Review Article

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Angiogenic switch is a potential step in the pathogenesis of COVID-Mouth via an interaction with ACE2/Furin receptors: Review Article

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Abstract

The current threats of coronavirus mainly cause respiratory infections in addition to their multi-system exposure potential including severe and distressing oral problems. In view of the rising documented oral lesions of COVID-19, this article aims to assess the underlying etiology of oral complications. An extensive literature search was conducted in PubMed library, Web of Science, and Google Scholar. Studies published in English language literature only were included. 36 articles were included in this review report, oral lesions in patients with COVID-19 were classified according to their putative etiologies. Among the common oral complications, ulcerative-erosive lesions, vesiclo-bollous eruptions, COVID tongue, maculo-papular plaques, pigmentation, bad smell, petechial eruptions, swelling, erythema, and spontaneous bleeding. Poor oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and a hyper-inflammatory response due to COVID-19 are the main playing factors for the establishment of oral complications. However, due to the interaction with Angiotensin Converting Enzyme 2 and Furin receptors, SARS-CoV-2 has a direct effect on oral mucosal tissues. Angiogenic switch is another step which has a basic impact in the pathogenesis of COVID-Mouth. Therefore, an angiogenesis mediated gate is proposed for deeper future investigations and targeted therapy to overcome the evolution of oral complications in COVID-19-affected cases, with their psychological and medical distressing impact on the patient's quality of life.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-chain RNA virus that leads coronavirus disease - 2019 (COVID-19) (1). It contains four subtypes, α- and β-viruses that cause infection in human being, in addition to gamma- and delta-viruses, which are only associated with animal infection (2).

The disease is generally expressed as headache, hyper-thermia, sore throat, dry cough and dyspnea. In addition to some gastrointestinal tract (GIT) symptoms like colic, vomiting and diarrhea (1), dysosmia, and dysgeusia (3).

Severe COVID19 infection triggers severely uncontrolled cytokine response known as a cytokine storm, endothelial inflammatory reactions and vascular system thrombi. These systemic complications may lead to the development of acute respiratory distress syndrome (ARDS), a major cause of death of COVID-19 patients. In view of COVID-19 patient, the higher risk of cardiac problems is noticed among patients with previous cardiovascular affection (4), these findings have driven various theories regarding the potentiality of COVID-19 on the circulatory system.

Despite the fact that SARS-CoV-2 may be found in salivary secretions (5), the pathways of infection are unknown, and nothing is clearly defined about the molecular pathogenic processes of disease propagation via the oral tissues. All of these points to COVID-19 having a direct effect on the oral mucosa. The exact mechanism behind such oral symptoms is yet to be fully elucidated and some studies are suggesting the possibility of direct SARS-CoV-2 infection of oral keratinocytes in addition to secondary effects of the systemic infection and related treatment.

Nonetheless, further clinical data and study are needed to validate SARS-potential CoV-2's to infect oral tissues and to fully comprehend the pathogenic processes at work in the oral mucosa. As a result, the current research was written with a main goal in mind: to clarify the probable pathophysiology of these lesions for deeper future investigations and targeted therapy to overcome the evolution of oral complications in COVID-19-affected cases, with their psychological and medical distressing impact on the patient's quality of life.

Methods

The authors used PubMed library, Web of Science, and Google Scholar to search for publications on oral manifestations in COVID-19 cases. Inclusion criteria encompassed studies reporting oral lesions in patients with PCR-confirmed COVID-19 diagnosis. In studies of mucocutaneous lesions in COVID-19, only cases with oral involvement were included. The following keywords were used: "COVID-19" or "SARS-CoV-2" or "coronavirus disease 2019" and "oral manifestations". The search process included articles from March 2020, to August 2021; a total of 198 records were selected. Finally, 36 articles were chosen after deletion of non-English literature and opinion articles. The primary outcome of interest was the prevalence of oral manifestations of COVID-19. Observational studies, including prevalence studies, case series, and case reports, were included in the review. Oral lesions in patients with COVID-19 were classified according to their putative etiologies, e.g.,: oral manifestations caused by SARS-CoV-2 infection, opportunistic co-infections, and iatrogenic lesions. For oral manifestations caused by SARS-CoV-2 infection, relevant data on patient and disease characteristics and oral manifestations were summarized and discussed.

