**INTRODUCTION**

The coronavirus disease 2019 (Covid-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization. Being highly transmissible, the coronavirus disease has spread fast all over the world. In general, studies on Covid-19 symptoms and signs indicate as the most common headache (70.3%), loss of smell (70.2%), nasal
obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%), sore throat (52.9%) and fever (45.4%). The mean duration of Covid-19 symptoms of mild-to-moderate cured patients observed is about 11–15 days.\(^1\)

Oral manifestations have been also observed in patients with Covid-19. However, growing evidence suggests that oral cavity may not only be a site of the clinical manifestations of SARS-CoV-2 infection but also can play a possible role in the virus entry and transmission.\(^2\)

This narrative review discusses potential connections of SARS-CoV-2 infection, Covid-19 and periodontal tissues in health and diseases as well as a likely role of periodontal healthcare in the virus spread.

### 2 | PERIODONTAL MANIFESTATIONS IN COVID-19 PATIENTS?

SARS-CoV-2 infection apart from systemic manifestations is associated with local, oral cavity signs and symptoms such as dysgeusia, dry mouth, taste loss as well as mucosal lesions (ulcerations, enanthema and macules) in about half of Covid-19 individuals.\(^3,4\) Clinical observations suggest that dysgeusia is the only oral symptom of Covid-19. Recently published meta-analysis supports the evidence that taste disorder (45%) is the most common oral symptom (odds ratio 12.68).\(^5\) The degree of disturbed taste varies, from abnormal taste (38%), blurred taste (35%) to loss of taste (24%), and loss of taste was evidenced to correlate with SARS-CoV-2 viral load.\(^6\) Other clinical manifestations of Covid-19 such as vesicles, vesicular bleeding, necrotizing gingivitis, desquamative gingivitis, which have been reported to involve periodontal structures/mucosa remain unclear to be directly associated with SARS-CoV-2 infection.\(^7-10\) These symptoms are rather ascribed to immune dysfunction associated with SARS-CoV-2 infection, superinfection with other microorganisms and disease-related emotional stress.

Long-term inflammatory process observed in Covid-19 patients may produce pathological responses in periodontal tissues leading to fibrinogen degradation and triggering coagulation cascade.\(^11\) SARS-CoV-2 infection also involves changes in the bacterial flora, with (among others) increased population of *Prevotella intermedia*, which may trigger or worsen periodontal disease (details see below).\(^12,13\)

