et al, 2020) and the stomatognathic system.

The objective of this study is to perform an integrative review regarding the possible changes that SARS-CoV-2 causes in the stomatognathic system, answering the following research question: "What are the main changes that SARS-CoV-2 causes in the oral cavity?"

2 MATERIALS AND METHODS

This study is characterized as an integrative literature review, which, according to Stetler (1998), is a systematic analysis aimed at synthesizing the research on a certain topic and is an important method when there is the need to solve a clinical problem or assess the use of concepts in the scientific context. It was developed based on the phases proposed by Botelho, Cunha and Macedo (2011), namely: 1. identify the theme and research question; 2. establish inclusion and exclusion criteria; 3. identify selected studies; 4. categorize selected studies; 5. perform the analysis and interpretation of results and, 6. present the review and synthesis of knowledge.

The question that guided this research was developed using the "PICO" strategy (STONE, 2002), where P (population) - patients confirmed with COVID-19; I (independent variable) - with oral changes; C (comparison) - without oral changes; and O (outcomes) - presence and type of changes. This applied strategy resulted in the following research question: "What are the main changes that SARS-CoV-2 causes in the oral cavity?"

The literature search was done in three databases: Scielo, Scopus and LiLacs and the definition of the descriptors was done by consulting the DeCS (descriptors in health sciences) platform. The terms used were "Coronavirus Infections", "COVID-19", and "mouth", with the aid of the Boolean operators "AND" and "OR". The inclusion criteria were broad due to the nature of the search, admitting publications from 2020 classified as original articles, review articles, clinical cases, and also short communications and letters to the editor. These broad inclusion criteria were thought to be due to SARS-CoV-2 being a new pathogen,

so an attempt was made to include as much pertinent information as possible. The inclusion criteria involved: articles that did not have as their scope oral changes related to COVID-19 or in vitro research.

Data were extracted using the instrument recommended by Pompeo (2007) and adapted by the authors to answer the research question. The level of evidence was based on Melnyk and Fineout-overholt's (2011) classification as follows: Level I - Evidence from a systematic review or meta-analysis of all relevant randomized clinical trials; Level II - Evidence obtained from well-planned randomized clinical trials; Level III - Evidence obtained from well-designed controlled trials without randomization; Level IV - Evidence from well-planned case and cohort studies; Level V - Evidence from systematic reviews of descriptive and qualitative studies; Level VI - Evidence from single descriptive or qualitative studies; Level VII - Evidence from authority opinion and/or expert committee reports.

Results are presented based on categorization of information according to convergent themes.

3 RESULTS AND DISCUSSION

An initial search identified 316 papers using the defined search criteria: 176 in Scielo, 107 in Scopus, and 33 in LILACS. This was followed by a pre-selection based on the established inclusion criteria, resulting in a total of 116 papers, 42 in Scielo, 65 in Scopus, and 9 in LILACS. After checking for duplicate publications, the number of studies to be read in full was 53. After applying the last filter and reading the full texts, 21 studies were left that met the inclusion criteria and, to a greater or lesser extent, answered the research question about the oral changes observed in patients confirmed with COVID-19.

Thus, 21 (100%) publications were included in this integrative review. They were organized according to the information pertinent to the research and methodological design and are presented in chart 1.

IDENTIFICATION	OBJECTIVE	METHODOLOGY	RESULTS AND CONCLUSIONS – regarding the research question
Gómez, J. L. M. <u>Odontol. sanmarquina (Impr.)</u> ;23(3), 2020-08-04	To present important aspects of COVID-19 and its relation to dental practice, with emphasis on preventive measures in order to avoid cross-infection.	Literature review	The virus genome was detected in saliva indicating possible infection of the salivary glands. Anosmia and agorusia was reported as a symptom of COVID-19, and in most patients (91%) these symptoms appeared before the respiratory ones. Descaling gingivitis, ulcers and vesicles compatible with recurrent herpetic stomatitis have been reported on the mucosa of the palate, as well as burning sensation and pain in the oropharynx. Untreated moderate to severe periodontitis may worsen in severe cases of COVID-19