Angiotensin-Converting Enzyme 2 (ACE2) expression in normal oral mucosa

The lock and key pattern was applied to delineate the triggering of a receptor by certain molecules that act as the only keys for this receptor. The angiotensin-converting enzyme 2 (ACE2) receptor is likely to be the receptor (lock) for the COVID-19 virus (key) according to a recent research (6). The ACE2 receptor is a well-known target for blood pressure regulation. Results of the ongoing research show that coronavirus occupies human cells via ACE2, through scRNA-seq data analyses (7). Herein, the virus will be attached to ACE2 using the spike-like protein located on its surface, and ACE2 will serve as a cellular gate for viral entrance into the cell to produce infection (8). ACE 2 receptor is located in various organs and tissues including; the kidney, liver, lung, sweat glands and GIT. Lately, COVID-19 has been isolated from saliva of infected patients (5) and it has been also stated that reverse transcriptase-polymerase chain reaction (RT-PCR) in saliva is a more sensitive test when compared to nasopharyngeal approach (1).

ACE2 as target molecule for corona-viruses into human target cells

Corona-viruses are basically structured of four proteins; Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N). Spike is a triple-monomer part that regulates the virus's variety and host tropism, as well as mediating the viral binding to superficial-specific receptors on host cells and the viral fusion, as well (9). SARS-CoV-2 is a member of coronavirus genus, according to recent study, and it is thought to interact with ACE2 located outside on human cells via Spike protein. As such, it can infect the human respiratory system (10). ACE2 was therefore recognized as the primary gate for SARS-CoV-2 penetration into the human cells (6, 11).

ACE2 is distinctly indicated in the epithelial cells of the respiratory tract, especially in the lung tissue, as well as in macrophage cells and alveolar monocytes (12). ACE2 is also excessively expressed by different cells, such as intestinal mucosal cells, vascular endothelial cells, heart cells, epithelial cells of the renal tubules, kidneys, immune cells and cerebral and neuronal cells, which are vulnerable to coronavirus infections, as well.

On top of that, ACE2 has been discovered in oral mucosal tissues, with higher densities on the dorsal tongue surface and salivary glands than what was noted in buccal or palate mucosa (1). As a result, cells harboring ACE2 receptor can become the viral host cells involved in causing inflammation in associated tissues like; tongue mucosa and salivary glands (6, 13). The interaction of SARS-CoV-2 with ACE2 receptors was also counted to reduce taste bud sensitivity; a finding that can explain the abnormal gustatory responses linked to the oral cavity complications in COVID-19-infection (14).

Furin: its role as a receptor of SARS-CoV-2 and in viral fusion with host cells

Furin is a co-manifested membrane endopeptidase of the ACE2 receptor, it is a kind of pro-protein convertase that is triggered by acid pH and is found in the trans-Golgi network. Furin may break precursor proteins with certain motifs to create biologically active mature proteins. Furin has the ability to particularly break the glycoprotein of the viral envelop, improving viral fusion with host cell membranes (15). Herein, the Furin enzyme might activate the particular location of SARS-spike CoV-2's protein, according to genomic analysis. Meanwhile, Li et al. (16) discovered that a possible Furin cleavage site in CoV-2's-spike-protein aids virus–cell fusion.

In COVID-19-infection model, the presence of Furin cleavage site resulted in unique clinical signs (17). Furin was also shown to be expressed in the target organs of the virus such as the cardiovascular system, lung organ, nose and various GIT-sites; according to a recent single-cell sequencing data inspection (16).

Furin protein has been recently discovered to be strongly expressed in normal oral mucosa in variable presentation, with a remarkable concentration of Furin-expressing cells in the labial, lingual, and gingival tissues (18). As a result, the expression and location of ACE2 and Furin in the oral mucosal tissues may share a key part in coronavirus invasion of host cells.

