

Association of Salivary Content Alteration and Early Ageusia Symptoms in COVID-19 Infections: A Systematic Review

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Eur J Dent:2020;14(suppl S1):S152–S158

Abstract

Coronavirus disease 2019 (COVID 19) is a major threat to the health and prosperity of human life at present. It has resulted in loss of thousands of lives globally and has brought countries to the brink of economic, social, and health collapse. A major issue of this infection is the ease with which it transmits through salivary droplets and its survival for long durations outside the body. Therefore, its early detection is critical in prevention, diagnostic, and management efforts of COVID-19 patients. Loss of taste and smell is one of the early symptoms reported in these patients and the virus is abundantly found in the salivary secretion of the infected symptomatic and asymptomatic patients. Infection and inflammation of salivary glands are common among viral infections, particularly in the early stages, which lead to salivary composition changes. Chemosensory sensation of taste is critically dependent on the salivary flow rate and its inorganic constituents, protein levels, specific 3',5'-cyclic adenosine monophosphate and 3',5'-cyclic guanosine monophosphate levels, ghrelins, pH levels, and enzymes. Therefore, the question arises, "Does COVID-19 infection alter the salivary components and composition leading to early transient symptoms of Ageusia and hypogeusia?" This review shows association of the COVID-19 and Ageusia, in addition to the early viral infection of salivary glands and possible changes in salivary flow and content. Therefore, suggesting a potential association between early ageusia in COVID-19 infection and salivary compositional changes.

Keywords

- ▶ SARS-COV-2
- ▶ COVID-19
- ▶ coronavirus
- ▶ saliva
- ▶ ageusia
- ▶ salivary gland
- ▶ viral infection

Introduction

Coronavirus disease (COVID-19) infection is a global pandemic and its transmission is mainly through human-to-human salivary and respiratory droplets.¹ It has resulted in millions of infections worldwide with more than hundred thousand deaths. It has resulted in not just loss of human life but also caused billions of dollars loss in the economy, a collapse of

the health care systems worldwide, and rise in social and psychological disorders in large populations.² A plethora of research is stimulated globally to find solutions with regard to prevention of transmission, diagnostic technology, early treatment, vaccination development, drug formulations, and management protocols in the form of laboratory and clinical trials.³ One critical aspect of the COVID-19 infection

DOI <https://doi.org/10.1055/s-0040-1716986>
ISSN 1305-7456.

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is its lack of early detection among infected individuals to present its transmission from asymptomatic but infected individuals.^{1,3} It is reported that anosmia (loss of smell) and ageusia (loss of taste) are one of the early signs of COVID-19 infections.^{4,5}

From the earlier reports on COVID-19, ageusia is reported among more than 40% of individuals tested positive with the infection.⁶ Saliva and its constituents play a critical role in the oral chemosensory perception of taste sensation. Zinc deficiency is linked with hyposalivation and taste changes.⁷ It is reported that deficiency of a zinc-binding protein, gustin, is linked to taste bud abnormalities.⁸ Moreover, hypogeusia or ageusia is also associated with low levels of 3',5'-cyclic adenosine monophosphate (cAMP) and 3',5'-cyclic guanosine monophosphate (cGMP) in the saliva, as cAMP is a possible growth factor for taste buds.⁹ In addition, multiple animal studies have suggested that hormones including glucagon, insulin, leptin, oxytocin, and ghrelin influence taste modalities.¹⁰⁻¹² Moreover, in cases of low salivary flow, sweet and sour taste is not influenced; however a persistent feeling of bitterness and astringency is reported.¹³ The perception of sourness falls when the pH increases, as the buffering capacity of saliva increases in line with the flow rate.¹⁴ Taste receptors are adapted to sodium levels in the saliva, and a threshold of sodium must be maintained for salty taste. Therefore, at high salivary flow rates, sodium concentration increases and with reabsorption in salivary ducts, sensitivity for sodium is lower.^{15,16} Furthermore, salivary enzymes including amylase are involved in the conversion of larger nutrients into molecules which are perceived by the taste receptors. Moreover, the presence of low salivary proteins including proline-rich proteins (PRPs) content is associated with higher percentage of astringency.¹⁷

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is reported in salivary secretions of infected patients for up to 4 weeks.¹⁸⁻²¹ In addition to the viral presence in the gingival crevicular fluid (GCF) exudate and presence in oropharyngeal sputum, viral infection of the minor and major salivary glands is a possible reason for its presence in saliva. Animal studies have suggested the presence of SARS-CoV in salivary epithelial cells among infected rhesus macaques.²² Salivary gland epithelial cells with angiotensin-converting enzyme 2 (ACE2)/cytokeratin receptors are the early target cells in the upper respiratory tract along with pneumocytes. This occurs in the early part of viral infection and is a proven source of virions in the patient saliva.²² In a study by Marder et al, parotid gland salivary constituents were assessed for proteins, electrolytes, antibodies, enzymes, and flow rate in the presence of cytomegalovirus in AIDS patients.²³ Potassium, protein, and immunoglobulin A (IgA) levels were higher among infected individuals in comparison to controls.²³ Suggesting that salivary gland infection can alter the salivary constituents.

