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COVID 19 AND PATHOGENESIS IN ORAL MANIFASTIONS REVIEW IN LITERATURE

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Abstract. *It is well known that coronavirus COVID-19 comprises a single plus strand of RNA (+ss RNA). SARS-CoV-2 is a β-CoV and mainly infects the respiratory, gastrointestinal and central nerves system of human and mammalians. It is transmitted trough respiratory droplets, aerosols, contact and vomits. Along with these symptoms, this virus can affect other organs including skin, olfactory system and oral cavity. The most common well recognized oral manifestations is dysgeusia leading to alteration of the taste, as a pathognomic symptoms. The reason for the loose of taste of COVID-19 are unknown and questionable. Some have speculated that the increasing number od ACE2 receptors on the tongue receptors keranocytes and association cell death and desquamation may block the taste perceptions. The same in the patients with SARS-CoV-2 (COVID-19) may be attack the mayor and minor salivary gland and the other oral mucosa with different lessons.*

1. INTRODUCTION

Coronaviruses (CoVs) are enveloped viruses with a positive sense RNA genome, that belong to the subfamily *Coronavirinae* within the family *Coronaviridae*, which is part of the *Nidovirales* order. They are classified in four genera (α, β, γ, and δ) and four lineages are recognized within the β-CoV genus (A, B, C and D). CoVs cause a variety of respiratory and enteric diseases in mammalian and avian species. Until recently, CoVs were considered to be pathogens with a largely veterinary relevance but with limited impact on human health [1]. Until recently when global pandemic burden has emerged by the human to human transmissions of a novel corona virus decease Covid-19. The most common symptoms are fever, and dry cough and in some cases shortness of breath dysosmia, and dysgeusia [2].

Current research shows that coronavirus invades human cells via the receptor angiotensin-converting enzyme 2 (ACE2) through scRNA-seq data analyses. The study identified the organs that are at risk and are vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [3]. Therefore, cells with ACE2 receptor distribution may become host cells for the virus and cause inflammatory response in related organs and tissues, such as the tongue mucosa and salivary glands [4,5,6,7,8]. SARS-CoV-2 interaction with ACE2 receptors may also impair taste bud sensitivity, which could induce dysfunctional gustatory responses [9]. Available evidence has not yet established an efficient and safe pharmacologic therapy against COVID-19, and the potential ones are related to several adverse reactions [10].

2. ACE2 AND ITS ANTI-INFLAMMATORY PROPERTIES

The human ACE2 protein is a zinc metallopeptidase, an ectoenzyme (family of dipeptidyl carboxydipeptidase), which contains 805 amino acids. This protein is a type I transmembrane glycoprotein and its expression is ubiq- uitous with a single extracellular catalytic domain that predominantly localizes at the plasma membrane [11, 12].

There are two functional forms of the ACE2 protein. The first form is the full-length ACE2 protein, which con- tains a structural transmembrane domain and spikes its extracellular domain to the plasma membrane. The sec- ond form is the soluble form, which lacks the membrane anchor and circulates in small amounts in the blood. ACE2 has also been shown to regulate cardiovascular functions in brain regions [13]. The soluble form rep- resents the circulating ACE2 blood vessels. ACE2 plays a major role in balancing the levels of Angiotensin II (AngII) and Angiotensin-(1–7) (Ang (1–7) [14].

Angiotensin-converting enzyme (ACE) 2 is a common binding site (“receptor”) for both SARS- CoV and SARS-CoV-2 [15]. The SARS-CoV-2 entry into host cells begins with its viral spike (S) protein binding to the host cell’s surface transmembrane ACE2, followed by a down regulation of membrane ACE2 expression [16]. The normal level of ACE2 is important to protect vital organs; However, as demonstrated in the models of acute lung injury (ALI) and ARDS [17, 18], the abnormal ACE2 levels were suggested to aggravate COVID-19 via the renin-angiotensin system (RAS), including promoting pathological changes in ALI [18] and being involved in inflammatory and fibrotic responses [19]. ACE2 exists in two forms, the full-length transmembrane ACE2 (ACE2) and the soluble ACE2 (sACE2). sACE2 is cleaved from ACE2 by ADAM17 (a disintegrin and metallopeptidase domain 17) and then released into the extracellular environment [20].

