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REVIEW

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Covid-19 and oral diseases: Crosstalk, synergy or association?

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Summary

The coronavirus disease 2019 (Covid-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that clinically affects multiple organs of the human body. Cells in the oral cavity express viral entry receptor angiotensin-converting enzyme 2 that allows viral replication and may cause tissue inflammation and destruction. Recent studies have reported that Covid-19 patients present oral manifestations with multiple clinical aspects. In this review, we aim to summarise main signs and symptoms of Covid-19 in the oral cavity, its possible association with oral diseases, and the plausible underlying mechanisms of hyper-inflammation reflecting crosstalk between Covid-19 and oral diseases. Ulcers, blisters, necrotising gingivitis, opportunistic coinfections, salivary gland alterations, white and erythematous plaques and gustatory dysfunction were the most reported clinical oral manifestations in patients with Covid-19. In general, the lesions appear concomitant with the loss of smell and taste. Multiple reports show evidences of necrotic/ulcerative gingiva, oral blisters and hypergrowth of opportunistic oral pathogens. SARS-CoV-2 exhibits tropism for endothelial cells and Covid-19-mediated endotheliitis can not only promote inflammation in oral tissues but can also facilitate virus spread. In addition, elevated levels of proinflammatory mediators in patients with Covid-19 and oral infectious disease can impair tissue homeostasis and cause delayed disease resolution. This suggests potential crosstalk of immune-mediated pathways underlying pathogenesis. Interestingly, few reports suggest recurrent herpetic lesions and higher bacterial growth in Covid-19 subjects, indicating SARS-CoV-2 and oral virus/bacteria interaction. Larger cohort studies comparing SARS-CoV-2 negative and positive subjects will reveal oral manifestation of the virus on oral health and its role in exacerbating oral infection.

KEYWORDS

Covid-19, cytokines, inflammation, oral diseases, SARS-CoV-2

Abbreviations: ACE2, angiotensin-converting enzyme 2; Covid-19, coronavirus disease 2019; CoVs, coronaviruses; Gal, galectin; HHV, human herpesvirus; IFN, interferon; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PD, periodontal diseases; RANK, receptor activator of nuclear factor kappa B; RANKL, receptor activator of nuclear factor kappa B ligand; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; Th-17, T-helper cell 17; TLR, toll-like receptor; TMPRSS2, transmembrane protease serine 2; TNF, tumour necrosis factor.

1 | INTRODUCTION

Viruses are molecular parasites that depend on host cells for reproduction.[1] Viral infection occurs when a virus releases its nucleic acid into a cell, followed by transcription and translation of proteins essential for viral replication, for which it relies on host protein machinery. Evidently, viruses require specific proteins to enter and replicate inside cells. Incessant evolution of viruses allows them to adapt with their host and also provides an opportunity to broaden their host(s) spectrum.

Coronaviruses (CoVs) constitute a family of single-stranded RNA viruses, with the potential to infect different animal species.[2] Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recent zoonotic CoV, results in coronavirus disease 19 (Covid-19). SARS-CoV-2 transmission primarily occurs via small airborne droplets, larger respiratory droplets and direct contact with infected individuals or contaminated surfaces.[3] SARS-CoV-2 appears to have originated from bats, as SARS-CoV-2 shares 96% of its genome with a SARS-like bat COV.[4,5] However, bat COVs cannot infect humans, which introduces the pangolin as the potential intermediate host where the virus may have acquired mutations to infect humans.

SARS-CoV-2 is a positive-sense RNA virus with icosahedral morphology and spike-shaped angiotensin-converting enzyme 2 (ACE2) binding proteins.[6] The spike proteins are responsible for high-affinity binding of SARS-CoV-2 to human ACE2 receptors, expressed on the lungs but primarily on salivary glands in the oral cavity.[2,7] In individuals with angiotensin-2-dominated expression (e.g., chronically ill or elderly), the binding of SARS-CoV-2 to intact ACE2 receptors possibly inactivates ACE2 proteins, therefore attenuating ACE2 receptor expression.[8] Ultimately, the inability to regulate the renin–angiotensin system leads to vascular inflammation.[9] Patients diagnosed with Covid-19 often experience mild-to-severe fever, cough and fatigue.[6] In severe cases, SARS-CoV-2 can also lead to obstruction of lung airways, resulting in pneumonia, cytokine storm syndrome and/or acute respiratory distress syndrome. Recently, it has been found that Covid-19 can result in multisystem inflammatory syndrome in children (MIS-C).[10] The diagnosis of MIS-C has also been found to coincide with other inflammatory markers such as elevated levels of troponin, interleukin-6 (IL-6), and procalcitonin.

With primary expression of ACE2 receptors occurring in the oral cavity, Covid-19 manifestations may be linked to oral cavity ACE2 expression as well and thus warrant further investigation.[7,10,11] The objective of this article is to conduct a review of a wide variety of oral manifestations observed in patients with Covid-19. We present evidences strongly suggesting adverse clinical presentations in Covid-19 patients and its impact on common oral diseases and their manifestations. Treatments prescribed to Covid-19 were largely aimed at bacterial or viral aetiological agents and improving oral hygiene. The favourable outcomes indicate presence of opportunistic pathogens or coinfection of SARS-CoV-2 and other infectious agents in oral cavity. Finally, we provide several plausible molecular and cellular mechanisms behind these occurrences. This article highlights clinical outcomes of an evolving microbiome interaction in Covid-19 patients and its impact on oral tissue homeostasis.