It is established that salivary infections occur in the early stages of viral infections and ageusia is an early sign of SARS-CoV-2 infection. Therefore, in the presence of SARS-CoV-2 infection, it is possible that the viral infection in the salivary gland cells may alter the salivary constituents and

composition. As presented earlier, salivary constituents including proteins, inorganic constituents, enzymes, hormones along with salivary flow rate, and pH play a critical role in taste perception. Therefore, the proposed research question is "Does COVID-19 alter the salivary components and composition leading to early transient symptoms of ageusia and hypogeusia."

Therefore, it is hypothesized that the early symptoms of ageusia among the COVID-19 patients could possibly be associated with the salivary constituent modifications due to salivary gland infections. However, to our knowledge from indexed literature, there are no studies assessing the influence of COVID-19 infection on the salivary, flow rate, pH, and constituents in comparison to noninfected subjects with respect to ageusia. Therefore, to identify the role of COVID-19 in salivary gland infection causing an alteration of salivary components and ageusia, we present a summary of this association from available literature in a systemic manner.

Materials and Methods

This review was performed with a PubMed, Google scholar, Scopus, and EMBASE search from 1975 to 2020. The search was conducted using the following key words: Corona Virus, SARS-COV 2, Ageusia, Saliva composition, Salivary gland, and Infection. The full text of articles was obtained where possible. In case of absence of full text, the electronic files of abstract were reviewed. The inclusion criteria for the studies were articles related to viral infections and salivary content, salivary gland infection in SARS-CoV and SARS-CoV-2 infection, taste sensation and salivary constituents, gland infection, and salivary composition alteration. Case reports, articles not in English language, short summaries, and editorials were excluded.

Results

The research resulted in 122 articles. The total number of articles suitable for the review was 36. Out of these, 22 articles were on the incidence of ageusia and COVID-19 and the remaining were reporting the association of viral infections and salivary changes, salivary composition changes and Ageusia, and salivary components related to taste changes.

COVID-19 Pandemic

The pandemic of COVID-19 is one of the greatest challenges mankind has seen in modern human history. The novel coronavirus disease started in December 2019 from the Chinese province of Wuhan infecting thousands of individuals in a matter of days. Initially considered to be a localized disease in China, the World Health Organization announced it to be a global pandemic infecting more than 200 countries around the world.¹ The viral disease has infected in excess of 1.5 million humans to date and caused more than hundred thousand deaths, in addition, it is projected to infect many more for the unseen future (www.who.int/emergencies).

Disease coronavirus).²⁴ The devastating social, economic, and health impacts of this pandemic are unprecedented, resulting in crashing of the trading markets, trillions of dollars lost to the economy, loss of jobs for even highly skilled individuals, health care systems collapsing around the world, a stark increase in psychological and psychiatric problems, and countries nearing the brink of collapse. It has suggested by many that this viral pandemic has impacted the modern human existence to such an extent that life will not be the same in its aftermath.