### 3 | PERIODONTAL STRUCTURES AS SARS-COV-2 INFECTION SITES

The SARS-CoV-2 enters cells via two pathways, that is, the principal one through the host cell membrane-bound peptidases or less efficiently via endocytosis (Figure 1). The SARS-CoV-2 infection of target cells begins with interaction between the virus Spike protein (S) and angiotensin-converting enzyme 2 (ACE2), a metalloproteinase harboured on the cell membrane of the host cell. The S protein is cleaved into S1 and S2 by furin, another host cell, membrane anchored, protease. The S1 subunit dissociates, and S2 is cleaved further by a host cell-derived transmembrane serine protease 2 (TMPRSS2). This process exposes the fusion peptide, which enables fusion of the virus with the host cell membrane, and subsequent cell invasion. In vitro studies also postulate a role of signalling protein – neuropilin-1 (NRP-1), which may act as an entry factor and potentiate SARS-CoV-2 infectivity.\(^14\) Other tissue-specific proteases (TMPRSS4 and TMPRSS11D) and endosomal proteases (CTSB, CTSL, BSG) can also participate in the SARS-CoV-2 cell entry process and replication.\(^15\) The endosomal entry pathway is triggered by interaction of the SARS-CoV-2 spike protein with the host cell membrane receptor ACE2, with subsequent internalization of the virus. In the endosome, cathepsin L cleaves the spike protein into S1 and S2, which allows fusion of the viral capsid with the endosomal membrane, and release of the virus genome. The ACE2 and TMPRSS2 are critical factors, of all the entry and transmission ones, in the infection process of SARS-CoV-2.\(^14\)
Recent observations suggest that the oral cavity tissues can play an important role in the SARS-CoV-2 virus entry and transmission. There is growing evidence that the virus can directly infect and replicate in oral structures, that is, including the periodontal tissues.\(^4\)\(^6\) (Figure 2). The gingiva is lined by stratified squamous keratinized epithelium and in the gingival sulcus epithelium is non-keratinized (stratified squamous epithelium). In gingival epithelial cells, ACE2, TMPRSS2 and furin are expressed in the suprabasal layer and periodontal pocket epithelium. The immunohistochemical staining demonstrated ACE2 immunolocalization in the nucleus and cytoplasm of the spinous–basal cell layer (but not the epithelial surface and horny layer). The non-keratinized gingival sulcular epithelium tended to be stained more intensively than the keratinized gingival epithelium. Another SARS-CoV-2 entry factor, that is, TMPRSS2 was defined in both the sulcular epithelium and the gingival epithelium, with stronger immunoeexpression in the non-keratinized tissue (sulcular epithelium).\(^17\) TMPRSS2 was localized in the superficial epithelium (in the cell membrane), horny layer (weak expression in the cell membranes) and spinous–basal cell layer (in spinous cells in the cell membrane and cytoplasm; in basal cells in the cytoplasm, but TMPRSS2-negative cells were focally noted). The next protease, furin, was revealed in the sulcular epithelium and in the gingival epithelium, with more intensive staining in the sulcular epithelium. It is stained in a dot-like pattern, more intense in basal cells than in spinous cells. The enzyme was not evidenced in the epithelial surface and horny layer.\(^17\) Immunostaining of cells harvested by liquid-based cytology from the gingival sulcus confirmed ACE2 expression in gingival cells collected from the gingival sulcus, which was stained at the same level as the tongue (which may be considered as one on the main SARS-CoV-2 entry routes along with salivary glands).\(^2\) The expression of SARS-CoV-2 entry factors is not a unique condition for the invasion, and these results should be analysed with caution. Recent studies have suggested that structural variations in human ACE2, producing spatial orientation changes of the key ACE2 interacting residues, may influence its binding with the SARS-CoV-2 spike protein.\(^18\)\(^19\)

Expression of SARS-CoV-2 entry and transmission factors in gingival tissues was confirmed by other molecular methods. A single-cell RNA in situ hybridization and immunofluorescence microscopy analysis of healthy gingival biopsies demonstrated ACE2 and proteases (TMPRSS2, TMPRSS4 and TMPRSS11D) expression in the gingival epithelium, with enrichment of all examined entry factors in suprabasal over basal cells (which can be shed and thus transmit the virus).\(^6\) Gingival keratinocytes were also evidenced to express ACE2 and TMPRSS2 as well as endosomal proteases CTSB and CTSL.\(^6\) The expression levels of SARS-CoV-2 entry factors were similar to the nasal and intestinal epithelial cells, being considered as one of the major entry route of SARS-CoV-2.\(^6\)\(^20\)\(^21\) The single-cell sequencing data of Xu et al. further proved the expression of ACE2 in the gingiva samples.\(^22\) Cellular localization of the SARS-CoV-2 entry and transmission factors in gingival tissue is slightly controversial. The above-mentioned studies, using different methodological approaches, demonstrate predominant expression in suprabasal or basal cells. The finding that the expression occurs in the spinous-basal layer and not in the superficial layers may entail a difficulty for the virus to reach its targets under normal conditions. On the other hand the expression of ACE2 and proteases in suprabasal layers of the gingival epithelium enables the virus infection. There is some evidence that support more directly than expression of the virus entry factors, the SARS-CoV-2 infectious potential in gingival tissues.\(^5\)\(^23\)\(^24\) In fact, colonization of the oral mucosa with SARS-CoV-2 was evidenced by Huang et al.\(^6\) The infection and viral replication in all layers of mucosa (primarily enriched in the differentiated epithelial cells) was observed. Likewise, a recent post-mortem study demonstrated RNA of the envelope (E) gene of SARS-CoV-2 in the samples (from interproximal mesial papillae of first upper molar) of Covid-19-positive patients up to 24 days after the first symptoms, with possible virus presence in crevicular fluid.\(^23\) Shed epithelial cells in saliva, which can originate from gingiva, were defined to harbour SARS-CoV-2, as the virus Spike protein was demonstrated inside the cells and on their membrane surface. Furthermore, infection and replication capacity of SARS-CoV-2 in shed mucosal cells in an acutely infected individual with Covid-19 was documented. Mucosal scrapings suggested that these cells retained infection and replication capacity after shedding.\(^6\) Therefore, populations of shed infected cells could be considered as binding sites for SARS-CoV-2 and/or act as virus carriers to promote infection stability and transmissibility to other oral cavity structures as well as the respiratory and gastrointestinal tract (see below). Functional role of the virus entry factors can be also reflected in block of SARS-CoV-2 invasion via ACE2 produced by TMPRSS2 inhibitor.\(^24\) The expression of ACE2, TMPRSS2 in the sulcular epithelium and periodontal pocket epithelium along with the microenvironment of periodontal pockets as well as gingival sulcuses may also provide favourable conditions for virus replication and maintenance.\(^5\)\(^6\)\(^25\)

