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Oral symptom manifestations in patients with COVID-19: gustatory and saliva secretion dysfunctions and pathogenetic hypotheses

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Coronavirus disease 2019 (COVID-19) is a highly contagious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease is characterized by a wide spectrum of symptoms, ranging from mild to severe, including fatal outcomes. This study aims to review gustatory and salivary secretion dysfunctions and determine their potential pathogenic mechanisms. Gustatory impairment and salivary dysfunction are prevalent among patients with acute COVID-19 and those recovering from the disease. The mouth serves as a critical entry route for SARS-CoV-2. The cells within the oral epithelium, taste buds, and minor and major salivary glands express key entry factors for SARS-CoV-2, including angiotensin-converting enzyme 2, transmembrane serine protease 2, and furin. The co-occurrence of gustatory and salivary secretion dysfunctions possibly has pathogenetic association with the following factors: the expression of SARS-CoV-2 cellular entry receptors in the taste buds and salivary glands and SARS-CoV-2–induced zinc deficiency, which is crucial for normal taste perception and saliva secretion. Furthermore, the cytokine storm triggered by COVID-19 contributes to secondary damage affecting gustatory and salivary functions.

Keywords: COVID-19, Taste disorders, Salivary gland diseases, Pathogenesis

Introduction

The coronavirus disease 2019 (COVID-19) pandemic triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread worldwide. And the pandemic resulted in unprecedented socio-economic and health impacts [1]. SARS-CoV-2 has resulted in > 775 million COVID-19 patients worldwide [2]. In Korea, Korea Disease Control and Prevention Agency (KDCA) [3] data indicate that > 34 million COVID-19 patients with > 35,000 deaths were reported from January 20th, 2020 to August 31st, 2023.

It has become clear that SARS-CoV-2 infection can present with a broad spectrum of manifestations, ranging from asymptomatic cases to severe respiratory distress syndrome and, in critical situations, death. It was observed that the risk of SARS-CoV-2 transmission increases with the length of exposure and the proximity of social interactions [4]. At the onset of illness, COVID-19 symptoms can vary widely and often include fever or chills, cough, shortness of breath or difficulty breathing, sore throat, congestion or runny nose, new

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loss of taste or smell, fatigue, muscle or body ache, headache, nausea or vomiting, and diarrhea [5]. In addition to these clinical manifestations, COVID-19 is also associated with several symptoms specific to oral tissues and functions. These include taste impairments such as ageusia and dysgeusia, which can be classified into severe, moderate, and mild hypogeusia. Also reported are impairments in saliva secretion, including dry mouth, xerostomia, and hyposalivation [6-8].

Initially, COVID-19 oral symptoms were thought to be transient and expected to disappear without treatment. However, growing evidence suggests that taste and saliva secretion disorders may persist in individuals who have recovered from COVID-19. The persisting symptoms following COVID-19 are difficult to determine as various health-related factors influence them [9]. Several studies have identified that COVID-19 has a wide range of long-term effects on nearly all body systems, including the respiratory, cardiovascular, muscular, neurological, gastrointestinal, psychiatric, and dermatological systems [10-15]. The most common syndromes are persistent fatigue, respiratory complaints, taste and smell disorders, and cognitive impairments [15-21]. Many COVID-19 survivors who were monitored after their recovery have reported persistent gustatory and salivary secretion dysfunctions [22,23].

While gustatory and salivary secretion dysfunctions are not life-threatening, their persistence can significantly impact the oral health-related quality of life for COVID-19 patients and survivors [24]. These disorders can diminish appetite, negatively affect nutrition, and potentially increase the risk of other health issues [25,26].

It is well-documented that the oral cavity functions as an entry portal for SARS-CoV-2, with the virus frequently being identified in saliva [27]. Hence, there has been more attention on the impact of SARS-CoV-2 infection on oral disease and the effect of post-COVID-19 on oral health care [28,29]. Therefore, addressing oral-related symptoms associated with COVID-19 has become a critical issue. The purpose of this study is to summarize oral symptoms, specifically gustatory disorders and salivary secretion disorders during the early stages of SARS-CoV-2 infection and after recovery. Furthermore, it aims to investigate the underlying pathogenic mechanisms of these conditions.