2 | ORAL DISEASE MANIFESTATION IN SARS-CoV-2 PATIENTS

Covid-19 is a viral infection caused by SARS-CoV-2 that has manifestations in multiple organs of the human body.[12–14] Patients infected with SARS-CoV-2 present a myriad of clinical signs and symptoms with variable severity.[15] In the oral cavity, the main manifestations are related to tongue depapillation,[16,17] *Candida*-associated lesions,[17] xerostomia,[18] aphthous like-lesions,[13,17] recurrent herpesvirus infection,[12,13,19] ulcers,[14,19–22] necrotising gingivitis,[23] erythema multiforme-like lesions[24] and salivary gland infections.[25] It has been reported that these oral manifestations, in general, appear concomitant with the loss of smell and/or taste a few days later (up to 14 days), and progress more rapidly and severely among older patients.[13] Interestingly, resolution of the oral lesions occurs in parallel with the resolution of Covid-19[13] indicating an association between virus infection, oral clinical manifestation and their recession.

The oral cavity is the entry portal for several pathogens, including SARS-CoV-2, which can be detected in the saliva of patients with laboratory-confirmed Covid-19. High viral load in saliva is detected at the beginning of infection and the titres reduce with disease resolution, suggesting that salivary shedding of virus correlates with disease manifestation.[11] SARS-CoV-2 binds to the ACE2 receptor that is expressed in the oral cavity, with a strong interaction between the receptor and viral spike protein (S).[7,10,11] Figure 1 illustrates the presence of ACE2 and virus in different oral tissues. The interaction of transmembrane protein ACE2 with the S protein allows the virus to fuse with the host cell, use cellular machinery to replicate and lyse the cell to trigger oral signs and symptoms.[7,16] Apart from this mechanism, that could explain the cause of some oral manifestations, oral lesions may also result from opportunistic infections facilitated by systemic damage, alterations in the immune system and adverse effects of treatment. In this section, we will present evidence that suggests an association of Covid-19 and oral disease as manifested by exacerbation of oral disease symptoms.

2.1 | Periodontal disease and Covid-19

Periodontal diseases (PDs) are a variety of inflammatory conditions of multifactorial aetiology that affect the supportive tissues around the tooth and are commonly associated with long-term biofilm accumulation. In Covid-19 infection, it has been reported that patients have a wide variety of oral manifestations, including acute periodontal lesions. The prevalence of patients who present periodontal manifestations associated with Covid-19 remains uncertain because of limited case reports with small cohort size.[23] For instance, Patel and Woolley[23] have described a case of necrotising gingivitis

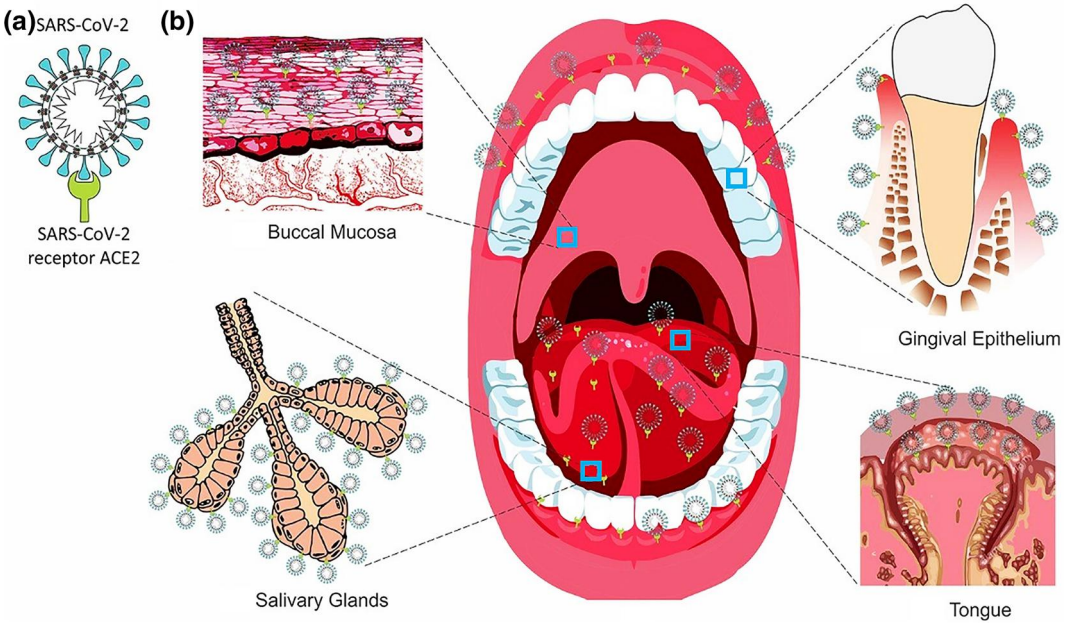

FIGURE 1 (a) The interaction between angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2 spike protein (S) will allow viral entry, replication and activation of innate antiviral response including proinflammatory cytokine production and infiltration of immune cells. This may result in manifestation of signs and symptoms in the oral cavity of Covid-19 patients. (b) Different sites of the oral cavity where virus and its receptors are reportedly detected including periodontal tissues, buccal mucosa, tongue and salivary glands. Covid-19, coronavirus disease 2019; SARS-COV-2, severe acute respiratory syndrome-coronavirus-2

with severe halitosis, generalised oedema and erythema, necrotic interdental papillae and spontaneous gingival bleeding. Table 1 lists the studies with reported clinical periodontal manifestations and prescribed treatment.

ACE2 and transmembrane protease serine 2 (TMPRSS2) are expressed in the sulcular epithelium and periodontal pocket epithelium.[16] Recently, it was shown that TMPRSS2 inhibitor blocked SARS-CoV-2 invasion via ACE2, presuming that there is a possibility of SARS-CoV-2 infection via periodontal epithelium and that periodontal epithelium may exhibit tropism for the virus.[27,28] Although SARS-CoV-2 has many pathways to invade the host cells, the receptor-protease-mediated pathway is valuable for increasing viral infectivity.[9,16] SARS-CoV-2 interaction with ACE2 might alter the function of oral epithelial cells and it is one of the mechanisms that could explain the appearance of ulcerated gingival lesions.[13] However, whether the periodontal lesions are a direct result of viral infection or a related manifestation caused by severe systemic impact is not understood.

