

# ORAL MANIFESTATIONS IN COVID-19 CASES: AN INTEGRATIVE REVIEW

## MANIFESTAÇÕES ORAIS EM CASOS DE COVID-19: UMA REVISÃO INTEGRATIVA

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### RESUMO

Atualmente, o mundo vive em um período de pandemia causada pelo coronavírus-19. O vírus causou a morte de mais de um milhão de indivíduos. A ciência tem procurado meios de combater e diminuir o seu alto poder de transmissão. Vários trabalhos estão sendo publicados com pacientes diagnosticados com o COVID-19 que apresentaram alterações na cavidade oral. A contaminação se dá por meio da ligação com a enzima conversora de angiotensina-2, presente em células epiteliais da mucosa oral, especialmente da língua, da mucosa jugal e da gengiva, locais os quais foram identificados a maioria das lesões. Os casos são semelhantes às viroses já conhecidas, os quais foram relatados ulcerações, petéquias, máculas e eritemas em maior quantidade. Deve-se considerar as possibilidades etiológicas dessas manifestações, como infecções oportunistas e complicações dos tratamentos aplicados, os quais não seguem um protocolo bem estabelecido. Muitos dos casos trazidos nesse trabalho apresentaram resultados negativos dos exames sorológicos para outras doenças virais e alguns não tiveram tratamentos intensos, o que sugere uma real relação direta entre o coronavírus-19 e as lesões em cavidade oral.

**PALAVRAS-CHAVE:** Infecção por Coronavirus 2019-nCoV; Manifestações orais; COVID-19

### ABSTRACT

Currently, the world lives in a period of pandemic caused by the coronavirus-19. The virus caused the death of more than a million individuals. The Science has been looking for ways to combat and decrease its high transmission power. Several studies are being published with patients diagnosed with COVID-19 who presented alterations in the oral cavity. Contamination occurs by means of binding with the angiotensin-2 converting enzyme, present in epithelial cells of the oral mucosa, especially of the tongue, cheek mucosa and gingiva, places in which most of the lesions have been identified. The cases are similar to viruses already known, in which ulcerations, petechiae, macules and erythema have been reported in greater quantity. The etiological possibilities of these manifestations must be considered, such as opportunistic infections and complications of the treatments applied, which do not follow a well-established protocol. Many of the cases brought up in this study showed negative

results from serological tests for other viral diseases and some did not have intense treatments, which suggests a real direct relation between coronavirus-19 and lesions in the oral cavity.

**KEYWORDS:** Coronavirus 2019-nCoV Infection; Oral Manifestations; COVID-19

### 1. INTRODUCTION

In December 2019, many cases of a new viral infection were recorded at the Chinese city Wuhan: the COVID-19 (Coronavirus Disease 2019). This disease soon demonstrated its high potential of transmission that determined a pandemic in a few months. Moreover, since the beginning of the contamination, a significant number has been reported in the prevalence of Severe Acute Respiratory Syndrome caused directly by the virus, SARS-CoV-2<sup>1</sup>.

Defined as retroviral, the coronavirus-19 carries an extensive RNA strand and is classified as betacoronavirus - a denomination for one of the four coronavirus family groups - that has as aim the cells of the respiratory tract, cardiovascular system and gastrointestinal tract. The disease has similar symptomatology to the other pandemic flu virus. The patients present varying degrees of fever, cough, myalgia, asthenia, headache, diarrhea, vomiting and dyspnea that can progress to respiratory failure, pneumonia and even death. It has also been reported anosmia and dysgeusia as recurrent symptoms, the last one is the first evident pathological effect in the oral cavity<sup>2</sup>.

The symptomatic patients have a bigger contagion degree than the asymptomatic ones. The transmission of the virus occurs in direct way through infected droplets from sneezing, coughing or saliva that penetrate the ocular, nasal and oral cavities, and in indirect way, through suspended aerosols in the air. The reports indicate that the virus demands an incubation period that varies from 6 to 14 days<sup>3</sup>.