Oral manifestations in COVID-19 patients

ACE2 receptors have been discovered in oral mucosa, with a particularly high concentration on the dorsal side of the lingual mucosa and salivary glands (1). The most frequent oral manifestation linked with COVID-19 is dysgeusia, with rates ranging from 5.6 %. A direct association between taste disorder symptoms and COVID-19 was recently reported (19), especially with less severe cases as compared with more severe ones.

The expression mode of ACE2 and Furin (Figure 1) in oral epithelial cells in both mRNA and protein levels revealed that tongue has shown a remarkable expression of ACE2 and

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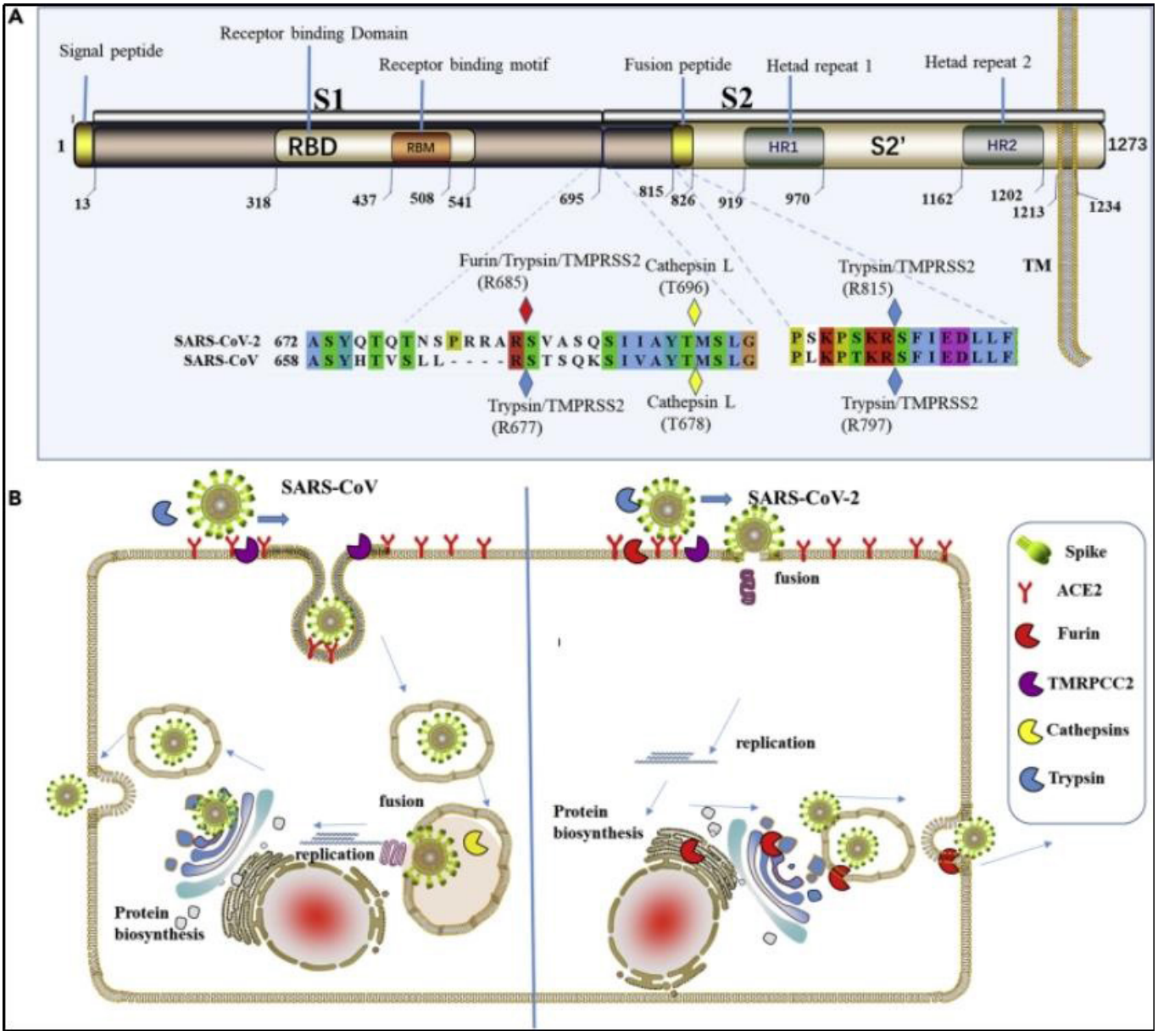
Furin, compared with other oral anatomical sites. This finding explains why the tongue is highly susceptible to COVID-19-invasion (18).