Not only cells of periodontal structures can harbour the virus but also crevicular fluids and dental biofilm were screened to be positive for the virus. The analysis of gingival crevicular fluid composition can reflect the functional state of the periodontium.\(^26\) In Covid-19 positive patients, mostly asymptomatic and mildly symptomatic, the SARS-CoV-2 RNA was revealed in gingival crevicular fluid,\(^27\) which contains acellular fraction along with connective tissue, epithelium or inflammatory cells, and microbial flora inhabiting the gingival margin or the sulcus/pocket.\(^28\) Methodological approach used for RNA isolation enabled to measure total SARS-CoV-2 RNA levels, that is, both in acellular and cellular fractions of the fluid. In comparison to the nasopharyngeal swab sampling as gold standard, the presence of SARS-CoV-2 RNA in the detection sensitivity of gingival crevicular fluid samples was estimated to 63.64% (confidence interval [CI], 45.1\%–79.6\%), and comparable to saliva in terms of its sensitivity to detect SARS-CoV-2.\(^27\)

The SARS-CoV-2 RNA was also found in dental biofilm collected from the buccal and lingual teeth surfaces along gingival margin, in patients with Covid-19 flu-like symptoms during an observational clinical study. However, the load of SARS-CoV-2 RNA in the dental biofilm was lower than in nasopharyngeal and oropharyngeal
Those observations may suggest that dental biofilms from symptomatic Covid-19 patients can harbour SARS-CoV-2, and potentially play a role in Covid-19 transmission. However, it is not known whether dental biofilm creates a favourable environment for SARS-CoV-2 to survive.

Clinical and experimental observations suggest that several factors can affect expression of SARS-CoV-2 entry and transmission factors. Peng et al. reported significantly increased expression levels of the mRNAs of ACE2 and TMPRSS2 in oral mucosa in relatively elderly population (>50–60 years of age) than in relatively younger individuals (both females and males). The RNA data are supported by ACE2 and TMPRSS2 proteomic assays, that is, Western blot and immunohistochemistry, showing higher levels in the elderly mucosa than in the younger. Mostly, the analysis did not reveal substantial differences between females and males in ACE2 and TMPRSS2 expression levels. Likewise, the increasing expression of ACE2 and TMPRSS2 with advancing age appears also from bioinformatic analysis in different cohorts (TCGA, GSE42743, GSE9844, GSE30784 databases). Higher levels of ACE2 and TMPRSS2 coincided with higher saliva positivity rate of SARS-CoV-2 in older cohorts. These findings suggest that elderly population might be more prone to SARS-CoV-2 infection through oral route of the virus transmission. This opinion corroborates with clinical findings of higher susceptibility to infection and more severe clinical symptoms manifestation of Covid-19 in elderly populations.

Smoking is a well-known factor associated with periodontal pathologies. Recent study has revealed that cigarette smoking/nicotine can promote the susceptibility to Covid-19. Cigarette smoke condensates upregulate ACE2 and TMPRSS2 expression in human gingival epithelial cells (immortalized human oral gingival keratinocytes, IHGK). There is also evidence that exposure to cigarette smoke condensates, potentiates the SARS-CoV-2 pseudovirus cellular internalization, which is mediated by AhR (aryl hydrocarbon receptor, that is, nuclear receptor responding to cigarette smoke components). Those experimental findings imply that smoking cessation, apart from numerous health benefits, could also reduce the SARS-CoV-2 infection susceptibility of the periodontium and other oral cavity structures.