Oral Cavity as an Entry Route and a Direct Infection Site for SARS-CoV-2

SARS-CoV-2, a zoonotic virus that causes COVID-19 belongs to the coronavirus family. It is a positive-sense, single-stranded RNA virus [30]. At the onset of the COVID-19 pandemic, the oral cavity was regarded as a passive route for transmitting SARS-CoV-2 from other respiratory tract regions, despite evidence of the virus's presence in saliva. However, recent reports indicate that all major oral mucosal sites and salivary glands are vulnerable to direct infection by SARS-CoV-2 [7,31,32]. It is critical to recognize that these initial infection sites may play a significant role in facilitating the spread of the virus to other areas of the body.

It was demonstrated that saliva and nasopharyngeal specimens exhibit comparable sensitivity in detecting SARS-CoV-2 [33]. Given the hypothesis that the oral cavity might be a site of direct infection in COVID-19 [34], periodontal disease has been identified as a risk factor for COVID-19 [35]. Additionally, less common oral symptoms, such as salivary gland inflammation and oral mucosal lesions, are increasingly reported in COVID-19 patients [36,37].

Following the identification of angiotensin-converting enzyme 2 (ACE2) as the cellular receptor for SARS-CoV-2 [38,39], its expression in the human tongue, gingiva, buccal mucosal cells, and salivary glands has indicated that the oral cavity is vulnerable to direct SARS-CoV-2 infection [40,41]. Furthermore, it has been reported that viral entry factors, including ACE2, furin, and the transmembrane serine protease (TMPRSS) protease family, are present in the epithelial cells of the glands and oral mucosae, as demonstrated by single-cell RNA sequencing of human minor salivary glands and gingiva. An ultrasound-guided postmortem biopsy was performed in cases of fatal COVID-19 and it was found through immunohistochemical analysis that ACE2 and TMPRSS2 are expressed in the ductal epithelium and serous acinar cells of the parotid, submandibular, and minor salivary glands [27]. Additionally, asymptomatic individuals can harbor infectious viruses, and the levels of SARS-CoV-2 in saliva have been found to correlate with the severity of taste alterations [7,42]. Epithelial cells exposed to the external environment, such as those in the gingiva, are particularly at high risk for viral infection [32]. Saliva from patients with asymptomatic or mild COVID-19 has been found to contain substantial amounts of virus and infected cells, indicating that the oral cavity may serve as a source of viral transmission both within and between individuals [32]. These findings suggest that the oral cavity functions not only as an entry route for SARS-CoV-2 but also as a site for direct viral infection and transmission.

Gustatory Dysfunction

The sense of taste is detected by taste buds, which convert taste stimuli into gustatory signals that are transmitted to the primary taste cortex. Taste buds, located in the stratified epithelium and distributed across the tongue, palate, and epiglottis, are specialized gustatory organs. Each taste bud is composed of clusters of columnar taste receptor cells (TRCs) with microvilli on their apical surface, housing various receptors that detect taste molecules [43]. TRCs can be categorized into three types—type I, type II, and type III—based on their ultrastructural features and gene expression patterns. These cells are continuously regenerated from stem cells within the taste buds and work together to transduce the five primary taste qualities: sweet, sour, bitter, salty, and umami [44-46].

Most reports are based on self-reported smell and taste disorders, with many indicating that long-lasting taste deficiencies may occur following SARS-CoV-2 infection. Such deficiencies can influence nutrition, safety, and quality of life. However, self-reports are often inaccurate and typically reflect olfactory disorders [47], with fewer reports addressing taste system disorders. It has been reported that approximately 40% of COVID-19 patients experience taste disorders, encompassing various forms such as hypogeusia, ageusia, and dysgeusia [48,49].

Saliva Secretory Dysfunction

Saliva secretion abnormalities have been described using various terms. The terms, such as xerostomia, dry mouth, and hyposalivation are collectively designated as saliva secretory disorders for simplification. Dry mouth can arise from various causes, including autoimmune, endocrine, and neurological conditions, as well as the use of certain medications. Additionally, it is evident that intensive medical treatments, particularly in intensive care units, can significantly contribute to complaints of dry mouth.