Currently, the best prevention method is the social isolation determined by the World Health Organization. There are multiple projects seeking to define the vaccine, which some of them are in the testing phase

and it is the greatest hope for regression of SARS-CoV-2 pandemic effects. There are several drugs being used to provide palliative treatments for the infection though there is not a pattern protocol yet. Despite the controversies in the scientific community regarding the efficacy of those drugs, it has been prescribed lopinavir/ritonavir, ribavirin, favipiravir, interferon alpha and beta, cyclosporine, ivermectin, chloroquine, hydroxychloroquine and azithromycin<sup>4</sup>.

The patients are diagnosed through the nasopharyngeal and the oropharyngeal swab to evaluate the reverse polymerase chain and serological assays for IgG and IgM antibodies. Among the clinical signs, those infected have leukocytopenia with a more evident decrease in lymphocytes, elevated C-reactive protein, thrombocytopenia and an increase in D-dimer<sup>5</sup>.

Some studies have reported oral manifestations in patients with COVID-19. This is possible by the historic infections that present oral symptoms and by the fact that coronavirus-19 contaminates the host cells through the angiotensin converting enzyme-2 (ACE-2), which is the only infection way. Thus, can be considered that the epithelial cells of the oral mucosa are viral receptors due to their significant expression of ACE-2, especially in the tongue, in the jugal mucosa and in the gums<sup>6</sup>. Moreover, the SARS-CoV-2 can reach the oral cavity through the upper and lower airways, through the gingival fluid and through the salivary ducts, which carry the contaminated salivary glands contents. The saliva has a considerable viral load that can even be collected as a sample for diagnosis through laboratory test<sup>7</sup>.

The oral mucosa may be the first contaminated area by coronavirus-19 and, assuming that it may be the first to present symptoms, the dentists can be determinants in disease identifying, increasing the diagnosis ways that would have regressive the transmission effects. However, as it is a recent infection, it is understandable that there is not any study to prove the evidence of symptoms in the oral cavity yet and there are many etiological possibilities for determining the reported oral lesions. The objective of this study is to search evidence in the occurrence of oral manifestations as a COVID-19 symptom. This study hypothesis is that SARS-CoV-2 has oral manifestations as a symptom.

## 2. MATERIALS AND METHODS

A quantitative integrative literature review was developed through a bibliographic research, looking for evidence to confirm the hypothesis that SARS-CoV-2 has oral manifestations as a symptom. For this, considering the DeCS (*Descritores em Ciências da Saúde*) e and the MeSH (Medical Subject Heading), the following descriptors were used: COVID-19, coronavirus infection and oral manifestations with the Boolean operator “AND”. The articles were searched in BVS and Europe PMC data banks and in PubMed database and 1,484 works were found in the search results.

The included works were those published between 2015 and 2020, in English and Portuguese languages of national and international journals with blind peer review. Case reports and literature reviews that addressed the characteristics of coronavirus-19 and oral manifestations in patients diagnosed with the disease and the pathophysiology of the lesions were also included. Articles that exclusively reported olfactory disorders and those dealing with new biosafety standards in dentistry were excluded. From the exploratory reading of the abstracts, 53 articles were selected. And from the integrative reading, 37 of them were selected as the object of study (Table 1).

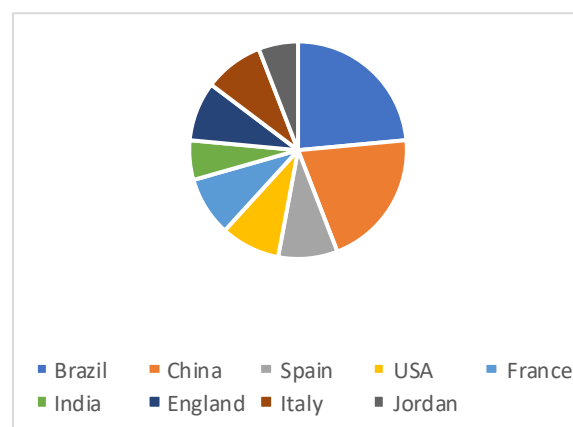
**Table 1.** Articles selected in the research.