Figure legends:

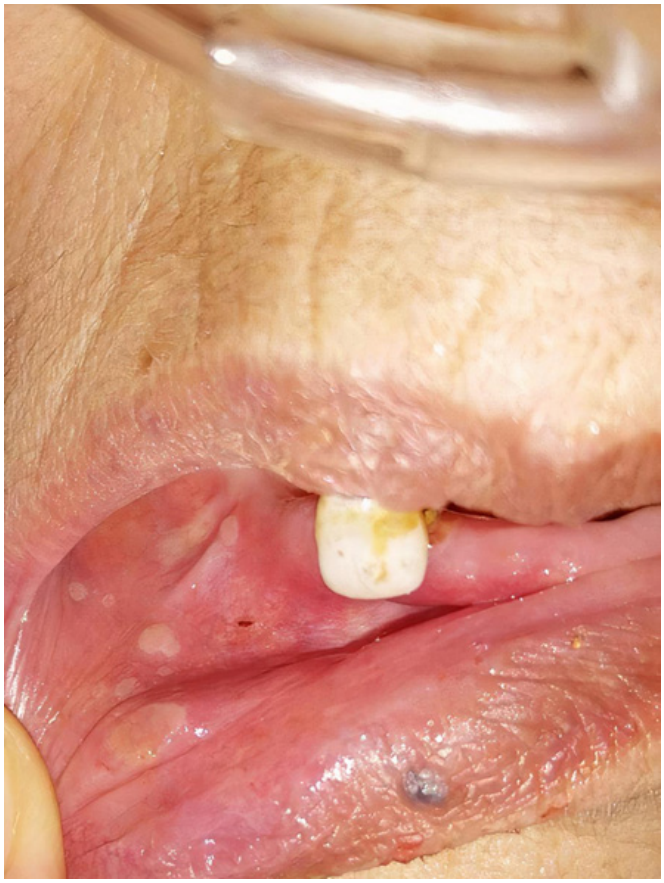
Figure (1): Analysis of SARS-CoV-2 Spike Protein and Its Membrane Fusion Mode (18).
(A) Sequence analysis of Spike protein in SARS-CoV-2. It contains an N-terminal signal peptide, S1 and S2. S1 contains N-terminal domain and receptor-binding region. S2 is mainly responsible for membrane fusion. The C-terminal region of S2 is S2', and it contains a fusion peptide, HR1, HR2, and a transmembrane domain. The amino acid sequence numbers of every domain are annotated below them. Cleavage sites contained in SARS-CoV and SARS-CoV-2 are marked by rhombus.
(B) A schematic diagram of the process of SARS-CoV and SARS-CoV-2-infecting host cells. Those proteases are presented by sector in different colors. Furin can cleave Spike in the process of viral maturation.



Oral ulcerative lesions have been recognized (Figure 2) as a primary sign of COVID-19-oral-infection. Aphthous-like lesions are commonly encountered in COVID-19 patients, and they usually appear as numerous shallow ulcers outlined by erythematous

inflammatory borders. Lesions are covered with yellow-white pseudo-membranes, and located on both the non-keratinized and keratinized mucosal tissues. A positive history of recurrent aphthous stomatitis (RAS) and herpes simplex viral infection were found in some instances (20, 21). Aphthous-like oral lesions (with no necrosis) were more prevalent in younger patients with mild grade infection, whereas necrotic aphthous like lesions with hemorrhagic crusts were commonly encountered in immune-suppressed elderly cases with severe forms of infection.

Figure (2): This female patient (62 years old) had these oral ulcers after 9 days of the onset of COVID-19 infection. The ulcers were very painful, located in her right side of the lower buccal vestibule.



