Article title: Salivary Glands, Saliva and Oral Presentations in COVID-19 infection

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Abstract
Since the outbreak of the novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, several published reports in the scientific literature called attention to the oral cavity as the potential route of infection, the implications for dental practice and the use of saliva in the diagnose of the COVID-19. Here, we would like to review the available literature on the salivary glands and saliva in the context of SARS-CoV-2 infection. A brief discussion of the oral manifestations is also presented.

Keywords: Infectious diseases; Sars-CoV-2; Salivary glands; Saliva; Oral manifestations.

Introduction

The first description of human coronavirus was published in 1965 [1]. It has generally been thought that coronaviruses could cause a future disease outbreak [2]. Since 2002, beta coronaviruses (CoV) have caused SARS-CoV in 2002-2003, MERS-CoV in 2012, and the newly emerged SARS-CoV-2 in December 2019 [3]. The first case of a novel coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was reported in Wuhan city, China [4]. Even though has been considerable debate on the origin of the COVID-19 causative virus, reports show that it is not a purposefully manipulated virus [4,5].

The SARS-CoV-2 is highly transmitted from man to man through close contact with infected patients, leading to rapid global spread by infected travelers from China [6,7]. Also, substantial undocumented infections were found to facilitate the rapid dissemination of COVID-19 [6]. On January 30, 2020, the World Health Organization (WHO) declared that COVID-19 is a public health emergency of international concern [6,7] as it is killing thousands of people worldwide. According to the most recent data from the Johns Hopkins Coronavirus Resource Center (coronavirus.jhu.edu/), the global number of confirmed cases of COVID-19 was 5.432.512 with 345.375 deaths on May 25.

Several published reports had drawn attention to the oral cavity as the main route of infection [8], the implications for dental practice [9] and the potential use of saliva in the diagnose of the COVID-19 [10,11]. A recent communication suggested the hyposalivation as responsible for exposing patients to a higher risk of getting coronavirus disease [12]. Besides, taste loss was reported in COVID-19-positive patients [13]. Here, we would like to critical review the available literature on the salivary glands and saliva in the context of SARS-CoV-2 infection. A brief discussion of oral manifestations is also presented.

SARS-CoV-2 infection

The SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE2) as an important receptor for entry into target cells and replication. SARS-CoV-2 employs the cellular transmembrane serine protease 2 (TMPRSS2) for spike protein priming and that inhibition of TMPRSS2 could at least partially protect against SARS-CoV-2 infection [14]. In addition, the viral spike protein of SARS-CoV-2 appears to be dependent of sialic acid-rich proteins and gangliosides GM1 [15]. Gangliosides are glycosphingolipids containing sialic acid found in mammalian tissues but are most abundant in the brain [16]. The gangliosides GM1 are primarily recognized as an essential component of membrane rafts, which play an important role in many cellular processes, including pathogen entry [17].

Salivary Glands and Saliva

The three pairs of major (submandibular, parotid and sublingual) and minor salivary glands secrete saliva in the mouth. Saliva presents diverse functions, including lubrication, initiation of digestion, and immunity [18]. It is a biofluid rich in water, ions, and several protein groups, including mucins, which are proteins glycosylated, and most have high sialic acid content [19]. Also, a range of disease biomarkers are recognized in saliva [20].

The expression of SARS-CoV-2 has been detected in the oral epithelium [8] and in cough out [10,21] and swabs of human saliva [22]. These studies point to the importance of saliva for diagnostic strategies. It is worth to note, however, that the source of the virus in some studies were not investigated [10,21]. In one study, the tongue of each patient was lifted and saliva was collected directly from the submandibular duct, which drains saliva from each bilateral submandibular and sublingual glands [23]. Interestingly, the expression of SARS-CoV-2 was found in four out of 31 (12.90%) COVID-19 patients [23]. Another important finding of the study of Chen and Colleagues [23] was that expression of SARS-CoV-2 was higher in critically-ill patients (3/4), which suggested the virus invasion due to high viral loads or destroyed salivary glands at the late stage of the disease. Additionally, analysis of ACE2 in human organs showed a high expression of

ACE2 in minor salivary glands [24]. Besides the high content of sialic acids in salivary mucin, the salivary glands were shown to present gangliosides GM1 [25] and TMPRSS2 [26]. Overall, the literature suggests that SARS-CoV-2 could infect salivary glands [23]. Given the actual body of evidence, it is not possible, however, to make speculations regarding them as reservoirs for SARS-CoV-2.