Data Banks and Database	Search Results	Selected Articles
BVS	52	9
Europe PMC	1.394	21
PubMed	38	7

## 3. DEVELOPMENT

### Number of cases and characteristics of the selected studies

Most of the reviewed works were produced in Brazil and China. Among them, 10 brought case reports of oral signs and symptoms in patients diagnosed with COVID-19 (Table 2), which 9 are letters to the editor and 1 is a case report article. Among the literature reviews, there is 1 systematic review article that addresses oral manifestations in patients with SARS-CoV-2. Most studies were produced in Brazil, representing 3 case reports.



**Figure 1.** Production place of the reviewed works. Colombia, Iran, Poland and Romania: 1 work each one. USA: United States of America.

Most patients are male (14). Their average age is 50.08 years old, ranging from 9 years to 83 years. In 19 cases, ulcerations were manifested. The anatomical regions most affected were the tongue (12), the lateral edge being the most reported, followed by the lower lip mucosa (9), the hard palate (6), and the upper lip mucosa (4).

About the treatment established for COVID-19, it

was observed a significant amount use of azithromycin (11 cases) and ceftriaxone (5 cases). Most of the patients required hospitalization (11), among which 2 were intubated in the ICU.

### Period of appearance of oral manifestations

Most of the manifestations appeared during the symptomatic period of COVID-19. Among the 23 patients, the period of appearance was reported in 22. Only 2 had oral lesions prior to the symptoms of

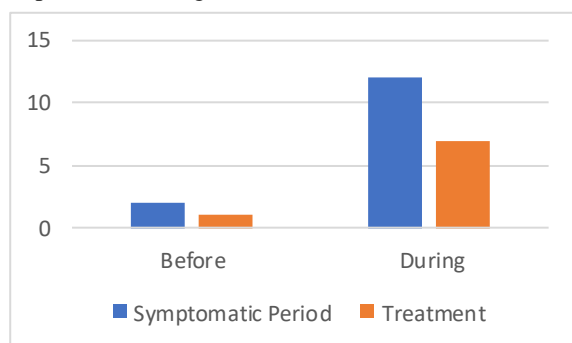
SARS-CoV-2. In 4 other patients, alteration in the oral cavity appeared concomitantly with the initial symptoms of the disease. The majority (11 cases) presented oral lesions after the initial symptoms of COVID-19, while 5 cases were recorded after hospitalization.