In COVID-19 patients, higher levels of tumour necrosis factor (TNF) were found, which is a cause for worry. As a result of this discovery, neutrophils may be drawn to the oral mucosa and aphthous sores may occur. In addition, stresses and immune-suppression caused by COVID-19 viral infection are proposed factors in the progress of these lesions (21). It is noteworthy to mention that a direct relation was reported between the improvement of oral lesions and the clinical retraction of the systemic disease severity; the lesions usually heal within 5 to 15 days (22).

COVID-19 patients frequently experienced ulcerative or erosive lesions. Lesions emerged as painful ulcers with uneven boundaries on variable sites of the oral mucosa. After a 4 to 7-day latency period, lesions formed. The ulcers emerged 3 days prior to the beginning of systemic manifestations in one case and faded 5 to 21 days afterwards. Although the specific cause is unknown, some variables are thought to have a role in the evolution of such ulcerative oral lesions, such as 1) vasculitis, 2) thrombotic vasculopathy related to COVID-19, or 3) NSAID drug eruption. Ibuprofen consumption was also linked to an increase in ACE2 expression (23). Given that ACE2 was mainly detected in epithelial cells of the oral cavity (24), NSAIDs are proposed to directly help in the dissemination of SARS-CoV-2 infection of the oral cavity, for future research.

Moreover, stresses and immune-suppression related to COVID-19 viral infection was the advocated causes for emergence of secondary herpetic mucosal lesions (21, 25), which may precede, coexist, or follow the systemic disease manifestations. Herpetiform lesions usually appear, on both the non-keratinized and keratinized mucosa; as unilateral, painful, round yellowish-gray painful ulcers with a red halo. Cases of erythema multiform (EM) have been documented in COVID-19 individuals following the pandemic. Other researchers reported similar cases in which mucocutaneous lesions appeared before the classic COVID-19 viral manifestations (26). Clinically, oral lesions typically appear as bullae, extensive atrophic/erosive lesions with bloody crust, erythematous macules, in addition to cutaneous target lesions (25). COVID-19 instances with angina bullosa-like lesions were also confirmed. Lingual and palatal lesions are usually manifested as asymptomatic erythematous blisters.

COVID-19 has been linked to a condition known as burning tongue (Burning Mouth Syndrome). As palmoplantarerythrodysesthesia has been documented in some cases, these symptoms might have a neurological cause (27). Dry mouth is also quite prevalent, and it's thought to be connected to the virus's attaching to ACE-2 receptors on salivary glands, which causes the glands to die (28). COVID tongue (**Figure 3**) is a more recently discovered oral symptom that is more common in SARS-CoV-2 patients (29). The tongue is characterised by lumps, edema, and inflammation. It might be induced by the virus attaching directly to the tongue receptors of ACE-2.

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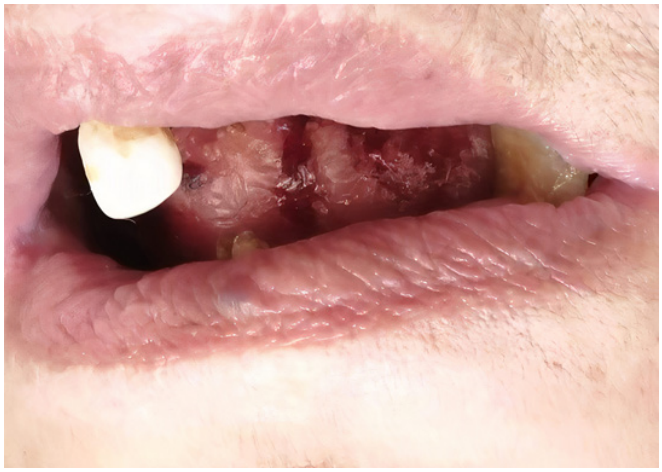
Figure (3): This female patient (62 years old) had very painful ulcerative tongue which emerged after 8 days of the onset of COVID-19 infection. The case is COVID-19 Tongue, it was resistant to treatment and remains for about 16 days in this case with very slow healing process. The patient suffered from severe disability and difficult eating and talking.



