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THE ORAL CAVITY MAY BE VULNERABLE TO SARS COV - 2 ENTRY DUE TO CERTAIN PHYSIOLOGICAL FACTORS AND PATHOLOGICAL CONDITIONS

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ABSTRACT

The coronavirus disease COVID19 has caused a public emergency by affecting the routine life of individuals, high death rate and anxiety. The disease is caused by the novel coronavirus also referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The common clinical manifestations are pyrexia, myalgia and dyspnea. Considering the oral manifestations there is still doubt and dispute among clinicians whether the same is primary or secondary. However, the oral cavity could be a portal of entry of the virus that could be attributed to the anatomy of the mouth and associated tissues. With the available information we hypothesize how the oral cavity could be congenial to SARS-CoV-2entry in both physiological and pathological states.

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported in the city of Wuhan, Hubei Province, Central China, and has then created havoc, spreading to many developing and developed nations of the world. COVID-19 is caused by a novel coronavirus also referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Considering the mammoth destruction caused by the disease, the World Health Organization (WHO) has announced COVID-19 as a public health emergency of international concern (PHEIC). Currently, scores of humans are being afflicted by this disease which causes severe respiratory distress and multi-organ failure in a few leading to severe morbidity and mortality. Social distancing has been followed worldwide to prevent disease spread as this condition is predominantly spread by droplet transmission.

Coronaviruses (CoVs) are a group of viruses belonging to the family Coronaviridae, subfamily Orthocoronavirinae, order Nidovirales Among the four genera in Orthocoronavirinae, Alphacoronavirus (α-CoV) and Betacoronavirus (β-CoV) are the two genera that can affect mammals and humans. [1,2] SARS-CoV-2, the 7th member of the coronavirus family that has been found to infect humans. HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 are the human coronaviruses that cause infections of the upper respiratory system, and SARS-CoV 2 and MERS-CoV cause atypical pneumonia. An insight into the virological aspects of the disease reveals that the SARS-CoV-2 genome is 30 kb in size encoding, ORF1a/b a big non-structural polyprotein that produces 15/16 proteins, 4 structural proteins that are required for assembly and infection namely the spike surface glycoprotein(S), the membrane protein(M), the envelope protein (E) and the nucleocapsid protein (N) and 5 other accessory proteins. (ORF3a, ORF6, ORF7, ORF8, and ORF9). [3,4,5] The (S) protein is required for host cell attachment which on cleavage by proteases from the host cell produces an N-terminal S1 subunit and a membrane-bound C-terminal S2 subunit. [6] The S1 subunit binds to the receptor present in the host cell and causes the destabilization of the prefusion trimer. This causes shedding and transition to a stable post-fusion conformation of S1 and S2 subunit respectively. [7] Dipeptidyl peptidase 4 (DPP4)

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and angiotensin-converting enzyme 2 (ACE2) present and expressed in the lower respiratory tract serve as receptors for the (S) glycoprotein of MERS-CoV and SARS-CoV, respectively which could be attributed as the specific infection sites of the coronaviruses.[8-10] Upon entry into alveolar epithelial cells, SARS-CoV-2 replicates rapidly and triggers a strong immune response, resulting in cytokine storm which is an aberrant phenomenon of excessive cytokine release and pulmonary tissue damage which finally could also result in multiorgan failure and death.

The Oral Cavity as a Portal of Entry of the SARS Cov 2 Virus

The common transmission routes of novel coronavirus include direct transmission (cough, sneeze, and droplet inhalation transmission) and contact transmission (contact with oral, nasal, and eye mucous membranes).

There have been some COVID-19 cases reporting oral manifestations. [11-12] There is still doubt and dispute among clinicians in this regard to ascertain whether these manifestations could be a typical pattern resulting from the direct viral infection of the mouth or whether the oral changes are secondary manifestations of the systemic infection.

However, beyond dispute remains the fact that the oral cavity could be considered a portal of entry of the virus considering the anatomical nature of the mouth and associated tissues. The oral cavity also called the oral stoma is composed of several hard and soft tissues with variable anatomic and histologic features. It is well known that the lips, buccal mucosa, floor of the mouth, gingiva, tongue, hard and soft palate form the soft tissue components while the teeth form the hard tissue components. The oral cavity is bathed by saliva which is a composite product of the salivary glands while there is another defense mechanism called the gingival crevicular fluid which also contributes to protection from various diseases. The oral cavity has several defense mechanisms that protect it from diseases and invaders like bacteria, viruses, and fungi. Among these are the beta-defensins produced in the mucosa, [13] alpha-defensins in the saliva [14] produced by the neutrophils which emigrate from the periodontium via the gingival crevice into the oral cavity forming a unique population of orogranulocytes.[15] Saliva and

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gingival crevicular fluid by themselves have a huge number of antibodies such as Ig A, [16] IgG [17,] and a variety of antimicrobial substances such as LL 37, Cathelcidin, kallikrein, lysozymes a few to name which contribute to defense. [18] Also noteworthy is the presence of mast cells and antigen-presenting Langerhans cells [19] in the oral mucosa that helps the body recognize foreign invaders. Despite the presence of all the above- mentioned factors the oral cavity is also afflicted by many pathological conditions. Dental caries, gingivitis, and periodontal disease are the most common oral diseases. Premalignant and malignant lesions of the oral cavity also are frequent and are associated with habits such as tobacco and alcohol use. In the following section, we hypothesize how the oral cavity could be congenial to SARS COV 2 entry in both physiological and pathological states.