**Table 2.** Reported cases of patients with COVID-19 who presented oral manifestations.

Reports	COVID-19 treatment	Sex	Age	Oral Manifestations	Localization
Ansari <i>et al.</i> , 2020	Hospitalization Remdesivir Azithromycin	F	56	Ulcers	Hard palate
	Hospitalization Azithromycin	M	75	Ulcers Dysphagia	Anterior dorsal tongue
Brandão <i>et al.</i> , 2020	Hospitalization Ceftriaxone Azithromycin	M	81	Dysgeusia Ulcers	Lower lip mucosa and upper lip mucosa Anterior dorsal tongue
	Hospitalization Azithromycin Ceftriaxone	F	71	Dysgeusia Ulcers	Lower lip mucosa and upper lip mucosa Anterior dorsal tongue
	Hospitalization	F	83	Ulcers Petechiae	Border tongue Hard palate
	Hospitalization Piperacilin/tazobactam Azithromycin Ceftriaxone	M	72	Ulcers	Lower lip mucosa and upper lip mucosa
	Dipyrrone	F	32	Ulcers	Lateral border tongue Apex tongue
	Not reported	M	35	Odinophagy Ulcer	Tonsillar pillar
	Ipratropium bromide Fenoterol hydrochloride	M	29	Ulcer	Ventral portion of the tongue
	Not reported	M	28	Ageusia Ulcers	Lower lip mucosa and upper lip mucosa Lateral border tongue
Cant; Bhujel; Harrison, 2020	Supplemental O2 in ICU	M	9	Ulcers Edema	Upper lip mucosa
Carreras-Presas <i>et al.</i> , 2020	Lopinavir/Ritonavir Hydroxychloroquine	M	65	Blisters Desquamative gingivitis	Upper lip mucosa; Gum
Chaux-Bodard; Deneuve; Desoutter, 2020	Not reported	F	45	Erythema Ulcer	Dorsal tongue
Corchuelo; Ulloa, 2020	Ibuprofen Vitamin D2 Azithromycin	M	40	Erythemas Plaque Macule Ulcers Xerostomia	Upper lip mucosa Gum Border tongue
Dominguez-Santas <i>et al.</i> , 2020	Not reported	M	19	Ulcer	Jugal mucosa
	Not reported	M	33	Ulcer	Upper mucogingival line
	Not reported	M	37	Ulcer	Lateral border tongue
	Not reported	F	43	Ulcer	Upper lip mucosa
Jimenez-Cauhe <i>et al.</i> , 2020	Hospitalization Lopinavir/Ritonavir Ceftriaxone Corticosteroids Azithromycin	F	58	Macules Petechiae	Palate
	Hospitalization Lopinavir/Ritonavir Corticosteroids Azithromycin	F	63	Macules Petechiae	Palate
	Hospitalization Lopinavir/Ritonavir Azithromycin	F	69	Macules Petechiae	Palate
Santos <i>et al.</i> , 2020a	Supplemental O2 in ICU Hydroxychloroquine Azithromycin Ceftriaxone	M	67	Sialorrhea Nodule Ulcers Whitish area Geographic tongue Fissured tongue Erythema	Upper lip Tongue Tonsillar pillar
Soares <i>et al.</i> , 2020	Not reported	M	42	Erythemas; Ulcers	Hard palate Tongue Lip

### Period of appearance of oral manifestations

Most of the manifestations appeared during the symptomatic period of COVID-19. Among the 23 patients, the period of appearance was reported in 22. Only 2 had oral lesions prior to the symptoms of SARS-CoV-2. In 4 other patients, alteration in the oral cavity appeared concomitantly with the initial symptoms of the disease. The majority (11 cases) presented oral lesions after the initial symptoms of COVID-19, while 5 cases were recorded after hospitalization (Figure 3)



**Figure 3.** Period of appearance of oral manifestations and number of patients.

### Differential diagnosis tests

Among the 23 cases, differential diagnosis was reported for other diseases that cause oral manifestations like those described in studies in 15 patients (Table 3).

**Table 3.** Differential diagnosis.

Serological Tests	Positive	Negative
Herpes Simplex Virus	3 patients	8 patients
Cytomegalovirus	0	7 patients
Epstein-Barr Virus	0	7 patients
Varicella-zoster	0	3 patients
Hepatitis B	0	4 patients
Hepatitis C	0	4 patients
Syphilis	0	4 patients
Celiac Disease	0	4 patients
Immunomediated Disease	0	4 patients
Rheumatoid Arthritis	0	4 patients
Recurrent Aphthous Stomatitis	1 patient	3 patients
Beçhet's Syndrome	0	4 patients

## 4. DISCUSSION

Some recent studies have reported cases of oral manifestations in patients diagnosed with COVID-19, although there is still no scientific evidence to prove whether there is a relationship between the virus and the lesions. The results of this study showed a majority of occurrence of oral manifestations during the symptomatic period. Some patients even developed lesions before the symptomatic condition and before the start of treatment for the disease, which suggests that the coronavirus could be the etiological factor of alterations in the oral cavity.

However, a detailed differential diagnosis is necessary to rule out the possibility of other infections. It is also important to consider the possibility of opportunistic infections and the various possible

etiological factors to which patients are exposed, such as hospital complications, emotional stress due to the pandemic context, immunosuppression and adverse drug reactions to treat SARS-CoV-2<sup>8</sup>.