Coronavirus Disease 2019

Research has suggested that COVID-19 is caused by a group of coronaviruses enveloped with a single-stranded RNA genome and a helical nucleocapsid. The genome size of coronaviruses ranges from ~26 to 32 kilobases, one of the largest among RNA viruses.²⁵ It is officially called SARS-CoV-2.²⁶ According to Chinese preventive medicine, it is similar to SARS-CoV and Middle eastern respiratory syndrome-CoV (MERS-CoV) with its origin in horseshoe bats and pangolins as intermediate hosts.^{27,28} The initial viral transmission was from animal to human followed by rapid human-to-human infection.²⁹ The main source of transmission are respiratory droplets, personal contact, and aerosols; however, fecal-oral transmission is also reported.³⁰ Although symptomatic patients are the main source of infection, asymptomatic carriers of virus in the 14-day incubation period are able to transmit the disease.^{27,31} The recent reports suggest that the fatality rate from COVID-19 ranges from 0.39 to 4.05% based on different reports from China.³ These are lower than SARS (~10%) and MERS (~34%) fatality rate however higher than common influenza (0.01–0.17%) infection.³² The symptoms of COVID-19 in majority of cases are mild, including fever, cough, muscle pain, fatigue, headache, vomiting, diarrhea, sore throat, and shortness of breath.³³ In some cases, a transient change of taste or total loss is also reported in COVID-19 patients. However, one-fourth of the symptomatic patients develops severe symptoms of respiratory distress syndrome, shock, and arrhythmia.³⁴ It is widely believed that patients with diabetes, hypertension, cardiovascular disease, and underlying comorbidities are associated with poor prognosis and in some cases death.³⁵ Currently, there is no specific and standard anti-CoV treatment strategy based on randomized trials and major management is supportive. This includes early diagnosis, limiting the infection symptoms with antibiotics, antipyretics and limiting transmission with quarantine, isolation, and disinfection. Potentially effective drugs on which trials are being conducted include antiviral therapies such as lopinavir and remdesivir.²⁹

Diagnosis of COVID-19

Diagnosis of COVID-19 is primarily by epidemiological information such as history of travel or close contact with infected patient followed by reverse transcription polymerase chain reaction on nasopharyngeal swabs, sputum, or saliva and computed tomography imaging of the infected lungs. Expecterated sputum respiratory tract samples in patients with lower respiratory tract infections are the primary used

for testing.³⁶ As transmission is primarily through aerosol salivary droplets entering the body via oral or nasal pathways, saliva is the primary carrier and mode for viral transfer. Studies have suggested that SARS-CoV-2 has been detected in saliva of COVID-19 patients.³⁷ Viral strains have been detected in saliva of infected patients up to 4 weeks of infection, indicating that diagnosis using salivary platforms is possible.¹⁹ Salivary collection is noninvasive, and does not require the close contact between the infected patient and health care workers, therefore, reducing the transmission of infection. In addition, production of oropharyngeal samples of sputum requires exertion and may cause bleeding, and according to one report can only be produced in 28% of infected patients. Suggesting that self-collection of saliva for patients with nasopharyngeal symptoms is a much easier method of viral detection with low risk and less trauma. SARS-CoV-2 is present in the saliva, as its main path of transmission is a liquid droplet through the oral cavity. Moreover, the viral RNA present in the blood can enter saliva through the exudate from GCF containing proteins and extracellular matrix.³⁸ However, it still needs to be assessed if use of salivary fluid in viral detection of COVID-19 is an effective and efficient method.

Occurrence of Ageusia (Loss of Taste) in COVID-19

One of the initial symptoms in COVID-19 infections as reported in various early reports are anosmia (loss of smell) and ageusia (loss of taste).⁴ These symptoms are associated with respiratory infections, trauma, oncology treatments, nasal polyps, and use of medications.^{4,5} A report by Prof. Claire Hopkins, King's College London, Guy's and St Thomas' Hospital, Department of Ear, Nose, and Throat suggested anosmia and ageusia as a viral occurrence in 40% of cases.⁶ It was also suggested that within a cohort of 2,000 COVID-19 patients in South Korea, 30% showed symptoms of anosmia or ageusia, indicating it as a trigger for self-isolation.⁶

Association of Saliva and Ageusia

Saliva and its constituents play a critical role in the oral chemosensory perception (► **Table 1**). It is a complex fluid compound mixture of glandular secretions, food particles, GCF exudate, and complex proteins. The food bolus is 50% saliva and the interaction between sensory cells for taste sensation and oral contents is not just intrinsic food particles but a major portion is salivary contents. Taste sensation is produced when volatile substances come in contact with taste bud receptors. Taste buds are mainly present on the tongue papillae in proximity to the minor salivary glands. Salivary fluids dissolve the food particles and bathe the taste buds, initiating taste perception. The basic five-taste senses include sweet, salty, bitter, sour, and umami. Saliva is considered to protect and modulate taste sensation through receptors. Zinc deficiency is linked with hyposalivation and taste changes.⁷ It is reported that deficiency of a zinc-binding protein, Gustin, is linked to taste bud abnormalities.⁸ A global oral sensitivity molecule, 6-n-propylthiouracil was recently reported to be inversely related to zinc concentration in saliva, associated

