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CRITICAL REVIEW

Salivary Glands, Saliva and Oral Findings in COVID-19 Infection

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Abstract

The world is under the threat of the novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite several efforts to contain the disease spread, it still constitutes a public health emergency of international concern. Several published reports in the scientific literature called attention of 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. The aim of this article is to provide an overview of the literature on the salivary glands and saliva in the context of SARS-CoV-2 infection. A brief discussion of taste disturbances and oral findings in COVID-19 patients is also presented. The literature shows that SARS-CoV-2 could infect the salivary glands. It is not possible, however, to make speculations regarding them as reservoirs for the SARS-CoV-2. In addition, patients with COVID-19 presented several oral repercussions, including hyposalivation and taste disturbances. A few reports showed oral ulcers and blisters associated with SARS-CoV-2 infection. However, it remains not fully understood and might lead to erroneous assumptions. Overall, further studies are necessary to understand the real role of salivary glands and saliva in the context of SARS-CoV-2 infection.

Keywords: Infections; Severe Acute Respiratory Syndrome; 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 future disease outbreaks [2]. Since 2002, beta coronaviruses 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 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]. In addition, 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 as a public health emergency of international concern [6,7]. According to the most recent data from the Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu), the global number of confirmed cases of COVID-19 was 8.407.325 with 450.716 deaths on June 18.

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]. The aim of this article is to provide a brief overview of the literature on the salivary glands and saliva in the context of SARS-CoV-2 infection. A brief discussion of taste disturbances and oral findings in COVID-19 patients 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 the 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 monosialotetrahexosylgangliosides (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 essential components 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]. In addition, 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 noting, 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 [22]. 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 [23].

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.

Saliva as a Diagnostic Tool

Early disease detection is crucial to reduce disease severity and prevent complications [27]. Saliva shows high potential for monitoring general health and disease due to its abundance in disease biomarkers and the advantages of being an easy, safe, cost-effective and non-invasive diagnostic approach [27,28]. Recent research suggests that saliva can be used as a viable diagnostic fluid for the detection of COVID-19 [11,29,30]. Saliva was found to be even more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs [31]. This biological fluid could also enable at-home self-administered sample collection for accurate large-scale SARS-CoV-2 testing [29,31].

Hyposalivation

The salivary gland secretion is dependent on several factors, including temperature, circadian rhythm and intensity and type of 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 [32].

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 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 [33-35]. It is known that salivary flow reduces with age and is not explained based on medications used by older adults [36]. Besides, diabetes and medications for systemic disorders have also been associated with hyposalivation [37,38]. It is known that infectious and inflammatory processes might also lead to hyposalivation [39,40]. 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 [41]. Amblygeustia, a diminished sensitivity of taste, was shown to be manifested by a relatively high proportion of patients with 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 [42,43], 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 [44,45]. Possible taste alterations as a 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 [46]. Numerous viral diseases can affect the oral cavity, either directly or secondarily as a result of a systemic disorder. In addition, the oral manifestations of viral infections may vary but are usually manifested as either ulceration or blistering in oral tissues [47-49]. To the best of our knowledge, the scientific literature lacks reports of oral findings associated with previous coronaviruses. The misdiagnose of the oral findings related to COVID-19 is possible as it shares a common etiological course with several other dermatological manifestations. A case report suggested that recurrent oral ulcers could be an inaugural symptom of COVID-19 [50]. In addition, a report of three cases (two suspicious and one confirmed) showed that pain and intraoral manifestations such as oral ulcers or blisters before seeking medical advice were a common finding in COVID-19 [51]. Thus, it was encouraged to perform intraoral examinations in patients suspected of SARS-CoV-2 [51].

As the 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 (e.g., herpes simplex, varicella zoster, and human immunodeficiency) [47-49]. As research is still ongoing and intraoral examinations have not yet been considered when screening for this disease, literature still lacks evidence to understand better the underlying mechanisms of the oral findings in COVID-19 patients. Thus, it is not possible to affirm that the oral findings, reported in the literature, are direct manifestations of SARS-CoV-2 infection.

Conclusion

The SARS-CoV-2 infection is responsible for several events in the mouth, including hyposalivation and taste disturbances. A few reports showed oral ulcers and blisters associated with SARS-CoV-2 infection. However, it remains not fully understood and might lead to erroneous assumptions. Studies are necessary to understand the real role of salivary glands and saliva in this disease context.

Authors' Contributions

MSP	0000-0002-4052-7208	Conceptualization, Methodology, Formal Analysis, Writing – Original Draft Preparation and Writing – Review and Editing.
CRS	0000-0002-5719-6505	Formal Analysis and Writing – Review and Editing.
FNN	0000-0002-6595-9154	Conceptualization, Methodology, Formal Analysis and Writing – Review and Editing.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

None

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