The expression of SARS-CoV-2 entry and transmission factors, mainly ACE2 and TMPRSS2 as well as the presence of the virus RNA in periodontal tissues suggest that the periodontium can act as an entry point for the virus or as a dissemination site of the virus from the systemic circulation into the periodontal tissues. The SARS-CoV-2 presence in gingival crevicular fluid may support its transmission pathway mediated by the periodontium. However, it should be noted that demonstration of the SARS-CoV-2 RNA, but not the presence of viable viral particles, does not provide direct evidence of the contagious potential. Studies in the upper respiratory tract evidenced that high viral RNA titre does not necessarily correlate with the presence of culturable and viable viruses.

**FIGURE 2** SARS-CoV-2 and its entry and transmission factors expression in healthy periodontium and periodontitis: SARS-CoV-2 RNA can be found in gingival tissue, crevicular fluid and dental biofilm. ACE2 (angiotensin-converting enzyme 2), TMPRSS2 (transmembrane serine protease 2) and furin are expressed in squamous stratified epithelium cells of gingiva. Non-keratinized gingiva lining of the gingival sulcus or periodontal pockets demonstrate stronger expression of the entry and transmission factors than the keratinized gingiva covering the external part of the gingival margin. Expression of the entry and transforming factors can be increased by local infections (periodontitis) like Porphyromonas gingivalis-derived lipopolysaccharide, and some inflammatory mediators IL-1β, TNF-α, PGE2 as well as in older patients. On the contrary periodontal intervention may decrease the expression of entry and transmission factors. ACE2 is expressed in spinous cell layer (scl), basal cell layer (bcl) and intermediate layer (il). In superficial layer (sl) and horny layer (hl) only TMPRSS2 can be defined besides in (scl) and (bcl). Furin is expressed mainly in bcl, weakly in scl. bm – basement membrane; gcl – granular cell layer.
ACE2 RNA. Therefore, is can be hypothesized that the cellular response to SARS-CoV-2 may be of defensive nature, protecting a cell from the virus overload.\textsuperscript{34}

The oral cavity tissues, including periodontium, can be the first to be infected with SARS-CoV-2 and oral lesions could be the first manifestations of Covid-19. So, dental practitioners could play an important role in the disease initial diagnosis, verified further by patients testing.\textsuperscript{35} Invasion of the gingival epithelial cells principally via the ACE2/TMPRSS2 mechanism may affect the function of oral epithelial cells, finally resulting in ulcerated gingival lesions. A post-mortem study in patients diagnosed with severe Covid-19 evidenced histopathologic abnormalities and showed alterations in keratinocytes of the junctional epithelium, characterized mainly by vacuolization of the cytoplasm in the samples harvested from interproximal mesial papilla of first upper molar.\textsuperscript{24} However, the observed changes cannot be directly ascribed to SARS-CoV-2 infection, and/or severe systemic mechanisms could also be postulated to be involved, as the virus infection and replication is associated with inflammation and local immune cells activation. The SARS-CoV-2 direct cytopathic effects were demonstrated in other epithelial cells, and this activity may also be operating in the periodontal tissues, contributing to local inflammation.\textsuperscript{36} Inflamed gingival tissue of the Covid-19 patients contains elevated levels of proinflammatory cytokines, such as IL-1\textgreek{b} and TNF-\textgreek{a}.\textsuperscript{6}

Disturbed function of the immune system being a consequence of local and systemic SARS-CoV-2 infection may promote expansion of periodontal pathogens in periodontal pockets, for example, Prevotella intermedia, Streptococci, Fusobacterium, with a known consequence of acute periodontal conditions development.\textsuperscript{37,38} Further events, like in a vicious circle, can include expansion of the SARS-CoV-2 entry and processing factors in human gingival fibroblasts induced by periodontal pathogens, that is, Porphyromonas gingivalis or inflammatory cytokines/mediators. Exposure of human gingival fibroblasts to Porphyromonas gingivalis-derived lipopolysaccharide (PgLPS) or IL-1\textgreek{b}, TNF-\textgreek{a}, PGE2 resulted in significant elevation of ACE2. Likewise, expression of TMPRSS2 was increased by some inflammatory mediators, that is, PgLPS, IL-1\textgreek{b} or PGE2. The expression of FURIN decreased after TNF-\textgreek{a} treatment.\textsuperscript{39} These findings suggest that local inflammation in gingiva may promote local infection spread and viral replication in periodontal structures, with potential further systemic expansion. A periodontal intervention may decrease the expression of ACE2 and other SARS-CoV-2 entry and transmission factors in gingival tissues and gingival sulcus, thus prevent the virus attachment and internalization as well as local replication.\textsuperscript{39}