Currently, there is evidence that coronavirus-19 leads to gustatory dysfunctions that may be associated with anosmia. In this study, 3 patients presented dysgeusia and ageusia. These alterations are difficult to identify because they are usually diagnosed using a questionnaire, configuring a subjective character. It is assumed that dysgeusia is due to the high expression of ECA-2 on the dorsal tongue and in the salivary glands<sup>9</sup>. In the first, the virus would affect the functionality of the lingual papillae and in the second, there would be a decrease in the salivary flow which, consequently, would decrease the perception of taste<sup>10</sup>.

Taste disorders are common in flu viruses. A systematic review evaluated the presence of oral symptoms in 10,228 cases of patients diagnosed with COVID-19. The results demonstrate a high prevalence of gustatory dysfunction, especially in mild and moderate conditions, corresponding to 45% of the cases, of which dysgeusia (38%), hypogeusia (35%) and ageusia (24%) were identified. Moreover, there was a predilection for the female sex, supposedly due to the exacerbated innate immune response and the influence of female hormonal modulation<sup>11</sup>.

Fantozzi *et al.* (2020)<sup>12</sup> investigated 111 cases of COVID-19 in an Italian hospital. The study determined a higher prevalence of dysgeusia, represented by 60% of the reports. Then, xerostomia was recorded in almost 50% of the cases and consequently, there were reports of dysphagia. A fifth of these patients reported dry mouth as one of the first symptoms. This is possible due to the high expression of ACE-2 in the salivary glands. Olfactory dysfunction had less expression amid symptoms.

Some studies point to the associated occurrence of chemosensory changes. Thus, gustatory dysfunction would be a symptom secondary to olfactory changes. However, there are several reported cases of patients presenting dysgeusia in isolation and even more prevalent than anosmia or hyposmia. It must be also considered the possibility of an adverse response to the treatment applied<sup>13</sup>.

The reviewed articles presented cases of oral lesions. Among the most recurring ones, are ulcerations of varying sizes and color. These manifestations vary between localized and diffuse, the majority being found in the tongue, labial mucosa and palate. Santos *et al.* (2020b)<sup>11</sup> affirms that there is no pattern between oral lesions in patients with SARS-CoV-2. Moreover, it is known that it is not common for symptoms in the oral cavity of viral diseases to vary. However, this study identified a standardization in the injury's type. Of the 23 patients, only 3 did not identify ulcers and there was a prevalence of macules, petechiae and erythema.

The first publication was made by Carreras-Presas *et al.* (2020)<sup>14</sup> involving 3 patients. The first two



patients were only under suspicion of COVID-19, which makes these reports very subjective due to the chance of representing other diseases, such as herpes simplex. Therefore, they were not considered in this work. The third case regards to a 65 years old obese and hypertensive patient who was diagnosed with SARS-CoV-2 and was treated with lopinavir/ritonavir and hydroxychloroquine. Unlike previous reports, the lesions appeared 29 days after diagnosis with blisters on her lower labial mucosa and desquamative gingivitis. She reported tongue pain since the onset of symptoms, but no intraoral examination was performed. Histopathology showed nonspecific morphology with characteristics suggestive of urticarial dermatitis, which may be an adverse response to the drugs used to treat the COVID-19, and a viral rash.

Some of the reviewed papers presented cases of patients with previous diseases that can potentiate the severity of the coronavirus. Among them, a 67-year-old man, hypertensive, with heart disease, with kidney disease and kidney transplantation, who, after presenting a severe symptomatic period, was diagnosed with COVID-19, intubated in the ICU and treated with hydroxychloroquine, azithromycin and sodium ceftriaxone. He was treated with immunosuppressant and sodium enoxaparin. During hospitalization, leukopenia and pneumonia were suspected, and he was treated using antibiotics. After 24 days of hospitalization, dentists observed excessive viscosity in the saliva, a possible fibroma of 1 cm on the lower lip and, on the dorsal tongue, yellowish ulcers and a white plaque suggestive of candidiasis that had already been treated with intravenous fluconazole and oral nystatin, but without success. Antifungals were maintained plus oral rinse of chlorhexidine and hydrogen peroxide at 1%. There was regression in 2 weeks. In a new intraoral examination, the patient presented severe geographic tongue, fissured tongue and erythema in the region of the palatine tonsil. Oral alterations can be associated with the patient's health condition and the use of various medications. They may also have been indirectly induced by the virus due to immunosuppression<sup>15</sup>.