There have also been cases of COVID-19 patients developing new-onset halitosis. Patients reported elevated levels sulphur-compound during the active stage of infection and then, normal levels were attained with the systemic improvement, according to a halimeter. The authors considered that viral-mediated changes can primarily affect the oral mucosa or certain secondary changes might act as a result of the reduced salivary flow as probable causes (30).

Extensive oral inflammatory lesions, erythematous macules, patches, papules and plaques in oro-pharyngeal mucosal tissues were also reported. Although the exact mechanism of oral mucositis (OM) is not clearly defined, certain mucosal changes may occur secondary to COVID-19 infection, and are proposed as involved causes like; hypersensitivity, thrombotic vasculopathy, and vasculitis, in addition to immune dysregulation (31).

The interaction between ACE2-/Furin-receptors in COVID-19 oral complications

In regards to oral involvement, tongue is the most commonly affected tissue (38%) followed by labial mucosa (26%), palatal mucosa (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%) and tonsil as the least affected tissue (1%) (20). As previously reported, the mucosal expressed-ACE2 receptor and Furin viral-cleavage site are the main arms involved in COVID-19-penetration into host tissues (24).

In terms of participation sites, oral tissues from various locations were recently examined for Furin expression using the scRNA-seq approach (18). The scientists found a substantial number of Furin-stained cells in the spinous layer of all studied tissues. Furin-positive cells were also found in larger numbers in the tongue, lip and gingiva than in the buccal mucosa and palate.

Similarly, the authors found that ACE2 expression was much greater in the basal cell layer in the lip tissue, tongue, and buccal mucosa, with faint positive ACE2 staining in the gingiva and palate epithelial cells. Collectively, the oral epithelial cells are considered as the probable targets of COVID-19-viral infection (5, 18), and also explain the high association with certain sites of involvement. Curiously, it was stated that Furin splits S1/S2 site during the process of S protein transfer and virus assembly. Moreover, a probable Furin cleavage site was confirmed at the S1/S2 interface of SARS-CoV-2, which is absent in the S protein of SARS-CoV (32). A fact that explain the more infective potentiality of SARS-CoV-2, and confirm the role of Furin expression in viral fusion to the host cells.

DISCUSSION

The oral cavity is a mirror that reflects the basic health problem. Because COVID-19 patients' dental health might be damaged by the infection, it's still unclear if the symptoms are a normal pattern arising from the direct viral infection or a systemic deterioration, given the risk of opportunistic infections and treatment-related side effects. As a result, the variety of oral complications in COVID-19 greatly attracted people's curiosity.

In this respect, Ma et al. (33) used online single-cell sequencing datasets to study the expression of the main receptor in host cells that facilitates viral entry to corroborate the involvement of ACE2 and its co-expressed membrane endopeptidases. Their findings suggested that differential expression of two members of the disintegrin and metalloproteinase (ADAM) family of proteases (ADAM10) and (ADAM17) might influence ACE2 shedding and membrane ACE2 abundance. They also confirm a possible Furin-cleavage site previously discovered in the SARS-CoV-2 spike protein, which may aid virus-cell fusion. As a result, the distribution pattern of ACE2 and Furin expression in the oral epithelium is crucial for coronavirus penetration of host cells 18); these findings also settle the conflict about the direct role of COVID-19 in oral manifestations.

Furthermore, it was reported that the severe COVID-19

infection is involved in triggering imbalanced and uncontrolled cytokine response (called cytokine storm), exuberant endothelial inflammatory reactions, and vascular thrombosis. The pathological changes in affected tissues are probably triggered by an imbalanced host reaction to the infection, e.g., excessive activation of immune and endothelial cells, and platelets (34). Most likely, oxidative stress accompanying cell activation may profoundly impact COVID-19 pathogenesis.

Chronic oxidative stress (OS) affects virtually all patients with viral infections, affecting disease pathogenesis such as compromised immunological functioning, apoptosis, inflammatory response, and organ and tissue malfunction (35). In this respect, OM was primarily reported to be initiated by OS, and the formation of reactive oxygen species (ROS) in response to somatotoxic doses of non-surgical oncologic treatment (36).