Table 1 Association of salivary constituent changes and ageusia

Salivary constituent	Function	Association with taste change and ageusia
Zn ions	<ul style="list-style-type: none"> – Metabolic agent – Antibacterial – Taste sensation 	<ul style="list-style-type: none"> – Deficiency of Zn; hypogeusia, hyposalivation – 6-n-propylthiouracil sensitivity is inversely related to Zn concentration
Gustin (Zn-binding protein)	<ul style="list-style-type: none"> – Zn-binding protein – Development of taste buds 	<ul style="list-style-type: none"> – Inhibition of its synthesis causes taste bud abnormalities
cAMP cGMP	<ul style="list-style-type: none"> – Growth of taste buds – Nutrient and sensor in hypothalamus – Interacts with Ca⁺ and proteins, signaling of chemosensory transduction 	<ul style="list-style-type: none"> cAMP and cGMP inhibition – Causes taste bud abnormalities – Hypogeusia – Ageusia
Salivary hormones – Glucagon – Leptin – Ghrelin – Insulin	<ul style="list-style-type: none"> – Modulation of taste perception 	<ul style="list-style-type: none"> – Lack of <i>glucagon</i> causes reduce response to sucrose – Increase of <i>leptin</i> suppresses sweet sensation – Lack of <i>ghrelin</i> causes reduced sour and salty taste – Presence of salivary <i>insulin</i> enhances salty taste
Electrolytes – NaCl – K ⁺ – MG	<ul style="list-style-type: none"> – Regulate pH – Maintain flow rate – Regulate taste 	<ul style="list-style-type: none"> – Taste adaptation due to salivary concentration – Low MG makes umami taste unpleasant
Enzymes – Amylase – Protease – Lipase	<ul style="list-style-type: none"> – Digestive of nutrients – Conversion of micronutrients into perceivable taste molecules 	<ul style="list-style-type: none"> – Higher caffeine perception with lower protease levels – Increased amylase causes hydrolysis of starch to maltose, reducing sweet taste – Amylase activity reduces salty taste
Proteins – PRPs – vEGP	<ul style="list-style-type: none"> – Salivary binding of molecules (tannins) – Assist in digestion – Binding aroma compounds to olfactory receptors 	<ul style="list-style-type: none"> – Low salivary protein shows high astringency – PRPs supplements show high response to bitter taste – PRPs supplements show perception of roughness – vEGP discrepancy can cause low perception of fatty taste
Flow rate	<ul style="list-style-type: none"> – Maintain concentration of taste compounds – Protection of taste buds – Taste perception, interaction with sensory stimuli 	<ul style="list-style-type: none"> Low flow rate is associated with – Bitter taste – Astringency – Increase flow rate is associated with reduced – Sour taste – Salty taste

Abbreviations: cAMP, 3',5'-cyclic adenosine monophosphate; cGMP, 3',5'-cyclic guanosine monophosphate; MG, monosodium glutamate; PRPs, proline-rich proteins; vEGP, von Ebner Gland protein; Zn, zinc.

with polymorphism of gustin gene.³⁹ Moreover, hypogeusia or ageusia is also associated with low levels of cAMP and cGMP in the saliva, as cAMP is a possible growth factor for taste buds.⁹ cAMP and cGMP play a critical role in chemosensory transduction.⁴⁰ cGMP is suggested to be vital in interaction with Ca and proteins in signaling of the gustatory and olfactory systems.^{41,42} A cAMP-activated protein kinase acts as a nutrient and sensor in the hypothalamus, and it activates cell surface and send signals in association with G proteins.^{43,44}

Salivary Hormones and Ageusia

Salivary hormones are also implicated in the development of taste buds and possibly influence the taste sensation. Multiple animal studies have suggested that hormones including glucagon, insulin, leptin, oxytocin, and ghrelin

influence taste modalities.¹⁰⁻¹² Glucagon and leptin have shown to modulate sweet taste by suppressing response to peripheral taste receptors.^{45,46} In addition, salivary insulin is shown to augment the salty taste, however, lack of ghrelin compromises sour (citric acid) and salty taste.^{47,48}

Flow Rate, Inorganic Components of Saliva, and Ageusia

Interestingly, salivary flow rate is linked to the taste sensation. The concentration of taste compounds is influenced by volume of saliva at the receptors.⁴⁹ In cases of low salivary flow, sweet and sour taste is not influenced; however, a persistent feeling of bitterness and astringency is reported.¹³ The salivary flow rate, by addition of artificial saliva, has shown a reduction in the perception

of citric acid (sour) and sodium chloride; however, this could be due to salivary dilution.⁵⁰ Inorganic compounds of saliva are also related to taste perception, for instance, minerals in saliva, especially sodium. The taste receptors are adapted to the sodium levels in the saliva, and for salty taste to be produced a threshold of sodium must be maintained. As a result at high salivary flow rates, sodium concentration increases and with reabsorption in salivary ducts, sensitivity for sodium is lower.^{16,51} Other substances, such as monosodium glutamate, are also associated with heightened taste perception of umami.⁵² Furthermore, one of the main functions of saliva is regulation of oral pH by producing bicarbonate. The perception of sourness falls when the pH increases, as the buffering capacity of saliva increases in line with the flow rate.¹⁴