It has been reported that 42.5% of patients in the acute phase of COVID-19 experienced complaints of xerostomia and dry mouth [22]. A similar prevalence of dry mouth, at 44.2%, was also documented [50]. Additionally, saliva secretory sequelae were observed in 18.5% of COVID-19 survivors who were followed up for 28–230 days [22]. Other studies reported similar dry mouth symptoms with and without Sicca syndrome in COVID-19 patients [51-53]. Although the prevalence of xerostomia and dry mouth decreases after recovery from COVID-19 compared to the acute phase, it is evident that saliva secretory dysfunctions can persist for an extended period.

Possible Pathogenic Mechanisms

From article search, it was found the association between gustatory dysfunction and saliva secretory dysfunctions. Tsuchiya [11] reported that a study on oral symptoms across various ethnic backgrounds, including Italian, Colombian, Chinese, Indian, Israeli, Egyptian, Turkish, and Saudi Arabian cohorts, concluded that persistent saliva secretory dysfunctions can occur concurrently with persistent gustatory dysfunctions, regardless of geographical or ethnic differences.

The detailed mechanism behind COVID-19-related gustatory and salivary secretion dysfunctions remains unclear. COVID-19 patients exhibit gustatory and saliva secretory dysfunctions, both of which can persist for an extended period in survivors. This provides insights into the pathogenic mechanisms underlying the concurrent oral symptoms.

1. Direct damage of oral symptoms-related cells

The pathological hypotheses for COVID-19-related oral symptoms are as follows. First, there is the possibility that SARS-CoV-2 directly damages the taste-related and salivary gland cells. It has been observed that SARS-CoV-2 induces cellular damage through mechanisms involving both autophagy and apoptosis [54,55].

SARS-CoV-2 binds to the cellular receptor ACE2 via its spike protein. This interaction is followed by the fusion of the viral and cellular membranes, facilitated by the cellular proteins convertase furin and TMPRSS2. Once the viral envelope merges with the host cell membrane, SARS-CoV-2 enters the host cells [42]. Considering the presence of viral entry-related biofactors and the virus detection in oral tissues, SARS-CoV-2 can target the oral cavity. The cytopathic effects of SARS-CoV-2 lead to functional disruptions in the affected cells [56-58]. Specifically, SARS-CoV-2 targets taste buds and salivary glands that express the viral receptor ACE2, causing collateral damage that negatively impacts taste perception and salivary secretion. These direct cell damages may cause malfunction of the gustatory system and salivary secretion.

2. Host zinc deficiency and SARS-CoV-2 infection

Secondly, zinc deficiency and the disruption of local zinc

homeostasis can be considered factors. Hypozincemia is frequently observed in COVID-19 patients, and the extent of zinc deficiency is associated with the extent of disease severity [59]. Zinc and zinc-binding proteins are important for the physiological processes of taste bud development, regulation, ion transport, and resistance to oxidative stress [22]. Zinc deficiency negatively impacts the vallate papillae, resulting in a reduction in both the number and size of taste buds [60]. Additionally, it leads to decreased taste sensitivity and impaired saliva secretion [61]. Although the exact mechanism is not yet known, clinical observations have shown that zinc supplementation improves taste function in patients [22,62].

3. Cytokine storm plays a role in cell death induction

The cytokine storm is critical to the pathogenesis of COVID-19 [63]. Elevated levels of proinflammatory cytokines and immune cell infiltration in the oral mucosa of COVID-19 patients indicate the involvement of inflammation and immune responses in the pathogenic process [58].

4. Other supporting hypothesis

One of the hypotheses involved in the pathogenetic process of taste disorder and xerostomia is the disruption of renin-angiotensin system (RAS) homeostasis. The host cell receptor ACE2, which is crucial for SARS-CoV-2 entry into the cell, plays a key role in maintaining the balance of the RAS – including renin, angiotensinogen, and ACE [48,64]. When the virus' s S protein blocks ACE2, it damages the RAS [65]. This local imbalance in the RAS may contribute to the formation of an inflammatory microenvironment in taste buds and salivary gland cells [53].

Additionally, it has been demonstrated that SARS-CoV-2 affects olfactory neurons, leading to impairment of chemosensory function [66]. Dysgeusia frequently arises as a consequence of impaired olfaction, owing to the complex integration and interaction between the gustatory and olfactory regions of the brain [67].