ACE2 is the predominant enzyme regulating the ACE2/Ang-(1-7)/Mas receptor (MasR) axis. The functi`on of sACE2 remains unclear. ACE is a close homolog of ACE2 with a 42% identical sequence in the catalytic domains, which function in an opposite manner to ACE for balancing [21]. ACE2 was identified as the binding "receptor" of SARS-CoV and SARS-CoV-2. ACE2 is expressed SARS-CoV-2, ACE2, and multiple organ failure predominantly in the epithelial cells of the lung and intestine, suggesting that these organs may be the primary infected sites of SARS-CoV-2. ACE2 is also present in arterial and venous endothelial cells [22]. These distributions of ACE2 are very likely associated with the characteristics of COVID-19: respiratory failure, colitis, microvascular injury, and inflammation. These data suggested that the intestine might also be an entry site for SARS-CoV-2, and the virus ability to be transmitted via the mouth/food intake is thus worth investigating.

ACE2 is widely expressed in many different cells of the body. In 2002, Harmer et al. [23] studied the expression of ACE2 and found that the mRNA is expressed in 72 different tissues obtained from three human donors. It was observed to be highly expressed in endocrine tis- sues, gastrointestinal tract (e.g. ileum, liver and gallbladder), cardiovascular tissues, kidney and urinary bladder, testes and muscle tissues. It was observed that central nervous system and lymphoid tissues express relatively low ACE2 levels. They found that that the receptor it is not expressed in red blood cells. In the lung, high mRNA ACE2 expression was detected in the parenchyma and in primary and tertiary bronchi. Relevant for the transmission and respiratory manifestations of SARS-CoV-2, ACE-2 positive cells were observed in oral, nasal, and nasopharynx epithelia, and in type I and type II alveolar epithelial cells (AT1 and AT2 cells).

3. ORAL MUSOCA MANIFESTATION

The first remarkable finding was that ACE2 was present in endothelial cells from small and large arteries and veins in all the tissues studied. Moreover, arterial smooth muscle cells were consistently positive for ACE2. Positive staining for ACE2 was also noted in myofibroblasts and the membrane of fat cells in various organs. Furthermore, ACE2 was found at specific sites in each organ as described below[23]. In nasal and oral mucosa and the nasopharynx, the ACE2 expression in the basal layer of the non-keratinizing squamous epithelium is found.

The most common well recognasized oral manifestations of COVID-19 is chemosensory dysfunction, leading to alterations of taste (dysgeusia) either with, or without, olfactory involvement (anosmia). There are now several reports and reviews in the literature on dysgeusia that could be characterized as a pathognomonic symptoms of COVID-19.[24]

Including meta analysis of 31 reports by Dos Santos et al.[25], they noted the global prevalence of taste disorders, 45% of COVID-19 patients, 24% with ageusia, 35% with hypogeusia, 38% dysgeusia. They also found that taste disorders are associated with COVID-19 positively, mild-to-moderate deceases in female sex. Some have evaluated the specific loose of different flavours, in COVID-19 - related dysgeusia, reported 77% with changes in their ability to taste spice, 80% softness, 79% of sourness and 91% for sweetness. However the veracity of these are questionable because they will obtained from a web based questionnaire survey [26]. The reason for the loss of taste in COVID-19 is unclear. Some have speculated that the increasing number of ACE-2 receptors on the tongue keratinocytes and the associated cell death and desquamation may block the taste buds and adversely affect taste perception [27,28]. Whether the dysgeusia is due to direct damage to the taste buds located in the filiform, fungiform and vallate papillae by the SARS-CoV-2 virus is unclear as yet. Dysgeusia is almost always temporary, and normal taste sensation returns by 4–6 weeks after recovery from the acute COVID-19 illness. Additionally, some reports indicate that women experience the condition more than men, although confirmatory evidence is required [29, 30]. Pathohistology for dysgeusia is some what speculative at present.

One contributory reason of dysgeusia or ageusia could be reduction in salivary flow or xserostomia associated with COVID-19. Considering that salivary tissue replayed with ACE2 reception witch are portals of cellular entry for SARS-COV-2 [31]. It is not surprising that salivary gland are profoundly affected by COVID-19, leading to a reduction of the salivary secretion. Other secondary cofactors for COVID-19 induce xserostomia are trough to be impaired nasal breathing due to nasal congestions and or rhinorrhea due to deceases with in term, may induce atheling of oral dryness and sense of xserostomia other apparent of real [32]. Pandemic induced physiological factors and chronic stress maybe contributed to the functionally of salivary glans and quantitative reductions of salivary secretions [33, 34].