Given that PD results from an uncontrolled immune response elicited against oral microbiome and the patients with severe Covid-19 exhibit immune derangement and higher rates of *Prevotella intermedia*, *Streptococci*, *Fusobacterium* and other infectious agents related to the development of acute periodontal conditions, it is suspected that the aetiology of these lesions may be associated with bacterial coinfection.[29,30] It has been hypothesised that the periodontal pocket could act as a favourable niche or reservoir for both active and latent SARS-CoV-2 forms. This would allow the virus to replicate in the periodontium, reach the oral cavity and saliva or progress through the bloodstream of the periodontal capillary network to reach distant organs, implying that periodontal condition contributes to the recurrence of clinical conditions of Covid-19[29,31]. Recently, a postmortem study confirmed the presence of SARS-CoV-2 RNA in the periodontal tissues of Covid-19-positive patients several days (up to 24 days) after the onset of first symptoms, suggesting that the oral cavity could be a source of the virus and emphasising the possibility of viral presence in gingival crevicular fluid.[32]

Importantly, there is evidence in the literature of a common inflammatory response pathway between PD and Covid-19. In PD, immune cell-mediated pathogenesis and greater levels of cytokines in inflamed gingival tissue induce altered serum levels of cytokines systemically. In addition, the signs and symptoms of Covid-19 have been associated with pathophysiological mechanisms related to "cytokine storm" derived from dysregulated immune reaction with overproduction of proinflammatory cytokines and chemokines such as IL-1β, IL-6, tumour necrosis factor-α (TNF-α), macrophage inflammatory protein 1a, IL-10 and interferon-γ (IFN-γ).[9,29,33–35] In this sense, it is reasonable to consider that PD influences Covid-19-related outcomes as a predisposing factor for more severe forms of the disease mediated by widespread inflammation.[27,29,35] It has been reported that affected nonsurvivor patients with severe Covid-19 had higher levels of circulating IL-6 compared to patients affected by the mild form of the disease.[9] Moreover, a recent study suggested that proinflammatory cytokines such as IL-1β and TNF-α from the inflamed gingiva could infiltrate saliva and aspirate to the lungs, contributing to acute inflammation in this organ.[29,34]

TABLE 1 Characteristics and treatment of periodontal lesions associated with Covid-19

Covid-19 oral manifestations	Author	Patients' number	Age (years)	Gender	Oral lesions onset	Local	Signals and symptoms	Coinfection	Treatment/outcome
Necrotising gingivitis	Patel and Woolley[23]	1	35	F	3 days	Gingivae (maxillary and mandibular labial sextants)	Erythematous and oedematous gingivae, necrotic interdental papillae, bleeding in gingival sulcus and halitosis	Bacterial	Metronidazole 400 mg three times per day for 5 days and chlorhexidine 0.12% mouthwash two times per day for 10 days/The signs and symptoms completely regressed after 5 days of treatment
Dark pigmentation	Corchuelo and Ulloa[26]	1	40	F	8 days	Palate and gingiva	Dark brown pigmentation	N/A	Ibuprofen/N/A

Abbreviations: Covid-19, coronavirus disease 2019; F, female; M, male; N/A, not assessed.

Following this line of interaction between PD and Covid-19, it is clear that good oral hygiene habits could reduce the incidence of acute viral respiratory infections in hospitalised patients, decrease the possibility of more severe forms of Covid-19 symptoms and prevent the recurrence of viral disease.[29,34]

2.2 | Endodontal disease and Covid-19

Inflammation of the dental pulp, or pulpitis, is a very painful disease and is the most predominant inflammatory oral infection in dentistry.[36] Multiple microbial infections in the root canal system caused by disruption of enamel integrity or periapical contamination may lead to inflammation of the pulp and periradicular tissues.[37] Severe odontogenic pain and necrosis of the tissue are the main signs and symptoms of the disease. In general, immediate procedures to access the pulp chamber and debride the root canal system are necessary to mitigate pain and control the inflammation response.[38] The role of Covid-19 in exacerbating endodontic infection is a matter of debate. Recently, Guo et al.[39] described an increase of more than 20% in dental pulp and periapical infections during the Covid-19 pandemic. Yu et al.[40] suggested the potential role of Covid-19 infection on the recovery of endodontic emergency patients (mean age: 42.24 ± 18.32 years, 52.08 % males while 47.92% were females). Four patients admitted in this study had previous Covid-19 history or possible Covid-19 cases that were identified by the designed questionnaire. Irreversible pulpits was the most common pathology observed in this study and the therapy recommended involved reduction in the time of dentist visit to minimise possible exposure of professionals to the virus from asymptomatic patients.[40] Although elective dental treatments were suspended during the Covid-19 pandemic, pulp and periradicular diseases are the most common dental emergency and immediate face-to-face treatment is deemed necessary. A global transcriptomic analysis reported that the receptors for SARS-CoV-2, ACE2 and TMPRSS2 are detected in healthy and inflamed human dental pulp without significant differences between healthy control and diseased biopsies.[28,41] In this regard, it has been inferred that healthy and inflamed pulp tissues have a similar tendency to be infected by SARS-CoV-2.[42,43] However, further studies are required to establish a direct correlation between exacerbation of pulpal disease among individuals positive or suspected positive for SARS-CoV-2 and pulpitis/periapical periodontitis.