Hyposalivation

The salivary gland secretion is dependent on several factors, including temperature, circadian rhythm and intensity, and type of taste and on chemosensory, masticatory, or tactile stimulation [20]. Hyposalivation, the reduction of unstimulated salivary flow rate, is a common finding in patients mainly reported as a consequence of the use of medication and psychological processes [27].

Dry mouth was shown to be manifested in a relatively high proportion of COVID-19 patients [23]. A recent communication has drawn attention to hyposalivation as responsible for exposing patients to a higher risk of getting coronavirus disease (COVID-19) once the presence of many proteins with antiviral properties in saliva could be reduced [12]. Interestingly, the SARS-CoV-2 infection is more severe in individuals over 50 years of age and with the presence of associated comorbidities such as diabetes, cardiovascular problems and diseases involving the nervous system [28-30]. It is known that salivary flow reduces with age and is not explained based on medications used by older adults [31]. Besides, diabetes and medications for systemic disorders have also been associated with hyposalivation [32,33]. It is known that infectious and inflammatory processes might also lead to hyposalivation and, thus, the possibility of qualitative and quantitative disturbances in saliva secretion by SARS-CoV-2 infection in the salivary gland should not be discarded.

Taste Disorders

Taste disorders have been reported in a variety of clinical problems [34]. Amblygeustia, a diminished sensitivity of taste, was shown to be manifested by a relatively high proportion of COVID-19 [23]. In a study in which patients with influenza-like symptoms underwent Covid-19 testing, smell and taste loss were reported in 68% (40/59) and 71% (42/59), respectively, of COVID-19-positive patients suggesting that chemosensory dysfunction should be considered when screening symptoms [13].

Low salivary rate and disturbances in salivary biomarkers were suggested to cause xerostomia [35,36], which has been associated with taste sensorial complaints. Moreover, oral neuropathy or neurological transduction interruption induced by salivary compositional alterations is responsible for oral sensory complaints and loss of taste function [37,38]. Possible taste alterations as result of the direct effect of SARS-CoV-2 infection in sensory neurons or other components of the peripheral gustatory system should also be considered.

Oral findings

It is known that the oral cavity may exhibit manifestations of underlying diseases such as oral ulcerations, gingival bleeding, glossitis, oral pain, or halitosis [39]. Viral infections usually manifest as either ulceration or blistering presentation of oral tissues [40,41]. A case report suggested that recurrent oral ulcers could be an inaugural symptom of COVID-19 [42]. Also, a report of three cases showed that pain and intraoral manifestations such as oral ulcers or blisters before seeking medical advice was a common finding in COVID-19 [43]. Thus, it was encouraged to perform intraoral examinations in patients suspected of SARS-CoV-2 [43]. As these oral findings are still new in the literature, their occurrence may vary significantly among COVID-19 patients and, thus, the associated systemic diseases and/or poor oral health may be a contributory factor to the oral presentations. Given the possibility of immunocompromised statuses of the patients, it is also possible that the oral manifestations may be related to other viruses or bacteria.

Conclusion

The Sars-CoV-2 infection is responsible for several events in the mouth. Studies, however, are necessary to understand the real role of salivary glands and saliva in COVID-19 patients.

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Author's Contributions

MSP contributed to the conception and design, performed the analysis and interpretation, wrote the manuscript and final approval of the version to be submitted.
CRS contributed to analysis and interpretation, critically revised the manuscript and final approval of the version to be submitted.
FNN contributed to conception and design, performed the analysis and interpretation, critically revised the manuscript, and final approval of the version to be submitted.

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