			(inflammatory state seems to act as a trigger of the coagulation cascade and is associated with higher levels of fibrinogen degradation products). Acute necrotizing periodontitis also had its occurrence rate increased in this period of increased cases of COVID-19,
Fantozzi, P. J. et al. Xerostomia, gustatory and olfactory dysfunctions in patients with COVID19	To assess the prevalence and characterize xerostomia and taste and olfactory dysfunctions in patients with COVID-19.	Retrospective cohort, where SARS-CoV-2 positive adults completed questionnaires regarding the symptoms dysgeusia, hyposmia/anosmia and xerostomia.	Xerostomia and gustatory and olfactory dysfunctions are common in patients with COVID-19, concomitant and in some cases the only manifestations of the disease. such symptoms should be considered in screening in order to identify patients with early-stage SARS-CoV-2.
Corchuelo, J.; Ulloa, F. C. Oral manifestations in a patient with a history of asymptomatic COVID-19: Case report	To report a case of oral manifestations in an asymptomatic patient with COVID-19.	Case report.	Reddish plaques on the lower lip, dark brown pigmentation on the inserted gingiva and petechiae on the palate.
Biadsee, A. et al. Olfactory and Oral Manifestations of COVID-19: Sex-Related Symptoms— A Potential Pathway to Early Diagnosis	To evaluate the early manifestations of COVID-19, with emphasis on olfactory and oral disturbances.	A prospective cohort, where adults with COVID-19 completed a six-section questionnaire regarding symptoms related to oral cavity, taste and smell.	The patients perceived olfactory and gustatory dysfunctions, xerostomia, frontal headache, pain in masticatory muscles. In addition, to a lesser extent, changes in tongue sensitivity, plaque-like lesions on the tongue, edema on the palate, tongue and gums, and bleeding in the oral cavity were also observed.
Cant, A.; Bhujel, N.; Harrison, M. Oral ulceration as presenting feature of paediatric inflammatory multisystem syndrome associated with COVID-19	Share the insight from the Department of Pediatric Dentistry at Saint Thomas Hospital, London regarding lip edema and ulcerations as an early symptom of developing pediatric multisystemic inflammatory syndrome associated with COVID-19.	Letter to the Editor	Lip edema and ulceration with subsequent development of pediatric multisystemic inflammatory syndrome associated with COVID-19.
Abalo-Lojo, J. M.; Pouso-Diz, J. M.; Gonzalez, F. Taste and Smell Dysfunction in COVID-19 Patients	To analyze the extent to which taste dysfunctions and anosmia were present in patients with COVID-19.	Letter to the editor, research methodology not described.	Taste dysfunction and anosmia are prominent symptoms in COVID-19 patients and, together with cough and asthenia, are the most frequently reported. In

			addition, they tend to appear in the first days of the disease and, therefore, can be valuable for early diagnosis.
dos Santos, J. A. et al. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations?	To report a relevant case of oral manifestations in a patient with COVID-19.	Case Report	Persistent white plaque on the dorsum of the tongue, as well as yellowish punctate ulcers - similar to a late stage of herpetic ulceration.
Lai, C.; Ko, W.; Lee, P.; Jean, S.; Hsueh, P. Extra-respiratory manifestations of COVID-19	To provide a review of the extra-respiratory manifestations of COVID-19 to aid in understanding the clinical presentations of the disease.	Review	Ageusia and dysgeusia, anosmia and hyposmia.
Ren, Y. F.; Rasubala, L.; Malmstrom, H.; Eliav, E. Dental Care and Oral Health under the Clouds of COVID-19	Review current evidence related to the impact of SARSCoV-2 / COVID-19 on dental care and oral health.	Review	Clinical, empirical, and biological evidence suggests that oral mucosa is a SARS-CoV-2 entry site and that oral symptoms, including dysgeusia or ageusia, xerostomia, hyposmia, or anosmia, may be the first symptoms of COVID-19 before fever, dry cough, fatigue or shortness.
Odeh, N. D. et al. COVID-19: Present and Future Challenges for Dental Practice	Address the medical and dental aspects of COVID-19 infection.	Review	Virus genome was found in most salivary glands of patients with COVID-19, suggesting infection of the salivary glands; another change cited in the review is the presence of gustatory changes.
Maciel, p. P. et al. COVID-19 Pandemic: Oral Repercussions and its Possible Impact on Oral Health	Discuss the likely dental and oral consequences of COVID-19	Review	Studies have been published on the vertical transmission of SARS-CoV-2 and the risk to the overall health of newborns, but few data are available on the effect of SARS-CoV-2 in pregnancy. Concomitant gustatory and olfactory dysfunction have been reported, as well as xerostomia; it is suggested that these changes may be related to ACE2 receptor expression in oral tissues. Ulcerations, petechiae, reddish macules, desquamative gingivitis, and blisters have been reported.