2.3 | Oral lesions

Covid-19 patients present with a broad variety of signs and symptoms, including a variety of oral lesions.[12–14,16,17,19–21,26,44–46] In Covid-19 patients, oral lesions may resemble dermatologic lesions and the prevalence of oral and dermatologic lesions are similar (about 2%–20%).[47,48] It has been stated that Covid-19 has a higher mortality rate among men compared to women; however, there is no

TABLE 2 Characteristics and treatment of oral lesions associated with Covid-19

COVID-19 oral manifestations	Author	Patients' number	Age (years)	Gender	Oral lesions onset	Local	Signs and symptoms	Coinfection	Treatment/outcome
Commissural fissures/ angular cheilitis	Rodríguez et al.[17]	3	43/78/53	F/F/M	14/Unknown/ 7 days	Labial commissure	Fissure and bleeding	N/A	Neomycin ointment, nystatin, and triamcinolone acetonide 0.05% three times per day and hygiene of the area using gauze with chlorhexidine for 10 days/ The lesions completely regressed after treatment
Dry mouth/ xerostomia	Rodríguez et al.[17]	2	43/78	F/F	N/A and early stage of the disease	Oral cavity	Dry mouth sensation	N/A	Solutions and gels to improve dry mouth sensation/ Xerostomia and dry mouth sensation were improved after the treatment
	Biadsee et al.[45]	72	18–73	F/M	N/A	Oral cavity	Dry mouth sensation	N/A	N/A/N/A
Burning mouth sensation	Rodríguez et al.[17]	2	43/53	F/M	14/7 days	Oral cavity	Burning sensation	N/A	Solution with triamcinolone acetonide 0.05%, three times per day for 10 days and N/A/Burning sensation disappeared after the treatment
	Tomo et al.[49]	1	37	F	N/A	Borders of the tongue and soft palate	Burning sensation in the tongue during 3 days	N/A	Chlorhexidine 0.12% mouthwashes three times per day/Burning sensation disappeared after the treatment
	Glavina et al.[12]	1	40	F	7 days	Hard palate	Pain and burning sensation	Herpes simplex virus	Systemic acyclovir 200 mg, five times per day for 5 days and local antiseptic, nystatin, panthenol, anaesthetic for 14 days/ Burning sensation disappeared after the treatment
Aphthous-like lesions	Rodríguez et al.[17]	1	43	F	14 days	N/A	Aphthous-like ulcers	N/A	Solution with triamcinolone acetonide 0.05%, three times per day for 10 days/ The lesions completely regressed after treatment

(Continues)

TABLE 2 (Continued)

COVID-19 oral manifestations	Author	Patients' number	Age (years)	Gender	Oral lesions onset	Local	Signs and symptoms	Coinfection	Treatment/outcome
	Brandão et al.[13]	7	28–81	F/M	2–10 days	Upper and lower lips mucosa, tongue (anterior dorsal, ventral and borders) and tonsillar pillar	Circular lesion (0.3–1.5 cm) with purulent membrane and erythematous halo	Herpes simplex virus	Intravenous acyclovir 250 mg/m^2 three times per day for 10 days, photobiomodulation therapy 10 days/Relief of the symptom after 2 days and complete resolution after 11 days
Pseudomembranous	Rodríguez et al.[17]	2	43/78	F/F	14 days/N/A	Tongue/hard and soft palate	Atrophy of the surface of the tongue and fungal patches	Candidiasis	Solution with triamcinolone acetonide 0.05%, three times per day for 10 days. Nystatin solution four times per day/The lesions completely regressed after treatment
Oral ulcers	Chaux-Bodard et al.[14]	1	45	F	Early stage	Dorsum of the tongue	Irregular ulcer	N/A	N/A/The lesion completely regressed after 10 days
	Carreras-Presas et al.[19]	2	56/58	M/M	N/A	Hard palate	Ulcers with erythematous halo/small ulcers with unilateral affection	Herpes simplex virus/N/A	Valaciclovir 500 mg 8/8 h for 10 days and topical antiseptics (chlorhexidine and hyaluronic acid)/Antiseptic mouthwash during 7 days/The lesions regressed 7 days after the treatment
	Soares et al.[21]	1	42	M	N/A	Hard palate	Ulcer with squemic aspect	N/A	Dexamethasone and dipyrone for 7 days/The lesion completely regressed after 21 days
	Ansari et al.[20]	2	75/56	M/F	7/15 days	Tongue/hard palate	Haemorrhagic and nonhaemorrhagic ulcers with irregular margins/Ulcers with irregular margins	N/A	Solution with diphenhydramine, dexamethasone, tetracycline, and lidocaine/the lesions regressed after 7 days

TABLE 2 (Continued)

COVID-19 oral manifestations	Author	Patients' number	Age (years)	Gender	Oral lesions onset	Local	Signs and symptoms	Coinfection	Treatment/outcome
	dos Santos et al.[50]	1	67	M	10 days	Dorsum of the tongue	Ulcers resembling herpetic recurrent lesions associated with candidiasis	*Candida* and herpes simplex virus	Intravenous fluconazole (200 mg/100 ml) for 10 days and oral nystatin (100,000 IU/ml) 8/8 h, for 30 days, chlorhexidine digluconate 0.12% mouthwash, and 1% hydrogen peroxide/the lesions regressed after the treatment and patient reported being asymptomatic
	Brandão et al.[13]	1	71	F	4 days	Dorsum of the tongue and upper and lower lips	Haemorrhagic ulcer	Herpes simplex virus	Intravenous acyclovir 250 mg/m^2 3x/day for 7 days and photobiomodulation therapy for 10 days/The lesions regressed 10 days after the treatment
	Riad et al.[22]	8	16–70	F/M	2–5 days	Dorsum or border of the tongue (92.3%) and ventral surface of the tongue (15.4%)	Ulcers resembling herpetic recurrent lesions (1–5 mm)	N/A	Paracetamol and chlorhexidine 0.12% mouthwash/N/A
Oral blister	Carreras-Presas et al.[19]	1	65	F	14 days	Lip mucosa	Blister compatible with an erythema multiforme	N/A	Hyaluronic acid and chlorhexidine 0.12% mouthwash and prednisolone 30 mg/day/the lesion regressed after 3 days
	Soares et al.[21]	1	42	M	N/A	Buccal mucosa	Vesicobullous lesions	N/A	Dexamethasone and dipyrone for 7 days/the lesions completely regressed after 21 days