Conclusion

Gustatory and salivary secretion dysfunctions are highly prevalent symptoms in COVID-19 patients. Although these oral symptoms are not life-threatening, they significantly affect the overall quality of life. To resolve these problems, it is essential to elucidate the pathogenesis of the disease. The concurrent presence of gustatory and salivary secretion dysfunctions is pathogenetically related to several factors: the expression of SARS-CoV-2 entry receptors in taste buds and salivary glands, and zinc deficiency induced by SARS-CoV-2 infection, which is essential for maintaining normal taste perception and saliva secretion. The cytokine storm caused by SARS-CoV-2 infection also induces an inflammatory microenvironment within the affected cells.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Liu Y, Wang Z, Rader B, Li B, Wu CH, Whittington JD, Zheng P, Stenseth NC, Bjornstad ON, Brownstein JS, Tian H. Associations between changes in population mobility in response to the COVID-19 pandemic and socioeconomic factors at the city level in China and country level worldwide: a retrospective, observational study. Lancet Digit Health 2021;3:e349-59. doi: 10.1016/S2589-7500(21)00059-5
2. World Health Organization (WHO). WHO COVID-19 dashboard [Internet]. Geneva: WHO; 2024 [cited 2024 Aug 22]. Available from: https://data.who.int/dashboards/covid19/cases?n=c
3. Korea Disease Control and Prevention Agency (KDCA). COVID-19 positive case (sample) surveillance status [Internet]. Cheongju: KDCA; 2024 [cited 2024 Aug 22]. Available from: https://ncv.kdca.go.kr/pot/cv/trend/dmstc/selectMntrgSttus.do
4. Sun K, Wang W, Gao L, Wang Y, Luo K, Ren L, Zhan Z, Chen X, Zhao S, Huang Y, Sun Q, Liu Z, Litvinova M, Vespignani A, Ajelli M, Viboud C, Yu H. Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. Science 2021;371:eabe2424. doi: 10.1126/science.abe2424
5. U.S Centers for Disease Control and Prevention (CDC). Symp-