Passarelli, P. C. et al. Taste and smell as chemosensory dysfunctions in COVID-19 infection	To review the literature regarding two clinical manifestations in patients with SARS-CoV-2: anosmia and ageusia.	Systematic Review	It demonstrated the presence of ageusia and anosmia in multiple cases of SARS-CoV-2, making the occurrence of these symptoms an important suspect for COVID-19.
Pedrosa. M. S.; Sipert, C. R.; Nogueira, F. N. Salivary Glands, Saliva and Oral Findings in COVID-19 Infection	Provide an overview of the salivary glands and saliva in the context of SARS-CoV-2 infection discuss oral disorders in patients with COVID-19.	Review	Hyposalivation was observed, but may be associated with stress or medications. Taste and smell dysfunctions also appeared. Regarding oral changes, the diagnosis can be confusing because of the clinical features that run the course of viral infections, but in general they appear as ulcers or blisters.
Samaranayake, L. P.; Fakhruddin., K. S.; Panduwawala, C. início súbito, perda aguda do paladar e do olfato na doença coronavírus 2019 (COVID-19): uma revisão sistemática	To systematically review the contemporary evidence regarding dysgeusia and anosmia as a trigger for prodromal symptoms in patients with COVID-19.	Systematic review	The review indicates a reasonable prevalence of acute onset olfactory and taste symptoms in patients with COVID-19.
Kahraman, F. C.; Çaskurlu, H. Mucosal involvement in a COVID-19-positive patient: a case report	To present the case of a patient with SARS-CoV-2 infection who had oropharyngeal lesions.	Letter to the Editor	Ageusia and anosmia, sore throat due to erythematous lesion on oropharynx and hard palate, with pustular enanthem on soft palate.
Soares, et al. Oral lesions in a patient with Covid-19	To report the clinical and microscopic features of the oral lesions of a SARS-Cov-2 positive patient.	Letter to the Editor	Painful ulceration on buccal mucosa, reddish macules on hard palate, tongue and lips. The authors suggest that SARS-CoV-2 causes oral changes.
Lechien, J. R. et al. Gustatory dysfunctions in COVID-19	Highlight the importance of considering taste impairment in patients with COVID-19.	Letter to the Editor	Patients report hyposmia and dysgeusia, which compromises their quality of life. In the case of COVID-19, ECA2 receptors were identified in the oral cavity, having high expression in tongue, which would explain the hypothesis that infection and inflammatory response could lead to alterations in saliva production, normal flavor translation, and continuous renewal of taste buds.
Melley, L. E.; Bress, E.; Polan, E. Hypogeusia as	Review the clinical course of SARS-CoV-2 in relation to	Case Report	The patient presented with the initial symptom of altered taste and smell perception

the initial presenting symptom of COVID-19	the reported symptom of hyposmia and hypogeusia.		prior to respiratory involvement. After a period of hospitalization, the patient recovered most of her sense of smell and was discharged with only persistent dysgeusia
Kitakawa, D. et al. Short report – Herpes simplex lesion in the lip semimucosa in a COVID-19 patient	Discuss the oral manifestations in a patient with a confirmed diagnosis of COVID-19.	Case Report	Vesiculo-bullous lesions on lip, with onset and resolution within 14 days.
Chen, L. et al. Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Patients	Provide an understanding regarding the detection of SARS-CoV-2 in saliva and the initial oral symptoms in oral tissue infection.	Observational - saliva was collected to analyze the presence of nucleic acids from SARS coronavirus 2 and a questionnaire was applied about 14 oral symptoms.	Saliva can be a means of detection of SARS-CoV-2. According to the analysis of the questionnaires, the main oral symptoms were xerostomia and dysgeusia.
Katz, J. Running Head: aphthous stomatitis and Covid 19	To provide and cross-reference information regarding the prevalence of recurrent aphthous stomatitis and COVID-19 and its strength of association.	Observational - compared prevalence rates of RAS of patients with and without COVID-19.	The prevalence of RAS was higher in patients infected with COVID-19.