(Continues)

TABLE 2 (Continued)

COVID-19 oral manifestations	Author	Patients' number	Age (years)	Gender	Oral lesions onset	Local	Signs and symptoms	Coinfection	Treatment/outcome
Enanthem	Jimenez-Cauhe et al.[51]	21	40–69	F/M	12 days	Hard palate	Petechiae, erythema, macules, papules, or vesicles	N/A	N/A/N/A
Erythema multiforme-like lesions	Jimenez-Cauhe et al.[51]	4	58–77	F	20 days	Palate	Macules and petechiae	N/A	Systemic corticosteroids/the lesions completely regressed after 14–21 days of treatment
White plaque	dos Santos et al.[50]	1	67	M	10 days	Tongue	Severe geographic tongue	*Saccharomyces cerevisiae*	Intravenous fluconazole (200 mg/100 ml) for 10 days and oral nystatin (100,000 IU/ml) 8/8 h, for 30 days, chlorhexidine digluconate 0.12% mouthwash, and 1% hydrogen peroxide/After 14 days the lesion showed almost complete resolution
Oral submucous fibrosis	Sarode et al.[53]	1	N/A	N/A	N/A	N/A	Reduced mouth opening	N/A	N/A/N/A
Facial pain/muscle facial pain	Biadsee et al.[45]	60	18–73	F/M	N/A	Forehead or face	Masticatory muscle pain	N/A	N/A/N/A
Sore throat	Biadsee et al.[45]	34	18–73	F/M	N/A	Throat	Pain	N/A	N/A/N/A
	Carreras-Presas et al.[19]	1	56	M	N/A	Throat	Pain	N/A	N/A/the symptoms regressed after 10 days of treatment
Facial nerve palsy	Homma et al.[46]	1	35	F	9 days	Right side of face	Motor weakness in the forehead and mouth	N/A	Ciclesonide and favipiravir/facial paralysis improved after 6 days

Abbreviations: Covid-19, coronavirus disease 2019; F, female; M, male; N/A, not assessed.

difference between genders with regard to prevalence of oral lesions.[22]

To date, the main sites of appearance of oral lesions described in the literature were: tongue,[13,17,20,22,49,50] palate,[12,17,19–21,24,49,51] lip mucosa[13,17,19] and gingiva[23,52] (Table 2). Previously published data have shown that most oral lesions can generally be categorised into two types. The first type refers to lesions similar to aphthous-like ulcers that occur in younger patients with mild Covid-19 symptoms. The second type resembles herpetic ulcers that are spread throughout the oral cavity and are commonly reported in older patients with some degree of immunosuppression.[13,48] Besides these two types, other types of oral lesions have also been reported, including tongue depapillation,[17,49] angular cheilitis,[17] ulcers,[13,14,19–22,50] blisters,[19,21] erythema multiforme-like lesions,[24] white plaques[50] and dark pigmentations.[44] The occurrence of facial pain,[45] oral submucous fibrosis,[53] burning mouth sensation[17,49] and xerostomia is also reported in Covid-19 patients[17,18] (Table 2).

The aetiology of oral lesions in patients with SARS-CoV-2 infection remains unknown; however, some hypotheses could explain the onset of these lesions. First, the virus may directly or indirectly interact with oral mucosal cells.[9,10,16] A recent study has also stated that interaction between the virus and host epithelial cells could disrupt the integrity of the tissue and trigger the lesion.[23] Second, lesions may be triggered by adverse reactions to drugs that are administered for treatment of viral infection. Some therapeutics could likely contribute to herpes simplex virus and *Candida* infection, xerostomia, nonspecific ulceration and gingivitis.[50] Third, the lesions could also be a result of systemic immune dysregulation and coinfection by opportunistic bacteria, fungi or other types of viruses mainly associated with the period of hospitalisation. Finally, it has been hypothesised that the oral lesions could be related to psychological factors such as restricted social interaction due to lockdown or work-related stress.[54] Several investigations have stated that long periods of hospitalisation can significantly increase the risk of developing oral lesions and emphasised the importance of multiprofessional care during this period and in the supportive treatment of patients at home.[23,50] Although the oral lesions present an onset and development course concurrent with the signs and symptoms of Covid-19, there is still no consensus among the medical and dental communities regarding the role of these lesions in the diagnosis of Covid-19.[48] It has been reported that tissues of the oral cavity could be the first to be infected with SARS-CoV-2 and hypothetically oral lesions could be the first signs of Covid-19. If this hypothesis is confirmed, dental practitioners will have an important role in the initial diagnosis of the disease and can send suspected SARS-CoV-2 patients for testing and appropriate treatment.[54]

In most reported cases of fungal coinfection (mainly *Candida*), the treatment options used were Nystatin solution 10,000 IU[17] and solutions containing triamcinolone acetonide 0.05%.[55] Systemic acyclovir or valaciclovir associated with photobiomodulation therapy and local anaesthetic were used in the management of secondary herpes infections.[13,48,56] Moreover, mouthwashes with chlorhexidine 0.12% were prescribed for preventing coinfections.[13,17,19,22,49] Topical or systemic corticosteroid therapy with dexamethasone, prednisone, or triamcinolone acetonide was employed in most cases of oral lesions.[17,19–21] Resolution of oral lesions posttreatment suggests that recurrence or growth of opportunistic oral pathogens is a common feature in Covid-19 patients, indicating that immunosuppressive or hyperinflammatory conditions may prompt virus reactivation and promote growth of certain infectious agents microbes.