toms of COVID-19 [Internet]. Atlanta: CDC; 2024 [cited 2024 Aug 22]. Available from: https://www.cdc.gov/covid/signs-symptoms/index.html
6. Tsuchiya H. Oral Symptoms associated with COVID-19 and their pathogenic mechanisms: a literature review. Dent J (Basel) 2021;9:32. doi: 10.3390/dj9030032
7. Huang N, Pérez P, Kato T, Mikami Y, Okuda K, Gilmore RC, Conde CD, Gasmi B, Stein S, Beach M, Pelayo E, Maldonado JO, Lafont BA, Jang SI, Nasir N, Padilla RJ, Murrah VA, Maile R, Lovell W, Wallet SM, Bowman NM, Meinig SL, Wolfgang MC, Choudhury SN, Novotny M, Aevermann BD, Scheuermann RH, Cannon G, Anderson CW, Lee RE, Marchesan JT, Bush M, Freire M, Kimple AJ, Herr DL, Rabin J, Grazioli A, Das S, French BN, Pranzatelli T, Chiorini JA, Kleiner DE, Pittaluga S, Hewitt SM, Burbelo PD, Chertow D; NIH COVID-19 Autopsy Consortium; HCA Oral and Craniofacial Biological Network; Frank K, Lee J, Boucher RC, Teichmann SA, Warner BM, Byrd KM. SARS-CoV-2 infection of the oral cavity and saliva. Nat Med 2021;27:892-903. doi: 10.1038/s41591-021-01296-8
8. Doty RL. Olfactory dysfunction in COVID-19: pathology and long-term implications for brain health. Trends Mol Med 2022;28:781-94. doi: 10.1016/j.molmed.2022.06.005
9. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-Coronavirus dsease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. J Infect Dis 2022;226:1593-607. doi: 10.1093/infdis/jiac136
10. Kayaaslan B, Eser F, Kalem AK, Kaya G, Kaplan B, Kacar D, Hasanoglu I, Coskun B, Guner R. Post-COVID syndrome: a single-center questionnaire study on 1007 participants recovered from COVID-19. J Med Virol 2021;93:6566-74. doi: 10.1002/jmv.27198
11. Tsuchiya H. COVID-19 oral sequelae: persistent gustatory and saliva secretory dysfunctions after recovery from COVID-19. Med Princ Pract 2023;32:166-77. doi: 10.1159/000531373
12. Appelman B, Charlton BT, Goulding RP, Kerkhoff TJ, Breedveld EA, Noort W, Offringa C, Bloemers FW, van Weeghel M, Schomakers BV, Coelho P, Posthuma JJ, Aronica E, Joost Wiersinga W, van Vugt M, Wüst RCI. Muscle abnormalities worsen after post-exertional malaise in long COVID. Nat Commun 2024;15:17. doi: 10.1038/s41467-023-44432-3
13. Goldstein DS. Post-COVID dysautonomias: what we know and (mainly) what we don't know. Nat Rev Neurol 2024;20:99-113. doi: 10.1038/s41582-023-00917-9
14. Greene C, Connolly R, Brennan D, Laffan A, O'Keeffe E, Zaporojan L, O'Callaghan J, Thomson B, Connolly E, Argue R, Meaney JFM, Martin-Loeches I, Long A, Cheallaigh CN, Conlon N, Doherty CP, Campbell M. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. Nat Neurosci 2024;27:421-32. doi: 10.1038/s41593-024-01576-9
15. Sk Abd Razak R, Ismail A, Abdul Aziz AF, Suddin LS, Azzeri A, Sha'ari NI. Post-COVID syndrome prevalence: a systematic review and meta-analysis. BMC Public Health 2024;24:1785. doi: 10.1186/s12889-024-19264-5
16. Mastrangelo A, Bonato M, Cinque P. Smell and taste disorders in COVID-19: from pathogenesis to clinical features and outcomes. Neurosci Lett 2021;748:135694. doi: 10.1016/j.neulet.2021.135694
17. SeyedAlinaghi S, Bagheri A, Razi A, Mojdeganlou P, Mojdeganlou H, Afsahi AM, Afzalian A, Paranjkhoo P, Shahidi R, Mirzapour P, Pashaei Z, Habibi MA, Shahbazi P, Nooralioghli Parikhani S, Farizani Gohari NS, Popoola Y, Mehraeen E, Hackett D. Late cmplications of COVID-19; an umbrella review on current systematic reviews. Arch Acad Emerg Med 2023;11:e28. doi: 10.22037/aaem.v11i1.1907
18. Bungenberg J, Hohenfeld C, Costa AS, Heine J, Schwichtenberg K, Hartung T, Franke C, Binkofski F, Schulz JB, Finke C, Reetz K. Characteristic functional connectome related to Post-COVID-19 syndrome. Sci Rep 2024;14:4997. doi: 10.1038/s41598-024-54554-3
19. Garmoe W, Rao K, Gorter B, Kantor R. Neurocognitive impairment in post-COVID-19 condition in adults: narrative review of the current literature. Arch Clin Neuropsychol 2024;39:276-89. doi: 10.1093/arclin/acae017
20. Jaywant A, Gunning FM, Oberlin LE, Santillana M, Ognyanova K, Druckman JN, Baum MA, Lazer D, Perlis RH. Cognitive symptoms of post-COVID-19 condition and daily functioning. JAMA Netw Open 2024;7:e2356098. doi: 10.1001/jamanetworkopen.2023.56098
21. Sharetts R, Moein ST, Khan R, Doty RL. Long-term taste and smell outcomes after COVID-19. JAMA Netw Open 2024;7:e247818. doi: 10.1001/jamanetworkopen.2024.7818
22. Tsuchiya H. Gustatory and saliva secretory dysfunctions in COVID-19 patients with zinc deficiency. Life (Basel) 2022;12:353. doi: 10.3390/life12030353
23. Barbara JM, Gatt J, Xuereb RA, Tabone Adami N, Darmanin J, Erasmi R, G Xuereb R, Barbara C, Stephen F, Jane Magri C. Clinical outcomes at medium-term follow-up of COVID-19. J R Coll Physicians Edinb 2022;52:220-7. doi: 10.1177/14782715221124617
24. Vaira LA, Gessa C, Deiana G, Salzano G, Maglitto F, Lechien