Brazil was the country that presented the most papers included in this review - five (24%), followed by Italy and the United States, with two papers (9%) each. The other studies were published by researchers from Taiwan, Peru, Saudi Arabia, United Arab Emirates, Colombia, Istanbul, Israel, China, and European countries - Spain, United Kingdom, France -, individually or in groups. The publications included literature reviews (6, representing 29% of the papers), two systematic reviews (9%), four case reports (19%), letters to the editor (five, representing 24%), and four observational studies (19%).

Regarding the level of evidence, the one found for the studies included in this review was good, taking into account that this is a new disease and that there is still little time to have more robust evidence. Of the 21 articles included, two have level I evidence, four have level IV, six have level V, four level VI, and five level VII. Thus, although there is scientific evidence that proves some relationship between COVID-19 and oral alterations, there is still the need to develop controlled and randomized studies in order to build bases to guide clinical practice.

Regarding the oral changes found in the published papers on the subject, sixteen (76%) of them cite taste dysfunctions - ageusia, hypogeusia, dysgeusia - as a symptom of SARS-CoV-2 infection (GÓMEZ, 2020; FANTOZZI, et al, 2020; BIADSEE, et al, 2020; SAMARANAYAKE, FAKHRUDDIN, PANDUWAWALA, 2020; KAHRAMAN, ÇASKURLU, 2020; LECHIEN, et al, 2020; MELLEY, BRESS, POLAN, 2020; CHEN, et al, 2020; ABALO-LOJO, POUISO-DÍAZ, GONZALEZ, 2020; LAI,

WNAG, HSUEH, 2020; REN, RASUBALA, MALMSTROM, ELIAV, 2020; ODEH, et al, 2020; MACIEL, et al, 2020; PASSARELLI, et al, 2020; PEDROSA, SIPERT, NOGUEIRA, 2020). The mucosa of the mouth has been considered as a potential route of entry for SARS-CoV-2 into the body (PENG et al, 2020), due to the high expression of the ECA2 receptor, which is responsible for facilitating the entry of the virus into cells (DIAS et al, 2020) and a survey done to assess the presence of these receptors in the oral cavity showed that there is expression of ECA2 in the mucosa of the mouth and that there is a higher concentration in epithelial cells of the tongue (XU, et al, 2020).

Olfactory changes were also widely reported, appearing in 13 of 21 papers (62%) (GÓMEZ, 2020; FANTOZZZI, et al, 2020; BIADSEE, et al, 2020; SAMARANAYAKE, FAKHRUDDIN, PANDUWAWALA, 2020; KAHRAMAN, ÇASKURLU, 2020; LECHIEN, et al, 2020; MELLEY, BRESS, POLAN, 2020; ABALO-LOJO, POUISO-DÍAZ, GONZALEZ, 2020; LAI, WNAG, HSUEH, 2020; REN, RASUBALA, MALMSTROM, ELIAV, 2020; MACIEL, et al, 2020; PASSARELLI, et al, 2020). Lechien and colleagues (2020) showed that women are proportionally more affected by hyposmia or anosmia when compared to men ($p < 0.001$). According to Petrescu et al (2020), dysfunctions such as anosmia and ageusia were observed as symptoms induced by the inflammation caused by COVID-19.

Xerostomia and hyposalivation were symptoms that appeared in six studies (29%) (REN et al, 2020; MACIEL, et al, 2020; FANTOZZZI, et al, 2020; BIADSEE, et al, 2020; PEDROSA, SIPERT, NOGUEIRA, 2020; CHEN, et al, 2020), while ulcerations - in different locations of the oral cavity - were cited in five (24%) (dos SANTOS, et al, 2020; MACIEL, et al, 2020; PEDROSA, SIPERT, NOGUEIRA, 2020; CANT, BHUJEL, HARRISON, 2020; SOARES, et al, 2020). Taste is the main stimulant for the formation of saliva, and this may be an explanation for the occurrence of hyposalivation and xerostomia; a study has already shown xerostomia occurring secondary to nasal congestion and rhinorrhea, due to mouth breathing (KNIGHT, 1995); Biadsee and team (2020) found 50% of their sample positive for COVID-19 presenting dysgeusia and xerostomia associated, corroborating this hypothesis. Another possibility for the decreased salivary flow is due to the installed infectious and inflammatory process, which is known to lead to hyposalivation (MORTAZAVI et al, 2014); Thus, the possibility of an infection of the salivary glands by SARS-CoV-2 inducing an inflammatory state and consequent decreased function should not be ruled out (PEDROSA, SIPERT, NOGUEIRA, 2020).