2.4 | Gustatory dysfunction

Gustatory and olfactory dysfunction are symptoms that have been reported by patients with Covid-19.[57–64] These symptoms are most commonly diagnosed between 2 and 14 days after contact with SARS-CoV-2[57] (Table 3). Due to a great variety of assessment methods for olfactory and taste dysfunction among Covid-19 patients, the prevalence of these disorders is variable in the literature. According to Giacomelli et al.,[65] 66% of Covid-19 patients presented with anosmia and dysgeusia dysfunctions. A systematic review and meta-analysis showed that the prevalence of gustatory dysfunction in patients affected by SARS-CoV-2 is about 63%.[66] Fjaeldstad[60] reported that approximately 88% of diagnostic-confirmed Covid-19 patients described some chemosensory loss. Lechien et al.[67] observed that among 30 patients with SARS-CoV-2, 60.7% showed changes in taste sensation. The high prevalence of gustatory and olfactory symptoms led to the Centers for Disease Control and Prevention to include dysgeusia/ageusia and anosmia as symptoms that manifest from 2 to 14 days after exposure to Covid-19, being considered as potential subclinical markers of SARS-Cov-2 infection.[57,68]

Changes in smell and taste are more common among younger patients with a milder course of the disease and approximately 14% of the hospitalised patients have these symptoms after hospitalisation.[26] This could explain the lower prevalence of gustatory and olfactory disorder among older patients that are more affected by severe viral infection.[59] While Covid-19 infection is more common in males with severe symptoms, women are more frequently affected by changes in taste and smell. According to Bodnia and Katzenstein,[56] about 77% of women, 40% of men, and 14% of children with Covid-19 have a loss of smell and taste sense.

The exact mechanisms involved in the smell and taste changes caused by SARS-CoV-2 viral infection remain unclear although some explanations have been cited.[66] Human ACE2 is the main host cell receptor for SARS-CoV-2 and is widely expressed by respiratory epithelial cells and in the oral cavity, mainly in the tongue. The damage caused by the virus to these cells may be related to the development of anosmia and dysgeusia/ageusia.[16,28] Furthermore, the pathogenic mechanisms underlying olfactory and gustatory alterations in Covid-19 have been related to injuries in the peripheral nervous system that might affect central processing pathways.[10] Mao et al.[69] have reported that almost 37% of patients with Covid-19 presented some neurologic symptoms with direct transmission of the

TABLE 3 Characteristics and treatment of taste alterations and tongue depapillation associated with Covid-19

Covid-19 oral manifestations	Author	Patients' number	Age (years)	Gender	Oral lesions onset	Local	Signs and symptoms	Coinfection	Treatment/outcome
Dysgeusia/ ageusia	Rodríguez et al.[17]	1	43	F	Early stage	Oral cavity	Loss of taste sensation	N/A	N/A/symptoms were persistent after the treatment
	Biadsee et al.[45]	67	18 -73	F/M	N/A	Oral cavity	Changes in taste sensation	N/A	N/A/N/A
	Glavina et al.[12]	1	40	F	7 Days	Oral cavity	Loss of taste sensation	N/A	N/A/N/A
	Amorim et al.[50]	1	67	M	10 Days	Oral cavity	Loss of taste sensation	N/A	N/A/N/A
	Homma et al.[46]	1	35	F		Oral cavity	Loss of taste sensation	N/A	N/A/improvement of the condition after 2 days
	Brandão et al.[13]	8	71/81	F/M	4/5 Days	Oral cavity	Loss of taste sensation	N/A	N/A/N/A
	Mohamud et al.[61]	60	45.7	F/M	Later stage	Oral cavity	Loss of taste sensation and loss of smell	N/A	N/A/almost 17% of patients recovery the sense of taste after 5 days
	Lee et al.[62]	3191	24.5–54	F/M	N/A	Oral cavity	Partial and complete loss of taste sensation	N/A	N/A/the patients were recovered from ageusia in the median time of 7 days
	Vargas-Gandica et al.[63]	10	32–86	F/M	1–10 Days	Oral cavity	Loss of taste sensation	Negative coinfection with influenza virus	N/A/the symptom persisted for a median of 8 days
	Vaira et al.[64]	76	43–55.2	F/M 106 patients	4 Days	Oral cavity	Loss of taste sensation and ageusia	N/A	N/A/the majority of patients completely recovered the taste sensation
	Hjelmesaeth and Skaare[45]	2	60/90	M	9 Days/ uncertain	Oral cavity	Complete loss/altered sense of taste	N/A	N/A/NA
Tongue depapillation	Rodríguez et al.[17]	1	43	F	14 Days	Borders of the tongue	Bilateral atrophy of the surface of the tongue	N/A	Solution of triamcinolone acetonide 0.05%, three times per day for 10 days/ tongue depapillation persisted after the treatment
	Tomo et al.[49]	1	37	F		Borders of the tongue	Depapillation with reddish spots	N/A	Chlorhexidine 0,12% mouthwashes three times per day/tongue depapillation completely regressed after the treatment

Abbreviations: Covid-19, coronavirus disease 2019; F, female; M, male; N/A, not assessed.

virus to the brain. Recent studies have also suggested that changes in taste may be secondary to olfactory problems or nasal obstruction.[70]

Probable hypotheses that justify dysgeusia and ageusia in Covid-19 also include the possibility of damage caused by SARS-CoV-2 to the epithelial cells of the salivary glands that are considered a target of the virus because of ACE2 expression.[25] It has been acknowledged that changes in salivary flow and composition can cause changes in taste perception. Moreover, the increased use of oral chemicals and disinfectants to prevent secondary oral infections could also injure the epithelial cells, thus disturbing taste sensation.[71]

In general, it is not yet known whether the olfactory and gustatory symptoms caused by Covid-19 are transient or can be permanent,[58] but most cases (about 75%) show improvement within a few weeks in parallel with the improvement of other Covid-19 symptoms.