Hypothesis

The spike (S) protein of coronaviruses facilitates viral entry into target cells. Entry depends on the binding of the surface unit, S1, of the S protein to a cellular receptor, which facilitates viral attachment to the surface of target cells. The S1 subunit contains a receptor-binding domain (RBD) and devotes to the initial viral attachment via recognizing a variety of host cell receptors, including angiotensin-converting enzyme-2 (ACE2) [20] and dipeptidyl peptidase 4 (DPP4). [21] Also, entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2' site and allows fusion of viral and cellular membranes, a process driven by the S2 subunit. SARS-Cov 2 engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor [20] and employs the cellular serine protease TMPRSS2 for S protein priming. [22] A genetic profiling study has shown the expression of ACE 2 in the buccal mucosa, tongue, gingiva, and the lymphocytes of the oral mucosa of human subjects. [23] This could be a major factor that paves way for SARS Cov 2 entry as the spike glycoprotein of the virus is known to bind to the ACE 2 enzyme. Concerning TMPRSS2, a study has shown moderate co-expression of ACE 2 and the above-mentioned TMPRSS2 in the oral mucosa and salivary glands that increase the potential of SARS Cov 2 entry. [24]

An important family of peptides that promote defense against infectious invaders is defensins. It is well known that beta-defensins

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are highly expressed in oral tissues. Alpha defensins are also called HNPS which are produced by neutrophils. HNP 1,2 and 3 are present in the oral tissues and saliva due to neutrophilic invasion. [14] However human defensin 5 which is also called the Paneth cell type defensin is the subtype of defensin that prevents SARS Cov 2 entry. [25] Also referred to as a lectin-like intestinal defensin, this HD 5 molecule indirectly binds to ACE 2 preventing the binding of the latter to SARS Cov2. A study on the expression of defensins from healthy oral tissue samples has shown absence or reduced expression of HD5 in a minority of samples. This factor could be a reason why the healthy oral mucosa could be an entry point of SARS Cov 2. [26]

Hence from the above-mentioned points, we can hypothesize that the healthy oral tissues are vulnerable to SARS Cov 2 entry due to the presence of viral binding proteins such as ACE 2, TMPRSS 2 and the absence or reduced expression of lectin-like intestinal defensin (HD 5) which protects against SARS Cov 2 entry.

At this point a few other mediators that facilitate SARS Cov 2 infection of host cells need mention. Furin an enzyme of the proprotein convertase family that is responsible for the cleavage and activation of precursor proteins. Furin belongs to the family known as subtilisin-like proprotein convertase. Several tissues demonstrate the expression of this type 1 membrane-bound protease. Interaction of the modified S glycoprotein of the SARS Cov 2 with ACE2, angiotensin I converting enzyme (host receptor for SARS Cov2) is facilitated by furin cleavage of the S glycoprotein into S1 and S2 subunits. [27] The S protein in the SARS-CoV 2 spike also exposes a protease-accessible loop between the S1 and S2 subunits that can be targeted by different enzymes, such as cathepsin L, [28] trypsin, [29] and elastase, [30] and EMMPRIN [31] which can also facilitate cleavage and entry of the virus into the host.

As previously described, diseases of the oral cavity could also pave way for the SARS Cov 2 entry and further infection. Of the diseases that affect the oral cavity, the most common and prevalent are dental caries and periodontal disease.

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Dental Caries as a Predisposing Factor for COVID19

Dental caries or tooth decay is a microbial disease of the teeth caused by bacteria in the dental plaque that cause demineralization and cavitation of the teeth enamel and dentin. The sequelae of untreated dental caries are the exposure of the dental pulp and its inflammation. This further spreads to the apex of the teeth causing apical periodontitis which is a painful oral infection. At this point, we can mention the relevance of this condition to the SARS Cov 2 entry. It could be hypothesized that the infected pulp exposed to the oral environment in these patients could serve as a point of virus entry due to the presence of furin in pulp cells which could facilitate viral entry. [32] Moreover, the presence of periapical pathologies and infection in the teeth further could increase the chances of SARS Cov 2 infection due to the increased expression of EMMPRIN which could facilitate viral entry. [33]

Chronic Periodontitis as a Predisposing Factor for COVID19.