Immunoglobulins against SARS-CoV-2 (also acting in saliva) present in crevicular fluid may modulate SARS-CoV-2 infection potential. IgA and IgG were detected in crevicular fluid in SARS-CoV-2-infected individuals screened 4–13 days after a real-time reverse transcription polymerase chain reaction diagnosis of Covid-19. The immunoglobulin responses in crevicular fluid and in plasma showed a similar time-profile in change. The median times to peak antibody was defined at 4 weeks for IgG and 3 weeks for IgA.\textsuperscript{40} Those antibodies can be considered as a specific defence mechanism, and potentially could be explored as a diagnostic parameter for the disease detection and monitoring of immunologic responses. The United States FDA made the antibody test available under an emergency access mechanism called an Emergency Use Authorization. The CovAb SARS-CoV-2 Ab Test is authorized for the detection of total antibodies to SARS-CoV-2 in human oral fluid (gingival crevicular fluid) (Diabetomics, Inc., USA). In the manufacturer product information an oral fluid collected across buccal gum line, which contains an antibody-rich fluid known as gingival crevicular fluid (more abundant in antibodies than saliva) is indicated as specimen collected for the detection of immunoglobulins against SARS-CoV-2. Likewise crevicular fluid, the above-mentioned specimen (collected by a dedicated sampling device) can be considered for diagnostic and monitoring applications.\textsuperscript{41}

## 5 | POTENTIAL ASSOCIATIONS BETWEEN PERIODONTITIS AND COVID-19

Periodontal disease is characterized by progressive destruction of the soft and hard tissues of the periodontal complex, produced by an interplay between disturbed bacterial flora and aberrant immune responses within gingival and periodontal tissues. Enriched periodontal pathogens and affected resident oral microbiota along with inflammatory responses produce tissue destruction, and thus trigger positive feedback loop of proteolysis, inflammation and enrichment for periodontal pathogens.\textsuperscript{42} Wang et al. evidenced that periodontal disease was significantly associated with higher susceptibility to Covid-19 and the disease severity.\textsuperscript{33} In this study, periodontal disease was characterized as periodontitis related-Socransky phenotype, suggesting a high correlation and positive loading with pathogens, including P. gingivalis, P. intermedia, P. nigrescens, T. forsythus, T. denticola, F. nucleatum and C. rectus.\textsuperscript{44}

It might be considered that the lytic activity of periodontal bacteria could produce synergistic activity with membrane proteases, which might favour early and prolonged SARS-CoV-2 colonization of the oral cavity.\textsuperscript{45–48} However, this hypothesis remains further verification. Likewise, Marouf et al. based on a case–control study in patients who suffered from Covid-19 complications, reported an association between periodontitis and severity of SARS-CoV-2 infection. The report revealed that periodontitis was associated with higher risks of death (8.8 times, CI 1.00–77.7), intensive care unit admission (3.5 times, CI 1.39–9.05) and need for assisted ventilation (4.5 times, CI 1.19–17.4) of Covid-19 patients. In the studied population periodontitis was associated with significantly higher blood levels of white blood cells, D-dimer and C reactive protein, which could explain worse prognosis/clinical outcome.\textsuperscript{46} Translocation of periodontal pathogens to blood, systemic inflammation and induced autoimmune damage significantly impact systemic health in patients with periodontal pathologies.\textsuperscript{48} It is well documented that periodontitis is associated with diabetes, cardiovascular diseases, chronic renal disease and even premature mortality. Likewise, it can be suggested (and evidenced in preliminary observations, see above) that also in Covid-19 patients it may lead to worse prognosis.
Periodontal pathologies, apart from direct effects on SARS-CoV-2 local infection and its consequences, may also produce systemic responses affecting Covid-19 clinical picture (Figure 3). Clinical study documented a higher risk of mortality in Covid-19 individuals who presented bleeding gums, and thus periodontal disease. Periodontal bacteria, as demonstrated for *Fusobacterium nucleatum*, were able to stimulate local production of pro-inflammatory cytokines (e.g. IL-1β, IL-6, IL-8, IL-17, TNF-α) by epithelial cells. So, the periodontium can serve as the source of bacteria inducing inflammatory responses as well as mediators of inflammation. Those factors could infiltrate saliva through gingival crevicular fluid and further can be aspirated/swallowed to cause inflammation or infection within the respiratory and gastrointestinal tracts, promoting Covid-19. The periodontal bacteria, such as *Veillonella*, *Prevotella*, *Treponema* and *Fusobacterium* were recovered from the bronchoalveolar lavage fluid of patients with Covid-19. Likewise, cytokines (e.g. IL-1β) and TNF-α from periodontally diseased tissues can infiltrate saliva and be aspirated, and thus cause inflammation or infection within the lungs. Periodontal intervention can reduce the bacterial pathogens load and control local inflammation, with subsequent general health positive consequences. Successful treatment of periodontitis has been shown to normalize/improve serum markers of systemic inflammation (CRP, IL-6, IL-17), systemic metabolic control, as well as reduce pneumonia mortality and prevent morbidity of influenza. In the case of periodontitis and Covid-19 such a causal link has not been established yet. However, the control of periodontal health could potentially improve the prognosis in Covid-19 patients.