Salivary Enzymes and Ageusia

Salivary enzymes including amylase, protease, and lipases are connected to taste perception of food. They are involved in the conversion of larger nutrients into molecules, which are perceived by the taste receptors. Hydrolysis of triglycerides in the diet with lipases release fatty acids which can be perceived by the taste system.⁵³ A protease inhibitor, cystatin-SN, is reported to be associated with perception of caffeine.⁵⁴ Moreover, a relation between reduced salty taste and amylase activity in NaCl containing starch food is suggested.⁵⁵ Therefore, in addition to digestion, these enzymes (amylase, protease, and lipase) play an important role in maintaining normal taste perception.

Salivary Proteins and Ageusia

Also, of concern, some of the salivary-binding proteins including PRPs are reported to be associated with astringency. PRPs are intrinsically produced and bind with tannins to prevent their digestive complications.⁵⁶ Therefore, based on this mechanism, the presence of low salivary protein content is associated with higher percentage of astringency.¹⁷ PRPs are also implicated in the perception of taste, a study suggested that supplementation of PRPs (Ps-1) in patients with low Ps-1 displayed high response to bitter taste.⁵⁷

Salivary Gland Infection and Salivary Composition

As suggested before that SARS-CoV-2 is reported in salivary secretions of infected patients for up to 4 weeks.^{18,19} In addition to the viral presence in the GCF exudate and presence in oropharyngeal sputum, viral infection of the minor and major salivary glands is a possible reason for its presence in saliva. Animal studies have suggested the presence of SARS-CoV in salivary epithelial cells among infected rhesus macaques.²² It is also reported that viral-specific IgA is produced in saliva of animal models intranasal immunized, further supporting the viral presence.⁵⁸ Salivary gland epithelial cells with ACE2/cytokeratin receptors are the early target cells in the upper respiratory tract along with pneumocytes. This occurs in the early part of viral infection and is a proven source of virions in the patient saliva.⁵⁹ Salivary

gland constituents and composition can be influenced by the viral infections of the gland. In a study by Marder et al, parotid gland salivary constituents were assessed for proteins, electrolytes, antibodies, enzymes, and flow rate in the presence of cytomegalovirus in human immunodeficiency virus patients.²³ Potassium, protein, and IgA levels were higher among infected individuals in comparison to controls.²³ Suggesting that salivary gland infection can alter the salivary constituents.

Recommendations for Future Studies

The presented association of COVID-19 salivary alterations and ageusia suggest that all precautions should be taken to avoid salivary contamination and droplet infections of SARS-CoV-2 and salivary gland infections. Limited evidence is available on assessing the influence of COVID-19 infection on the salivary, flow rate, pH, protein (PRPs), inorganic constituents (sodium, potassium, and zinc), immunoglobulin, enzymes (protease, amylase, and lipase), and hormone (insulin, glucagon, ghrelin, and leptin) levels in comparison to noninfected subjects. Future studies can correlate salivary changes in COVID-19 infection and ageusia as a novel finding. In addition, correlation of salivary constituent changes and early symptoms of COVID-19 (ageusia) will allow early diagnosis of SARS-CoV-2 infected patients and prevention of disease transmission. Studies can also explore the causes of ageusia and anosmia in COVID-19 disease and the association of cAMP and cGMP in taste bud and sensory cells growth in COVID-19.

Conclusion

Literature suggests that ageusia is associated with COVID-19 infections and the viral infection of the salivary gland cells may alter the salivary constituents and composition. Salivary constituents including proteins, inorganic constituents, enzymes, hormones along with salivary flow rate, and pH play a critical role in taste perception. Therefore, the early symptoms of ageusia among the COVID-19 patients are potentially associated with the salivary constituent modifications due to salivary gland infections.

Conflict of Interest

None declared.

Acknowledgment

The authors are grateful to the Deanship of Scientific Research, King Saud University for funding through Vice Deanship of Scientific Research Chairs, Research Chair for Biological Research in Dental Health.

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