JR, Saussez S, Piombino P, Biglio A, Biglioli F, Boscolo-Rizzo P, Hopkins C, Parma V, De Riu G. The effects of persistent olfactory and gustatory dysfunctions on quality of life in long-COVID-19 ptients. Life (Basel) 2022;12:141. doi: 10.3390/life12020141

25. Oliveira WQ, Sousa PHM, Pastore GM. Olfactory and gustatory disorders caused by COVID-19: how to regain the pleasure of eating? Trends Food Sci Technol 2022;122:104-9. doi: 10.1016/j.tifs.2022.01.022
26. Yom-Tov E, Lekkas D, Jacobson NC. Association of COVID19-induced anosmia and ageusia with depression and suicidal ideation. J Affect Disord Rep 2021;5:100156. doi: 10.1016/j.jadr.2021.100156
27. Matuck BF, Dolhnikoff M, Duarte-Neto AN, Maia G, Gomes SC, Sendyk DI, Zarpellon A, de Andrade NP, Monteiro RA, Pinho JRR, Gomes-Gouvêa MS, Souza SC, Kanamura C, Mauad T, Saldiva PHN, Braz-Silva PH, Caldini EG, da Silva LFF. Salivary glands are a target for SARS-CoV-2: a source for saliva contamination. J Pathol 2021;254:239-43. doi: 10.1002/path.5679
28. France K, Glick M. Long COVID and oral health care considerations. J Am Dent Assoc 2022;153:167-74. doi: 10.1016/j.adaj.2021.08.007
29. Naqvi AR, Schwartz J, Brandini DA, Schaller S, Hussein H, Valverde A, Naqvi RA, Shukla D. COVID-19 and oral diseases: assessing manifestations of a new pathogen in oral infections. Int Rev Immunol 2022;41:423-37. doi: 10.1080/08830185.2021.1967949
30. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species *Severe acute respiratory syndrome-related coronavirus*: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-44. doi: 10.1038/s41564-020-0695-z
31. Azzi L, Carcano G, Gianfagna F, Grossi P, Gasperina DD, Genoni A, Fasano M, Sessa F, Tettamanti L, Carinci F, Maurino V, Rossi A, Tagliabue A, Baj A. Saliva is a reliable tool to detect SARS-CoV-2. J Infect 2020;81:e45-50. doi: 10.1016/j.jinf.2020.04.005
32. Marchesan JT, Warner BM, Byrd KM. The "oral" history of COVID-19: primary infection, salivary transmission, and post-acute implications. J Periodontol 2021;92:1357-67. doi: 10.1002/JPER.21-0277
33. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, Warren JL, Geng B, Muenker MC, Moore AJ, Vogels CBF, Petrone ME, Ott IM, Lu P, Venkataraman A, Lu-Culligan A, Klein J, Earnest R, Simonov M, Datta R, Handoko R, Naushad N, Sewanan LR, Valdez J, White EB, Lapidus S, Kalinich CC, Jiang X, Kim DJ, Kudo E, Linehan M, Mao T, Moriyama M, Oh JE, Park A, Silva J, Song E, Takahashi T, Taura M, Weizman OE, Wong P, Yang Y, Bermejo S, Odio CD, Omer SB, Dela Cruz CS, Farhadian S, Martinello RA, Iwasaki A, Grubaugh ND, Ko AI. Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. N Engl J Med 2020;383:1283-6. doi: 10.1056/NEJMc2016359
34. Mariz BALA, Brandão TB, Ribeiro ACP, Lopes MA, Santos-Silva AR. New insights for the pathogenesis of COVID-19-related dysgeusia. J Dent Res 2020;99:1206. doi: 10.1177/0022034520936638
35. Pitones-Rubio V, Chávez-Cortez EG, Hurtado-Camarena A, González-Rascón A, Serafín-Higuera N. Is periodontal disease a risk factor for severe COVID-19 illness? Med Hypotheses 2020;144:109969. doi: 10.1016/j.mehy.2020.109969
36. Fisher J, Monette DL, Patel KR, Kelley BP, Kennedy M. COVID-19 associated parotitis. Am J Emerg Med 2021;39:254.e1-3. doi: 10.1016/j.ajem.2020.06.059
37. Amorim Dos Santos J, Normando AGC, Carvalho da Silva RL, De Paula RM, Cembranel AC, Santos-Silva AR, Guerra ENS. Oral mucosal lesions in a COVID-19 patient: new signs or secondary manifestations? Int J Infect Dis 2020;97:326-8. doi: 10.1016/j.ijid.2020.06.012
38. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol 2020;5:562-9. doi: 10.1038/s41564-020-0688-y
39. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3. doi: 10.1038/s41586-020-2012-7
40. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8. doi: 10.1038/s41368-020-0074-x
41. Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary glands: potential reservoirs for COVID-19 asymptomatic infection. J Dent Res 2020;99:989. doi: 10.1177/0022034520918518
42. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. Nat Rev Mol Cell Biol 2022;23:3-20. doi: 10.1038/s41580-021-00418-x
43. Doyle ME, Premathilake HU, Yao Q, Mazucanti CH, Egan JM.