Lymphocytopenia is considered one of the markers of SARS-CoV-2. This condition could facilitate the installation of opportunistic infections, such as candidiasis, or reactivate viruses in a latent state, such as herpes simplex. Furthermore, hospital complications can induce the development of fungal lesions, especially in cases where the patient is intubated. There are great possibilities that these 2 associated points are the cause of the appearance of white plaques. The literature points out that many cases of candidiasis were identified during hospitalization, especially in the ICU<sup>16</sup>.

Ansari *et al.* (2020)<sup>17</sup> describes 2 cases of COVID-19 that presented lesions in the oral mucosa and had health complications. The first patient, 56 years old, is diabetic and was hospitalized with fever and apnea. Drug treatment was done with remdesivir and

azithromycin. In the 5 days after the onset of symptoms, ulcers with irregular edges and of varying sizes, erythematous and painful were reported in almost the entire hard palate. The second patient is 75 years old and hypertensive. He was admitted to the hospital with hypoxia and was treated with azithromycin. After 1 week of hospitalization, he presented dysphagia and painful ulcers with irregular reddish margins in the anterior area of the tongue. Biopsy and serological tests were performed in both cases. The histopathology of the 2 patients showed similar results: infiltration of mononuclear cells and neutrophils with secondary bacterial infection. Tests for herpes simplex were negative. The lesions healed in 1 week using dexamethasone, diphenhydramine, tetracycline and topical lidocaine. The authors do not rule out the possibility of emotional stress as the etiology of ulcers.

In Soares *et al.* (2020)<sup>18</sup>, a 42 years old patient with COVID-19, diabetic and hypertensive, reported erythematous lesions and ulcers on the hard palate, tongue and lip. As symptoms of the infection, fever, dyspnea, cough and vesicles and petechiae were recorded on the skin. The lesions were treated with dexamethasone and dipyrone and regressed in 3 weeks. Histopathology showed excessive vacuolization, exocytosis and vascular thrombosis in the epithelium, suggesting that it may be related to the coronavirus.

There have been cases of patients who had oral lesions before developing the symptoms of COVID-19. A 45-year-old patient presented with symptomatic inflammation in the lingual papilla and erythema that evolved the irregular and painless ulcer on dorsal tongue. In 10 days, the lesion regressed without leaving a scar. Soon after, there was a mild asthenia and painful erythematous lesion appeared in the big toe that also became asymptomatic. The patient underwent a nasopharyngeal swab test and tested positive for coronavirus-19. Thus, it could be suggested that coronavirus-19 induces oral ulcerations before the establishment of classic symptoms, which would be one of the reasons for there being few reports of such manifestations due to the possibility of patients omission of symptoms or due to professional negligence during anamnesis<sup>19</sup>.

Another case was reported in Cant, Bhujel, Harrison (2020)<sup>20</sup>. A 9-year-old epileptic patient who had fever, malaise, gastrointestinal disorders and two episodes of yellowish ulcerations and lower lip edema for 2 weeks. The lesions were treated with hydrocortisone and regressed in 3 days. However, he had to be admitted to the ICU because he was diagnosed with pediatric multisystemic inflammatory syndrome associated with SARS-CoV-2. Other 8 children were admitted to the same hospital reporting yellowish oral ulcers that had previously appeared to the symptoms of COVID-19, reinforcing the theory that oral lesions may appear as a primary symptom.