**6 | ORAL FLUID AS A POTENTIAL TRANSMISSION FACTOR AND PREVENTIVE MEASURES**

The periodontal pocket can be considered as a favourable niche or reservoir for both active and latent SARS-CoV-2 forms, from where the virus can reach not only the oral fluid and saliva but also might spread to the lower respiratory tract and/or the gastrointestinal tract, to the bloodstream of the local periodontal capillary network and further progress to distant organs. So, the oral cavity could not only contribute to external infectious potential (via aerosol droplets) but also might promote development and recurrence of Covid-19 systemic disease.

Respiratory droplets, originating from the nose, oral cavity and airways constitute one of the principal transmission routes of SARS-CoV-2. The SARS-CoV-2 RNA load in oral fluid globally ranges from $9.9 \times 10^6$ to $7.1 \times 10^{10}$ copies/ml, peaking at the first week of the symptom onset and declining over time with recovery. It contains SARS-CoV-2 in cellular and acellular fractions, to which crevicular fluids and shed keratinized and non-keratinized epithelial cells from the gingiva contribute. The suprabasal mucosal cells, as mentioned above, demonstrate expression of the virus entry factors and evidence of SARS-CoV-2 infection. Those cells are shed from the most terminally differentiated mucosa tissue layers about every 3 h, and may mediate virus transmission (but also the shedding can be postulated as a potential local protective mechanism from oral tissue infection). Those cells were able to transmit the virus to Vero cells (cell line derived from monkey kidney epithelial cells) ex vivo.

Not only the infected cells but also cell-free oral fluid can constitute the SARS-CoV-2 infectious medium. The viral particles from supernatants of cultures showing the virus cytopathic effect were able to demonstrate infectious potential in new cell monolayers. Those findings reveal the infectious SARS-CoV-2 potential of oral fluids, as expelled oral droplets containing infectious virus and infected cells, even from asymptomatic/pre-symptomatic subjects being a source of airborne transmission. However, these in vitro and ex vivo findings on the SARS-CoV-2 infectivity of oral fluids, mainly saliva, are still to be confirmed in vivo.

Public health recommendations, such as full-face mask (oronasal) use and social distancing reduce aerosol droplet transmission. The oronasal masks demonstrate a more than 10-fold decrease in expelled droplets, including asymptomatic individuals with positive nasopharyngeal or saliva viral load.

Dental practitioners are additionally exposed to other SARS-CoV-2 infectious material during routine oral cavity/periodontal-related procedures. The SARS-CoV-2 entry and transmission factors were evidenced in the periodontium, pulp tissues and...
periapical lesions (periapical abscesses, preapical granulomas, and radicular cysts) as well as crevicular fluid and dental biofilm. Therefore, the risk for infection for the dental practitioners may be expected during the dental procedures, including periodontal interventions, in patients with SARS-CoV-2 infection. In fact, aerosol-generating procedures, for example, prophylaxis with ultrasonic scaler and polishing or periodontal treatment with ultrasonic scaler, are enumerated among SARS-CoV-high-risk procedures. A special preventive procedure should be implemented to prevent the spread of disease during oral cavity-related procedures, also in the periodontal area.