Different viral diseases can cause problems to the stomatognathic system, directly or in a secondary manner; the manifestations may vary but, in general, they appear as ulcerations or blisters in the oral tissues (SANTOS, MUDDANA, 2020). Corroborating this information, vesiculo-bullous lesions were cited by Katz (2020), Kitakawa et al (2020) and Maciel et al (2020).

Maciel et al also cited reddish patches in the oral cavity, as did Corchuello and Ulloa (2020) and Soares et al (2020). Table 2 summarizes the main changes raised in the literature review of the included studies.

tt	REPORTS
Ageusia/ disgeusia	16/21 (76%)
Hyposmia/ anosmia	13/21 (62%)
Xerostomia/ hyposalivation	6/21 (29%)
Ulcerations	5/21 (24%)
Vesiculobullous lesions	3/21 (14%)
Desquamative gingivitis	2/21 (9%)
Reddened lesions (palate, tongue, oropharynx, lips)	3/21 (14%)
Petechiae	2/21 (9%)
Plaque-like lesions on tongue	2/21 (9%)
Table 2. Main oral changes observed in patients with COVID-19.	

In addition to the changes mentioned in table 2, recurrent herpetic stomatitis, pain and burning in the oropharynx (GÓMEZ, 2020), dark brown pigmentation in the inserted gingiva (CORCHUELLO, ULLOA, 2020), changes in tongue sensitivity and bleeding in oral cavity, frontal headache and pain in masticatory muscles (BIADSEE, et al, 2020) have been described. Brown pigmentation in the gums can be explained by the relationship that different factors produced during the inflammatory state - prostaglandins, leukotrienes, cytokines, and inflammatory mediators - may play a role in increasing melatogenesis (LAMBERT, et al, 2019).

A higher prevalence of recurrent aphthous stomatitis has also been cited in patients confirmed with COVID-19 than in those healthy (KATZ, 2020). Xu et al (2020) point to the oral cavity as a target for SARS-CoV-2, explained by the wide distribution of ECA2 receptors in oral tissues and the spectrum of changes published in the literature associated with COVID-19 includes aphthous and vesicular ulcerations (MARTÍN CARRERAS-PRESAS et al, 2020).

Gómez (2020) cites Vieira (2020) who hypothesizes that periodontitis in the moderate to severe stages may lead to a worsening in COVID-19 cases, mediated by the persistent inflammatory state (seen in periodontal disease) that triggers the coagulation cascade and is related to higher levels of fibrinogen degradation products, such as D-dimer. Gómez (2020) also cites, based on Patel and Woolley (2020), the increased occurrence of acute necrotizing periodontitis in the period of the new coronavirus pandemic - the etiology of which may be related to bacterial co-infections occurring in the intraoral environment of patients with COVID-19.

The publication of material that speaks to the occurrence of oral changes from COVID-19 is still very recent in the literature and thus may vary significantly; moreover, underlying diseases, both systemic and local, may be a contributing factor to oral cavity lesions. Thus, it is not yet possible to state that the

oral findings in patients infected with SARS-CoV-2 reported in the literature are direct manifestations of COVID-19 (PEDROSA, SIPERT, NOGUEIRA, 2020).

FINAL CONSIDERATIONS

This integrative literature review pointed out the presence of taste and smell disorders in patients infected with SARS-CoV-2, making such symptoms to be considered an important suspicion of the patient's infection, as other studies have already indicated. Furthermore, it has pointed to the occurrence of xerostomia or hyposalivation associated with COVID-19. Other oral changes observed in some papers were ulcerations, which are also a very common manifestation of viral infections in the mouth. Studies are needed to understand the real role of the virus in the occurrence of the symptoms that were raised.

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