Dominguez-Santas *et al.* (2020)<sup>21</sup> reports 4 cases of minor canker sores during COVID-19 infection in

young patients between 19 and 43 years, in which a thorough differential diagnosis had been made. Tests for herpes simplex, syphilis, hepatitis B and C, Epstein-barr, cytomegalovirus, celiac disease, autoimmune diseases, rheumatoid arthritis and Behçet's syndrome were negative. There was only 1 patient with a history of recurrent aphthous stomatitis. The authors quantified from 1 to 7 yellowish lesions smaller than 1 cm, and with an erythematous halo located close to the retromolar triangle on the jugal mucosa, on the upper mucogingival line, on the lateral border tongue and on the lower lip mucosa close to the labial commissure. Ulcerations appeared between the first day of symptomatic manifestation of SARS-CoV-2 and 4 days after the onset of symptoms. Unlike other reports, this article reports alterations in the oral cavity during the symptomatic period of the disease. Despite narrowing the possibility of a direct relationship with coronavirus-19, it is important to consider possible responses to emotional stress or adverse reaction.

COVID-19 causes a considerable increase in cytokines, including the tumor necrosis factor alpha (TNF- $\alpha$ ) and it is possible that this increase is enough to induce ulcerations in the oral cavity through an immune response. In recurrent aphthous stomatitis, there is an increase in the concentration of granulocytes and lymphocytes that generate high expression of TNF- $\alpha$ . This increases the likelihood of direct pathogenic action of the coronavirus on the oral epithelium<sup>22-23</sup>.

It is possible that, during the inflammatory process, there may be increase in melanogenesis. The inflammation mediators are responsible for triggering the proliferation of melanocytes and the inflammation products potentiate. These agents lead to melanin pigmentation associated with inflammatory responses in infections<sup>22</sup>. This could be the justification for one of the cases studied, in which a patient diagnosed with COVID-19 presented melanic pigmentation in the inserted gums. It is relevant to consider that he also presented erythema and plaques in the lower lip mucosa and ulcers in gingival tissue<sup>24</sup>.

Considering the data brought in Jimenez-Cauhe *et al.* (2020)<sup>25</sup> to the fact that 90% of erythema multiforme (EM) are caused by infection by the herpes simplex virus and mycoplasma pseudominae, it could be assumed that the coronavirus has a similar action. In the report, three female patients, 58, 63 and 69 years old, had SARS-CoV-2 and had cutaneous and mucosal lesions suggestive of EM. These patients received treatment with lopinavir/ritonavir, hydroxychloroquine, azithromycin, corticosteroids and ceftriaxone. Serological tests were requested for other infections that tested negative for Epstein-barr, herpes simplex, varicella-zoster and cytomegalovirus. In the oral cavity, petechiae and macules on the palate were identified. Within a week after discharge, they all returned with enantomas and pseudovesicles on the skin and there was lymphocytopenia, increased C-reactive protein and D-dimer, demonstrating the continuous action of COVID-19.

In another study, from the 8 patients with COVID-19, 3 had tested positive for herpes simplex. However, none of the cases had regression using acyclovir. It was necessary to treat with phototherapy, which brought positive results. In the same study, it was observed that older patients had more serious oral lesions and had fewer effective responses to treatments than younger patients, who had faster involution. The previous health condition of patients can also contribute to a lower occurrence of these manifestations, since a large part of the elderly had diabetes. Although serology was performed in some of the cases, the safest would be a histopathological test<sup>26</sup>.

Due to the contamination of the epithelium of the major and minor salivary glands, saliva becomes a source of infection by COVID-19. In addition to the epithelium, the virus infects acinar cells and, consequently, provides an increase in amylase in the peripheral bloodstream, allowing this enzyme to be used as one of the disease markers. During the involvement of the glands, the inflammation generates a constant high concentration of cytokines and this acute condition of sialadenitis can evolve to a chronic state. These characteristics can be decisive in the installation of associated oral alterations, such as xerostomia, which facilitates the establishment of traumatic injuries and generates uncontrolled oral homeostasis, justifying one of the cases mentioned that reported excessively viscous saliva<sup>27</sup>.