3 | SARS-CoV-2, IMMUNE DYSREGULATION AND ORAL DISEASE

Evaluation of the molecular mechanisms underlying the pathogenesis of PD and Covid-19 positive subjects will unravel the nature and extent of crosstalk in the manifestation of symptoms. Immune dysregulation in a susceptible host is central to the pathogenesis of oral diseases and SARS-CoV-2. The multifactorial, microbial aetiology of oral diseases suggests impaired host–pathogen interaction. The overpowering response by host immune cells can have a detrimental impact on tissue integrity. Synergistic interaction between resident oral microbes and SARS-CoV-2 may elicit an overt immune response that could further exacerbate oral inflammation. Multiple inflammatory mediators including cytokines, prostaglandins and histamines generated in response to oral pathogens may exert pleiotropic effects on local cells and facilitate infiltration of innate and adaptive immune cells, further amplifying the immune response. While a large percent of SARS-CoV-2-infected individuals are asymptomatic, approximately 10% exhibit mild to severe manifestations. Among these, copious secretion of proinflammatory cytokines including IL-6, TNF-α, IL-1β, IL-8 and IL-12 are frequently detected in infected tissues as well as plasma/blood.[9,29,33–35] A rapid production of inflammatory cytokines, termed cytokine storm, is commonly reported in severe Covid-19 subjects and increases risk of vascular hyperpermeability and multiorgan failure.[72] The lytic nature of SARS-CoV-2, coupled with its broad tropism due to ubiquitous expression of ACE2, allows the virus to promptly replicate. To counter this, massive immune activation is required to contain the virus. In addition, these cytokines can amplify inflammatory functions by paracrine and autocrine positive feedback signalling. Activation of different pattern recognition receptors can trigger various inflammatory pathways that can reinforce each other, leading to uncontrolled immune activation. Therapeutic blockage of IL-6 by tocilizumab can significantly reduce invasive mechanical ventilation or death in severe Covid-19 pneumonia, strongly supporting that suppression of inflammation can mitigate severe manifestations of virus infection.[73] Increased levels of proinflammatory cytokines acts as a double-edged sword by activation of osteoclasts, bone resorbing cells critical in the alveolar bone loss observed in chronic periodontitis. IL-6-mediated induction of receptor activator of NF-kB ligand (RANKL) in osteoblasts augments the differentiation of osteoclasts and hence augments bone resorption. Similarly, TNF-α induces osteoclastogenesis by inducing RANKL in osteoblasts and RANK in osteoclast precursors. Obitsu et al.[74] showed that SARS-CoV-2 protein 3a/X1 induces expression of TNF-α in human lung epithelial A549 cells and RANKL expression in mouse bone marrow stromal ST2 cells, suggesting that the virus can perturb bone metabolism. Thus, the proinflammatory environment is pro-osteoclastic and hence detrimental to periodontal health.

In addition to local inflammation, systemic diseases may exacerbate oral diseases and their manifestation in Covid-19 patients. Indeed, Covid-19 subjects with systemic disease are reported to present with worse clinical outcomes.[75] Similarly, individuals with systemic diseases like obesity, rheumatoid arthritis, atherosclerosis and so forth, are predisposed to oral inflammatory diseases, in particular periodontitis, suggesting that systemic inflammation may augment localised inflammation.[76] This could be attributed to dysbiosis or overt activation of immune cells. In the context of oral disease, however, there is a complete lack of studies assessing this correlation. Cytokine analysis in SARS-CoV-2 negative and positive subjects with PD will reveal whether the virus directly impacts oral inflammation. Equally important is to longitudinally evaluate periodontal health in Covid-19 subjects to examine outcomes in recovering patients. This will further signify the role of SARS-CoV-2 in the initiation and progression of periodontitis.

Another molecular circuitry that links Covid-19 and PD is the T helper-17 (Th-17) pathway. IL-17 is a member of the IL-23 family and is comprised of six isoforms (IL-17A–F); their role in autoimmune disorders is well established.[77,78] These cytokines are secreted predominantly by adaptive immune cells including Th-17, γδ T cells, innate lymphoid cells 3 and natural killer cells. Higher expression of IL-23 family cytokines is associated with various immunopathologies including Covid-19 and PD.[72,79,80] Covid-19 patients with severe disease exhibit pulmonary oedema and lung fibrosis. With regard to PD, IL-17 is secreted by myeloid cells challenged with the periopathic bacteria *Porphyromonas gingivalis* and by IL-1-stimulated fibroblasts, further supporting the notion that innate cytokines reinforce inflammatory status by activating distinct yet mutually overlapping functions. Moreover, elevated levels of IL-23 in the GCF is detected in chronic periodontitis subjects, indicating the role of activated Th-17 cells and suggests their role in periopathogenesis. Destruction of the periodontium is mediated by effector Th-17 cells that secrete copious levels of IL-17 family cytokines and facilitate production of IL-6, IL-1β and TNF-φ.