7 | PERIODONTAL HEALTHCARE IN COVID-19

The periodontium infection by SARS-CoV-2 may initiate local inflammation, which can promote periodontal pathologies. Aspiration of oral secretions associated with periodontal disease (containing microorganisms such as P. gingivalis, F. nucleatum, P. intermedia) potentially can produce contamination of lower airways and infection. Likewise, cytokines (e.g. IL-1β and TNF-α) from periodontally diseased tissues can infiltrate saliva and be aspirated, and thus cause inflammation or infection within the lungs. Therefore, adequate oral hygiene could reduce the inter-bacterial exchanges between the lungs and the mouth, decreasing the risk of respiratory infections and potentially post-viral bacterial complications. Reduction of oral inflammation can also contribute to better SARS-CoV-2 infection control affecting favourable microenvironment in periodontal pockets, and reduce cellular entry of the virus (see above). Likewise, poor oral hygiene results in the formation of niches, which retain the virus (see above), being possible sites of favourable virus retention. A tight oral hygiene control may reduce viral particle load in the oral cavity/periodontium. In fact, preliminary clinical observations suggest that improvement of oral care can decrease the time of oral viral shedding.

There is also some evidence from clinical studies that application of oral antiseptics could support elimination of SARS-CoV-2 from the oral cavity. Povidone-iodine, hydrogen peroxide and cetylpyridinium chloride are the most recommended oral antiseptics against SARS-CoV-2. These agents were shown to decrease viral load in saliva for up to 2-3 h post mouthwash in up to 50% of Covid-19 patients. Based on the evidence collected so far, it may advisable to use antiseptics, especially prior to the oral examination/treatment, that is, 0.2% povidone-iodine, 0.05%-0.07% cetylpyridinium chloride or 1% hydrogen peroxide. Likewise to antiseptics, general ingredients of toothpastes and mouthwashes might be able to affect the SARS-CoV-2 spike protein interaction with ACE2 and TMPRSS2 protease activity. In vitro assays detected inhibitory effects of sodium tetradeccene sulphonate, sodium N-lauroyl-N-methyltaurate, sodium N-lauroylsarcosinate, sodium dodecyl sulphate and copper gluconate on the interaction between receptor-binding domain of spike protein and ACE2. Molecular docking simulations revealed that these agents could bind to inhibitor-binding sites of ACE2. Sodium tetradecene sulphonate, sodium N-lauroyl-N-methyltaurate, sodium N-lauroylsarcosinate, sodium dodecyl sulphate and copper gluconate and tranexamic acid produced also inhibitory effects against the serine protease activity of TMPRSS2. Thus, oral hygiene with commonly available toothpastes and mouthwashes might be useful in prevention of SARS-CoV-2 infection and interfere with Covid-19 complications development and improve the disease course.

8 | CONCLUSIONS

The available information demonstrates that the selected periodontal tissues, keratinized and non-keratinized gingiva, possess SARS-CoV-2 entry and transmission factors, among them ACE2 and TMPRSS2, which are the principal mediators of the virus cell invasion. Clinical observations confirm the presence of the virus RNA in periodontal structures suggesting that the periodontium may act as an entry point for the virus or as a dissemination site from the systemic circulation into the periodontium. The SARS-CoV-2 RNA presence in crevicular fluid suggests that the periodontium constitutes the virus infection site. However, it remains to be established whether it is only the virus residence site or might contribute to SARS-CoV-2 further transmission. However, there is also evidence that the viral RNA does not necessarily correlate with the presence of culturable and viable viruses, but preliminary observations prove infection potential of gingival crevicular fluid and shed epithelial cells from the periodontium.

Periodontal pathologies, especially periodontitis, could impact SARS-CoV-2 infection. Periodontitis can promote local infection and spread of the virus and vice versa local SARS-CoV-2 effects within the periodontium may favour development of periodontal pathologies. However, the latter phenomenon requires further studies. Implementation of periodontal health control and treatment might prevent the virus attachment, internalization and local replication in the periodontium as well as impact progression of Covid-19. Further efforts should be directed to verify and establish a local pharmacotherapeutic approach targeting SARS-CoV-2 in the oral cavity. Immunization of dental professionals is "strongly" encouraged by dental societies (e.g. American Dental Association), and was demonstrated to reduce the risk of SARS-CoV-2 infection in health care workers. However, it is not known how vaccination against SARS-CoV-2 affects periodontal status in health and disease. It can be assumed that vaccination triggers immune system responses, which more efficiently control the virus infection, reduces local inflammatory processes in gingival tissues and thus contribute to periodontal disease prevention.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest in this study.

DATA AVAILABILITY STATEMENT

The manuscript does not contain original data to be shared.
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