Badran *et al.* (2020)<sup>28</sup> suggests the possibility that periodontal pockets (PP) may be a reservoir for coronavirus since other viruses benefit from the condition, such as herpes simplex, Epstein-barr and cytomegalovirus. Moreover, periodontal ligament fibroblasts express ECA-2. According to the authors, contamination would occur in the epithelial wall of PP through an inflammatory infiltrate with infected leukocytes. Some studies assume that COVID-19 also has the capacity to bind to CD147, a differentiation group that is increased in periodontal inflammatory processes.

During the pandemic, dentists have noticed an increased incidence of necrotizing ulcerative periodontal disease. Some metagenomic analysis of patients with SARS-CoV-2 revealed significant increases in *Prevotella intermedia*, *Fusobacterium* spp. and *Treponema* spp. These species are present in necrotizing ulcerative periodontitis (PUN), a disease aggressive to the periodontium prevalent in HIV-positive patients. With these data, it is relevant to consider that coronavirus-19 predisposes to PUN, which could still aggravate the symptomatic period such as fever<sup>29</sup>.

Coronavirus contamination is consolidated through the integration of the virus with epithelial cells. The furin enzyme, found in the host cells, activates the binding domain to the coronavirus Spike (S) protein receptor and this way it allows the virus to bind with the angiotensin-2 converting enzyme, present in the plasma membrane, integrating<sup>30</sup>. The furin is highly

expressed in most malignancy processes, including oral cancer, as well as ECA-2, which would possibly facilitate the consolidation of COVID-19 and increase viral load. Besides the pathophysiology of cancer, radiotherapy can also induce an increase in furin<sup>31</sup>.

It must be considered that, as it is a recent infection, there are limitations in the information about its actions in the human body and in the treatment methods, which are being applied intensely in some cases, which may reflect on oral heatudies relating caseslth. Moreover, health teams on the front lines against the disease are focused on saving lives due to the higher mortality rate comparing to common flu viruses. Among the drugs used for therapy for COVID-19, the literature demonstrates oral effects, such as xerostomia and thrush, in chloroquine, lopinavir/ritonavir and interferon alpha and beta<sup>32</sup>.

Other viral diseases mimic the mild symptoms of COVID-19 and cause injuries to the oral mucosa. However, some of the reported cases expose the performance of serological tests that tested negative for different infections<sup>33</sup>. Oral integrity can also be compromised through supportive therapy, resulting from hospitalization, intubation, tracheostomy, oxygen gas supplementation and oral breathing that can unbalance the oral microbiota and predispose to hyposalivation<sup>34</sup>.

Although there are similarities in some cases with other pre-existing infections, the coronavirus can directly induce the formation of these alterations due to the presence of ECA-2 in oral epithelium as well as promoting dysgeusia. Many diagnosed patients are having neglected oral health, which may be masking the actual incidence of injuries<sup>35</sup>.

Despite published studies reporting lesions and oral alterations, each case should be interpreted and evaluated very carefully to exclude other possible etiological factors and so avoid anxiety in patients and provide better preparation for dentists resulting in decreasing effects on the rate transmission of the virus for identifying neglected symptoms, once the hypothesis is confirmed<sup>36</sup>. Concrete research is needed on the true virology of SARS-CoV-2 in the oral cavity.

## 5. CONCLUSION

In this work, case reports of oral integrity alteration in patients with COVID-19 were analyzed. The new coronavirus is known to resemble other viral infections. Therefore, the coronavirus can cause oral manifestations, in addition to olfactory dysfunctions, through ACE-2, being the means of contamination that cause cellular modifications.

A pattern of lesions was found among the 23 patients with reported cases: ulcerations on the tongue, palate and lip mucosa. A prevalence of macules, petechiae and erythema was also found. In most patients, other diseases that could cause such injuries were ruled out.

Therapy applied to coronavirus-19 and the presence of previous patient comorbidities may

influence the appearance of lesions. Patients who received more intense treatment had greater oral complications. It is necessary to carry out further studies on the topic to identify the relationship of the virus with the treatment and the health status of infected patients.

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