Physiology of the tongue with emphasis on taste transduction. Physiol Rev 2023;103:1193–246. doi: 10.1152/physrev.00012.2022
44. Rodriguez YA, Roebber JK, Dvoryanchikov G, Makhoul V, Roper SD, Chaudhari N. "Tripartite synapses" in taste buds: a role for type I glial-like taste cells. J Neurosci 2021;41:9860–71. doi: 10.1523/JNEUROSCI.1444–21.2021
45. Roper SD. Chemical and electrical synaptic interactions among taste bud cells. Curr Opin Physiol 2021;20:118–25. doi: 10.1016/j.cophys.2020.12.004
46. Wilson CE, Lasher RS, Yang R, Dzowo Y, Kinnamon JC, Finger TE. Taste bud connectome: implications for taste information processing. J Neurosci 2022;42:804–16. doi: 10.1523/JNEUROSCI.0838–21.2021
47. Rass V, Tymoszuk P, Sahanic S, Heim B, Ausserhofer D, Lindner A, Kofler M, Mahlknecht P, Boehm A, Hüfner K, Pizzini A, Sonnweber T, Kurz K, Pfeifer B, Kiechl S, Peball M, Kindl P, Putnina L, Fava E, Djamshidian A, Huber A, Wiedermann CJ, Sperner-Unterweger B, Wöll E, Beer R, Schiefecker AJ, Bellmann-Weiler R, Bachler H, Tancevski I, Pfausler B, Piccoliori G, Seppi K, Weiss G, Löffler-Ragg J, Helbok R. Distinct smell and taste disorder phenotype of post-acute COVID-19 sequelae. Eur Arch Otorhinolaryngol 2023;280:5115–28. doi: 10.1007/s00405–023–08163–x
48. Okada Y, Yoshimura K, Toya S, Tsuchimochi M. Pathogenesis of taste impairment and salivary dysfunction in COVID-19 patients. Jpn Dent Sci Rev 2021;57:111–22. doi: 10.1016/j.jdsr.2021.07.001
49. Nanjo Y, Okuma T, Kuroda Y, Hayakawa E, Shibayama K, Akimoto T, Murashima R, Kanamori K, Tsutsumi T, Suzuki Y, Namba Y, Makino F, Nagashima O, Sasaki S, Takahashi K. Multiple types of taste disorders among patients with COVID-19. Intern Med 2022;61:2127–34. doi: 10.2169/internalmedicine.9065–21
50. Tuter G, Yerebakan M, Celik B, Kara G. Oral manifestations in SARS-CoV-2 infection. Med Oral Patol Oral Cir Bucal 2022;27:e330–9. doi: 10.4317/medoral.25259
51. Katz J. Prevalence of dry mouth in COVID-19 patients with and without Sicca syndrome in a large hospital center. Ir J Med Sci 2021;190:1639–41. doi: 10.1007/s11845–020–02480–4
52. Melo TS, Beltrão RC, Mendonça AFT, Duarte ÂLBP, Gueiros LA. Sicca symptoms in post-acute COVID-19 syndrome. Oral Dis 2022;28 Suppl 2:2620–1. doi: 10.1111/odi.14159
53. Tarcha R, Khalayli N, Kudsi M. Sicca syndrome as complication of COVID-19 infection: a case report. Clin Case Rep 2024;12:e9177. doi: 10.1002/ccr3.9177
54. Wang P, Luo R, Zhang M, Wang Y, Song T, Tao T, Li Z, Jin L, Zheng H, Chen W, Zhao M, Zheng Y, Qin J. A cross-talk between epithelium and endothelium mediates human alveolar-capillary injury during SARS-CoV-2 infection. Cell Death Dis 2020;11:1042. doi: 10.1038/s41419–020–03252–9