Oral manifestations included ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and

spontaneous bleeding. The most common sites of involvement in descending order were tongue (38%), labial mucosa (26%), palate (22%), gingiva (8%), buccal mucosa (5%), oropharynx (4%), and tonsil (1%). Suggested diagnoses of the lesions were aphthous stomatitis, herpetiform lesions, candidiasis, vasculitis, Kawasaki-like, EM-like, mucositis, drug eruption, necrotizing periodontal disease, angina bullosa-like, angular cheilitis, atypical Sweet syndrome, and Melkerson-Rosenthal syndrome. One of the most common oral complications associated with COVID-19 confirmed or suspected individuals is erosion and ulcerative lesen of the oral cavity [34-42].

Tongue (dorsum and lateral boarder) is the most common reported site followed by hard palate and buccal mucosa. Irregular and painful ulcers either appear alone (single ulcers) or in the form of multiple tiny ulcers. Clusters of ulcers either resemble herpetiform ulcers or multiple apthoid ulcers with diffuse erythematous base. These multiple apthoid ulcer later on coalesce to form large ulcers with yellowish fibrin covering them, resembling erythema multiform-like disease.[43]. Candidal plaque-like lesions are also observed in association with Covid-19. Both red and white plaques were observed. They are located on the dorsum of the tongue and palate. They were also observed along with multiple tiny ulcers, taste changes, tongue and masticatory muscles pain [43]. Immune system suppression as a result of antibiotic therapy, deteriorating general health and neglected oral hygiene can be possible causes of these plaques.

Many times the blisters are observed in the soft palate and the cheek in the patients with COVID-19. Gingival changes such as general erythematous and edematous gingiva, gingivo-periodontal bleeding, necrotic interdental papillae and desquamative gingivitis are reported in literature. Symptoms such as halitosis, tongue and masticator muscle pain and swelling, geographical tongue, hyperplasia of papilla associated with taste changes and macroglosia are also reported along with fatigue and mayor symptoms of COVID-19 in case reports. There seem to be at least four possible pathways by which SARS- CoV-2 infection leads to dysgeusia,

as outlined below:

- As ACE-2 receptors for SARS-CoV-2 are common in the epithelium of taste buds, as well as in the human salivary glands, it is likely that these entities may be targeted in the pre-symptomatic phase of the infection, resulting in salivary gland dysfunction. The resultant impairment of the quality and the quantity of salivary flow may be reflected as dysgeusia (see below).
- A neurological pathway, where it has been hypothesized that, as dysgeusia and anosmia are closely linked, impairment of the olfactory system (with an abundance of ACE-2 receptors for SARS-CoV-2) may have an indirect impact on taste sensation, leading to dysgeusia.
- The infection could directly damage peripheral taste neurosensory chemoreceptors through the cranial nerves responsible for gustation and, in particular, the chorda tympani (CN VII) nerve. It has been posited that the virus could access the chorda tympani, first by travelling from the nasopharynx to the eustachian tube and then colonizing the middle ear from where it could access the chorda tympani, eventually causing dysgeusia.
- Lastly, another inflammatory response pathway has been proposed wherein the SARS-CoV-2 virus enters ACE-2-expressing epithelial cells of the taste buds, triggering an inflammatory response, leading to cellular changes that could alter taste.
  The interaction of SARS-CoV-2 with gustatory components and ACE2 receptors supports a direct effect in COVID-19-related taste disorders. First, the peripheral nervous system is affected by the new coronavirus, and as gustatory buds are innervated by cranial nerves, related functions may be impaired, resulting in taste disorders [44, 45]. Second, SARS-CoV-2 may bind essential salivary mucin components, such as sialic acid, consequently accelerating taste particle degradation and disturbing gustatory sensation [46]. Moreover, the tongue presents a high expression of ACE2 [22], and its interaction with SARS- CoV-2 may affect normal gustatory functions through dopamine and serotonin synthesis pathway coregulation [44, 45]. In addition, ACE inhibitors and ACE2 blockers are frequently associated with impairment of taste sensation [46, 47]. These drugs play a role in taste disorders by G protein–coupled and sodium channel inactivation. Similar to what patients with COVID-19 experience after infection recovery, the effect on gustatory sense by ACE inhibitors regresses a few weeks after discontinuation. Furthermore, ACE2 high expression was demonstrated in the taste buds of rats and was associated with angiotensin II production in mice taste buds. These findings might also suggest the inability of ACE2 to degrade this protein during COVID-19 infection, resulting in disorderly taste responses [48, 49].

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