Galectins are a class of soluble-galactoside-binding proteins with proinflammatory or proresolution functions.[81] Recent studies indicate galectins as a potential connecting link between PD and Covid-19. Higher plasma levels of galectins (including Gal-1, Gal-3 and Gal-9) are reported in Covid-19 subjects.[82] In addition, macrophages, monocytes and dendritic cells in patients with severe symptoms

compared with mild symptoms suggests their pathological role in the disease severity.[83,84] Inhibition of Gal-3, a proinflammatory galectin, suppresses cytokine secretion in macrophages indicating its therapeutic potential as a target for Covid-19 treatment.[85] Interestingly, subjects with severe PD also exhibit increased expression of Gal-3.[35] Expression of Gal-9, another galectin isoform, was induced in periodontal ligament cells challenged with *P. gingivalis*-derived lipopolysaccharide, suggesting that higher Gal-9 expression further exacerbate periodontal inflammation.[86] Multiple reports have demonstrated that proinflammatory cytokines TNF-α induce Gal-9 expression,[87] while overexpression of Gal-9 in monocytes upregulate IL-1α, IL-1β and IFN-γ levels[88] suggesting a feedforward correlation between inflammatory cytokines and Gal-9 in maintaining inflammatory microenvironment. Importantly, expression of these cytokines are significantly higher in inflamed tissues and contribute to periopathogenesis. Thus, it is plausible that higher levels of Gal-9, in conjunction with proinflammatory cytokines, may exacerbate periodontal inflammation. However, a direct association of Gal-9 in Covid-19 patients presenting periodontal lesions requires further studies.

In addition, higher levels of Gal-3 and Gal-9 were detected in periapical granulomas compared to control by in situ immune-histochemical staining.[89] Increased galectin expression correlated with elevated toll-like receptor 2 (TLR2) and TLR4 levels. Secreted galectins (Gal-3 and Gal-9) bind to TLRs and activate the NF-kB pathway and production of proinflammatory cytokines IL-1, IL-6 and TNF-α; this positive feedback cycle can amplify inflammatory signalling.[81,90] These evidences indicate a role of galectins in the pathogenesis of oral inflammatory diseases. Systemic (due to Covid-19) and local (due to oral disease) induction of galectin expression may further exacerbate inflammation and perturb resolution pathways.

3.1 | SARS-CoV-2 and oral pathogens: Synergy or superinfection?

The case studies of Covid-19 patients show presentation of recurrent herpetic lesions. Stress, inflammation and corticosteroid use are well-known factors that can drive human herpesviruses (HHV) reactivation. A subject described by dos Santos et al.[50] was on immunosuppressants that are known to reactivate herpesviruses.[50] Recurrence of HHV in the exacerbation of oral pathologies and their synergy with bacterial aetiological agents is proposed. Indeed, members of HHV accumulate in various oral pathologies including periodontitis, periapical periodontitis, inflamed pulp, peri-implantitis and so forth.[91–97] Interestingly, HHV-encoded microRNAs, small noncoding regulatory RNAs, are frequently detected in inflamed periodontal and pulp tissues suggesting reactivation of virus. Viral microRNAs, by virtue of their suppression of multiple host transcripts, can contribute to evasion of host defence responses including antiviral responses and clearance of virus infected cells by blocking antigen presentation.[98,99] Detection of viral microRNAs can provide important information on copresence of SARS-CoV-2 and active HHV. Whether Covid-19 infection in the oral mucosa and tissues favours an ecological niche suitable for opportunistic viral and/or bacterial infections remains unclear; however, a subtle shift in some pathogens is evident in the form of clinical manifestations. This is supported by a recent metagenomic analysis of Covid-19 subjects which revealed abnormally high bacterial reads of *P. intermedia* and other common microbes (such as the *Streptococci*, *Fusobacterium*, *Treponema* and *Veillonella* genera) implicated in the onset and progression of oral diseases.[30] Interestingly, animals coinfected with *Streptococcus pneumoniae* and the periopathic bacteria *P. intermedia* exhibit severe bacteraemia, inflammatory cytokines and low survival rate.[100] Similar effects of *P. intermedia* were observed in human alveolar epithelial cells A549 with increased *S. pneumoniae* adhesion. These results indicate that periopathic bacteria can exacerbate systemic manifestations of respiratory disease, which are a hallmark of Covid-19. Improving oral health has been shown to reduce the risk of acute viral respiratory infections, in particular pneumonia.[101] Thus, bacterial superinfection in PD can not only exacerbate local inflammation, but can also impair respiratory functions and worsen outcomes of Covid-19 by augmenting systemic inflammation. Further multicohort and longitudinal analysis will be required to reveal the impact of SARS-CoV-2 on the oral microbiome, which pathogenic genera/species are enriched in virus-infected subjects, and whether that correlates with disease manifestation.

4 | CONCLUSION

The main oral manifestations in Covid-19 patients are related to ulcers, blisters, necrotising gingivitis, coinfection by opportunistic bacteria, fungi or other viruses, salivary gland alterations, white and erythematous lesions and gustatory dysfunction. Emerging evidences support the presence of virus in the oral cavity, including saliva and periodontal tissues and correlates with the presence of viral entry receptors in these tissues. Various small cohort studies and case reports suggest similar oral manifestations of a newly evolved pathogen, in line with Koch's postulates. The oral signs and symptoms presented by patients with Covid-19 are a direct result of SARS-CoV-2 infection or secondary disorders facilitated by systemic damage, alterations in the immune system, or adverse effects of treatment and require further investigation with larger cohort sizes. It is strongly recommended that health professionals complete a detailed oral examination with extra attention to oral manifestations for ensuring patient support and pain control.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Afsar R. Naqvi and Daniela A. Brandini conceived of the presented idea. Daniela A. Brandini, Aline S. Takamiya, Pari Thakkar, Samantha Schaller, Rani Rahat and Afsar R. Naqvi wrote different sections of the manuscript. Daniela A. Brandini and Aline S. Takamiya compiled tables and figures. Daniela A. Brandini, Samantha Schaller and Afsar R. Naqvi revised the manuscript. All authors contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during the current study.

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