Periodontal disease / Chronic periodontitis is another prevalent oral condition that is initiated and perpetuated by pathogenic bacteria in dental plaque. Initially, there is an inflammation of the gingival tissues following subgingival plaque accumulation which if left untreated progresses to involve the deeper tooth-supporting structures to produce bone destruction. It is noteworthy that immune cells such as neutrophils, monocytes, and lymphocytes mediate the pathogenesis of the periodontal disease. Amongst these immune cells, the monocytes are important as antigen-presenting cells and also exist in subsets namely classical, intermediate, and non-classical. The non-classical monocytes deserve mention as they produce higher levels of cytokines when exposed to an antigenic stimulus. In chronic periodontitis patients, a study has shown a higher proportion of non-classic monocytes in blood and gingival tissues which are proposed to mediate a greater amount of tissue destruction. [34] In addition to this an elevation of EMMPRIN, [35] Cathepsin L [36,] and elastase (neutrophil-derived) [37] in sites undergoing periodontal destruction have been demonstrated by various research studies. Also, a mechanism of furin elevation in periodontal disease has been suggested through the indirect increase in osteopontin.[38] Considering all these factors periodontal disease could be a significant risk

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factor for SARS Cov 2 infection. Moreover, if patients with the periodontal disease develop COVID 19 infection there could be an aggravated systemic impact. It is well understood that the SARS Cov 2 virus could infect the alveolar epithelial cells of the lung and produce severe inflammation causing an aberrant release of cytokines. This is termed as a cytokine storm. The cytokine storm could produce multiorgan failure and death in these subjects if untreated. It is plausible that chronic periodontitis patients if affected by COVID 19 could have a greater impact on the cytokine storm due to increased numbers of non-classic monocytes as discussed earlier. It is also noteworthy that non-classic monocytes retain their destructive phenotype when they transform into tissue macrophages. [39] So, the greater number of non- classical monocytes in blood implicates a greater number of non-classical tissue macrophages in organs such as the lung where destruction occurs in COVID 19. The polymicrobial nature of periodontal disease could also increase the risk of COVID 19 complications. The red complex pathogens comprised of *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola* are one of the major aetiological factors responsible for the tissue and bone destruction noted in chronic periodontitis. [40] These pathogenic bacteria have been reported to enter the systemic circulation causing transient bacteremia following tooth brushing. [41] They have also been identified in vital organs such as the heart in atheromatous plaques where they form vegetations. [42] Aspiration of periodontal pathogens from dental plaque into the respiratory system is a well-established phenomenon. [43] In chronic periodontitis, the periodontal pathogens (red-complex) in the bloodstream or lung tissues augment the potential for platelet aggregation through the release of the enzyme gingipain R which is an arginine specific enzyme. [44] The red-complex pathogens also aid in the conversion of prothrombin to thrombin. [45] COVID-19 patients have also shown to exhibit pro-coagulative features such as platelet aggregation, an increase in clot strength, and hyperfibrinogenemia. [46] Hence, it can be hypothesized that when a patient with chronic periodontitis develops COVID-19, there could be a conglomeration of the above-mentioned coagulative risk factors from both conditions substantially increasing the risk of abnormal coagulopathy and thrombo-embolism.

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Potentially Malignant Disorders and Oral Squamous Cell Carcinoma as Predisposing Factors for COVID19

Another group of diseases that afflict the oral cavity are premalignant lesions like leukoplakia and oral lichen planus and a malignant condition termed oral squamous cell carcinoma or in common words oral cancer. These conditions are known to be associated with the use of tobacco, alcohol, and areca nut. The conversion of oral premalignant conditions into oral cancer is termed as carcinogenesis. Research has found increased expression of EMMPRIN in both oral premalignant cells and oral cancer cells. [47] This explains how patients with these lesions could be more vulnerable to SARS Cov 2entry. Also, sites with oral squamous cell carcinoma have known to abundantly express TMPRSS, [48] Furin [49,] and Cathepsin L [50] which could promote SARS Cov 2 entry.

Conclusion:

With the available background literature, it is evident that the entry-level factors for SARS Cov 2 virus are well established in the mouth. The hypothesis suggested by us highlights the oral cavity in states of health and disease as a vulnerable portal of entry of SARS Cov 2. Oral diseases could also have a systemic impact thereby worsening COVID 19 complications. It has been demonstrated in a previous study that the nose is vulnerable to SARS-CoV-2 entry. [51] The findings of the above-mentioned research highlight the presence of abundant ACE 2 expression in the nasal epithelial cells which could bind the SARS-CoV-2 virus. It is well known that the nasal and oral cavity communicates with each other and with the pharynx. Hence the virus could use both the nose and mouth as entry portals to reach the respiratory system. Given the intercommunication between the 2 portals, viral entry and consequent infection are easily facilitated. The findings of this hypothesis paper highlight the importance of the oral cavity in initiating SARS-CoV-2 infection. The dental fraternity needs to understand this hypothesis as they are a high-risk group of health workers who regularly perform intraoral examination and procedures. Use of proper barrier techniques and an aseptic protocol is highly deemed essential in the COVID 19 pandemic to prevent health workers from getting infected from patients and in turn becoming carriers of the SARS-CoV-2 virus.

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