55. Zhu N, Wang W, Liu Z, Liang C, Wang W, Ye F, Huang B, Zhao L, Wang H, Zhou W, Deng Y, Mao L, Su C, Qiang G, Jiang T, Zhao J, Wu G, Song J, Tan W. Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells. Nat Commun 2020;11:3910. doi: 10.1038/s41467–020–17796–z
56. Doyle ME, Appleton A, Liu QR, Yao Q, Mazucanti CH, Egan JM. Human type II taste cells express angiotensin-converting enzyme 2 and are infected by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Am J Pathol 2021;191:1511–9. doi: 10.1016/j.ajpath.2021.05.010
57. Nguyen HT, Zhang S, Wang Q, Anang S, Wang J, Ding H, Kappes JC, Sodroski J. Spike glycoprotein and host cell determinants of SARS-CoV-2 entry and cytopathic effects. J Virol 2021;95:e02304–20. doi: 10.1128/JVI.02304–20
58. Henin D, Pellegrini G, Carmagnola D, Lanza Attisano GC, Lopez G, Ferrero S, Amendola A, De Angelis D, Tanzi E, Dellavia C. Morphological and immunopathological aspects of lingual tissues in COVID-19. Cells 2022;11:1248. doi: 10.3390/cells11071248
59. Gonçalves TJM, Gonçalves SEAB, Guarnieri A, Risegato RC, Guimarães MP, de Freitas DC, Razuk-Filho A, Junior PBB, Parrillo EF. Association between low zinc levels and severity of acute respiratory distress syndrome by new Coronavirus SARS-CoV-2. Nutr Clin Pract 2021;36:186–91. doi: 10.1002/ncp.10612
60. Chou HC, Chien CL, Huang HL, Lu KS. Effects of zinc deficiency on the vallate papillae and taste buds in rats. J Formos Med Assoc 2001;100:326–35.
61. Wessels I, Rolles B, Rink L. The potential impact of zinc supplementation on COVID-19 pathogenesis. Front Immunol 2020;11:1712. doi: 10.3389/fimmu.2020.01712
62. Abdelmaksoud AA, Ghweil AA, Hassan MH, Rashad A, Khodeary A, Aref ZF, Sayed MAA, Elsamman MK, Bazeed SES. Olfactory disturbances as presenting manifestation among egyptian patients with COVID-19: possible role of zinc. Biol Trace Elem Res 2021;199:4101–8. doi: 10.1007/s12011–020–02546–5
63. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021;93:250–6. doi: 10.1002/jmv.26232

64. Sawa Y, Ibaragi S, Okui T, Yamashita J, Ikebe T, Harada H. Expression of SARS-CoV-2 entry factors in human oral tissue. J Anat 2021;238:1341-54. doi: 10.1111/joa.13391
65. Dai Q, Xu M, Yao M, Sun B. Angiotensin AT1 receptor antagonists exert anti-inflammatory effects in spontaneously hypertensive rats. Br J Pharmaco 2007;152:1042-8. doi: 10.1038/sj.bjp.0707454
66. Lyoo KS, Kim HM, Lee B, Che YH, Kim SJ, Song D, Hwang W, Lee S, Park JH, Na W, Yun SP, Kim YJ. Direct neuronal infection of SARS-CoV-2 reveals cellular and molecular pathology of chemosensory impairment of COVID-19 patients. Emerg Microbes Infect 2022;11:406-11. doi: 10.1080/22221751.2021.2024095
67. Small DM, Prescott J. Odor/taste integration and the perception of flavor. Exp Brain Res 2005;166:345-57. doi: 10.1007/s00221-005-2376-9