This conclusion was recently used to support the results of (37) about OM in COVID-19 patients. The authors reported that the increased formation of ROS in the mucosal tissues of the severely affected cases can elucidate the direct relation between the severity of COVID-19 in one hand and the extent time of OM and pain potency on the other hand.

Overall, virtually all patients with viral infections are affected by chronic oxidative stress impacting the disease pathogenesis including impaired immune functions, apoptosis, inflammatory response, as well as organ and tissue dysfunction. At the same time, ROS induced by viral infection should not be considered solely as harmful agents, because ROS are necessary for eradicating viruses phagocytosed by immune cells and also take part in signal transduction between various immune cells (38).

Thus, the adequate response to viral infection must involve strictly maintained redox homeostasis. Its shift towards excessive ROS production results in the development of oxidative stress followed by cell and tissue damage.

An unbalanced host response to infection, such as excessive activation of immune and endothelial cells is likely to cause pathological alterations in organs and tissues (34). In COVID19 instances, OS associated with cell activation may have a significant influence on aetiology and severity of symptoms. SARSCoV2 has been shown to successfully infect monocytes with enhanced production of pro-inflammatory cytokines; interleukin- (IL-1, IL-6 and TNF) (39). Subsequently, endothelial cells release adhesion molecules (ICAM1, VCAM1, E-selectin) on their surfaces which aid in the leukocyte adherence and penetration through the arterial wall into bodily tissues, followed by damage during infection. Hence, the release of pro-inflammatory cytokines and chemokines can recruit immune cells which produce free radicals while fighting off invading germs. These free radicals can destroy healthy cells and mediate inflammation within the oral mucosa leading to their destruction

Interaction of AGE2 and Furin has an impact on hypoxia-induced angiogenesis

The release of pro-inflammatory cytokines, along with the increased energy needs of activated invading immune cells and inflamed resident cells, causes hypoxia and mitochondrial dysfunction. Surprisingly, in hypoxic circumstances, the expression of Vascular Endothelial Growth Factor (VEGF) is up-regulated in macrophages and endothelial cells due to the increased ROS during oxidative stress. Following IL-6 exposure, VEGF was observed to be expressed at a greater level (40).

Angiotensin II also stimulates VEGF release by the wall of vascular smooth muscle cells (41). Similarly, it was discovered that pulmonary angiogenesis was enhanced by 2.7 times during COVID-19 (42). It's worth noting that the stimulated intussusceptive angiogenesis seen in normal development, wound healing, and a variety of pathological situations might be a plausible explanation for this phenomena, as reported by De Spiegelaere et al., (43). Of note, Chen et al. (44) further discovered that the infusion of endothelial progenitor cells overexpressing ACE2 promotes angiogenesis in experimental animals.

Taking into consideration that the cells expressing ACE2 are targeted by COVID-19 viral infection (7, 35) including oral mucosal tissues, ACE2 receptor-mediated hypoxic action can therefore be proposed to have a significant role in promoting angiogenesis, and increasing the severity of oral manifestations in COVID-19 infected persons via the up-regulation of VEGF. Hypoxia is also involved in angiogenesis through the activation of Hypoxia-Inducible Factor-1 (HIF-1α), induced by ROS, resulting in VEGF upregulation (45).

By-products of ROS such as lipid peroxide can interact with VEGFR2 and induce angiogenesis in vivo. Notably, the expression of Furin is markedly promoted by hypoxia, as all the Furin inducers harbour binding sites for HIF-1 (46). Furin deficiency in myeloid cells was also mentioned as a leading

factor to impaired angiogenesis (47). In this aspect, a tumor has to initiate angiogenesis to grow; a step in tumorigenesis that is known as angiogenic switch. Furin activity has been shown to promote tumor vascularization and angiogenesis (48).

Stimulation of vessel neoformation is dependent on secretion of pro-angiogenic growth factors like VEGF-C and VEGF-D, both of which require processing through furin or furin-like proprotein convertases (PCs) to stimulate VEGF signaling and angiogenesis. Likewise, secretion of mature Platelet Derived Growth Factor (PDGF)-BB favors tumor angiogenesis through paracrine stimulation of PDGF receptor-β, which is located on endothelial cells, leading to proliferation, migration and sprouting (49).

Hence, decreased VEGF-C and PDGF-BB processing is likely responsible for reduced microvessel density in vivo, and delayed the angiogenic switch. The authors suggested (44) that the delay in initial tumor growth with reduced furin activity may be attributed to impaired furin substrate processing.

Accordingly, a direct relation between the oral complications of COVID19 cases and angiogenesis is similarly suggested via Furin activity which has been found to be responsible for the activation of various matrix metalloprotienases (50). This last mentioned finding might further explain the ability of Furin enzyme on activating the particular location of SARS-spike CoV-2's protein (51), an integral step for the viral invasion and fusion to tissues.

Yet, immunosuppression and poor oral hygiene led to secondary manifestations like enanthematous and fungal lesions (52). In addition, with the continuation of the global vaccination campaign, the incidence of oral adverse effects will inevitably increase. Adverse events are increasingly being reported with the growing vaccination rate regardless of vaccine type (53). Clinicians should be therefore able to recognize and understand the possible oral complications following COVID-19 for accurate diagnosis and precise treatment.

Numerous reviews have addressed the question of oral manifestations in patients with COVID-19, however, no common consent has been reached regarding the classification of the oral lesions in COVID-19 and their causative relationship with the diseases process. In this aspect, the oral complications following COVID-19 can be categorized as following: directly related to viral invasion (8), secondary complications due to the steroid therapy, or following COVID-19 vaccination.

These three categories of lesions are better and respectively named and managed as follows; i) COVID-Mouth "This category should be targeted using immunmodulatory therapy", ii) Cov-Steroid-Mouth "For this category, anti-fungal therapy and hygiene are the corner stone", and iii) Cov-Vaccine-Mouth "The emerging symptoms were generally mild and responded well to conventional treatment (53)".

Eventually, the features reported in COVID-Mouth are a prime consequent of ACE2 and Furin receptors via their dual action. First: a direct role is played via their unique expression in endothelium and gastrointestinal mucosa; Second: An indirect role is suggested via the hypoxia-driven angiogenic mechanism which can be advocated in the pathogenesis of COVID-19 induced pathological and inflammatory oral changes. These notes may in turn elucidate the intimate association between the expression of these two receptors, and the pronounced pathological tissue changes, for further investigations.

Ultimately, the present review reflects certain limitations. COVID-19 is a rapidly spreading disease and many of its related features, including the oral manifestations, are still under examination. As yet, no consensus has been reached regarding the exact nature of the oral lesions in COVID-19, and this limitation may affect the conclusive data regarding etiologic classification of oral lesions and treatment, especially with the various mutations expected in COVID-19.

Findings in conclusion

Deranged cell to cell connections, swelling, and missing interactions with the basement membrane were among the endothelial damage caused by COVID19 infection. Our study identifies the role of ACE2 and Furin activity in the oral inflammatory changes leading to COVID19-Mouth. Angiogenesis appears to be a consequence of COVID19-induced inflammatory endothelium damage and hypoxia inside endothelial tissues. Increased ACE2 and Furin levels may play a role in increased angiogenesis via adjustable expression after viral-mediated inhibition of enzymatic function; which is mediated by proteolytic activation of key substrates involved in proliferation, but further research is warranted to affirm this speculation. AGE2 and Furin-like proteases, might be valuable therapeutic targets for anti-COVID-19 therapy.

Antioxidants appear also to be a promising strategy for reducing oxidative stress and its associated consequences in viral infections. It's also possible that, in addition to the anti-cytokine therapy commonly employed in COVID19 treatment, medicines that inhibit VEGF and related signaling pathways might be of therapeutic relevance. Clinical trials are necessary to confirm the aforementioned proposed mechanisms and to reveal therapeutic potential for such approach.

Conflicts of interest

No conflict of interest is declared by the authors.

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