Oral Oncology 108 (2020) 104821

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Oral saliva and COVID-19

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ARTICLE INFO

Keywords:
COVID-19
Dentistry
Saliva
Salivary glands

ABSTRACT

Outbreak pneumonia announced in Wuhan, China, in December 2019, had its causative factor classified as a new coronavirus (SARS-CoV-2). Since saliva can host several viruses including SARS-CoV-2, the transmission chance of viruses through saliva, particularly those causing respiratory infections, is unavoidable. COVID-19 can be detected through salivary diagnostic testing which has lots of advantages for medical care professionals and patients. It should be noted that not only does saliva offer an ecological niche for the colonization and development of oral microorganisms, but it also prevents the overgrowth of particular pathogens such as viral factors. The aim of this study is to gather all the information about saliva and its association with COVID-19 for the whole health care professionals across the world.

Introduction

Outbreak pneumonia announced in Wuhan, China, in December 2019, had its causative factor classified as a new coronavirus. On March 11, 2020, the World Health Organization (WHO) announced that the epidemic of the latest coronavirus, Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), is pandemic currently known COronaVIrus Disease (COVID-19). Until May 20, 2020, the number of confirmed cases is 4,789,205 with over 318,789 deaths in 213 countries or territories [1,2].

The clinical symptoms of COVID-19 are cough, fever, shortness of breath, muscle pain, sore throat, confusion, chest pain, headache, rhinorrhea (4%), diarrhea, and nausea and vomiting. SARS-CoV-2 transmits human-to-human by either direct transmission such as cough, sneeze, and droplet inhalation, or contact transmission like ocular contact, saliva, mucous membranes of the nose and eyes [2,3].

Since saliva can host several viruses including SARS-CoV-2, the transmission chance of viruses through saliva, particularly those causing respiratory infections, is unavoidable in a dental office. Based on experience in combating the COVID-19 outbreak, stopping disease transmission by saliva in the dental clinic is vital to the safety of doctors and patients.

The analysis of saliva in COVID-19 cases can help to explain the pathogenesis because epithelial oral cavity cells demonstrated ample expression of the Angiotensin-Converting Enzyme 2 (ACE2) receptor that plays a critical role in allowing SARS-CoV-2 to enter the cells [4].

A quick and efficient diagnosis of COVID-19 is essential in monitoring the pandemic. The suggested upper respiratory tract specimen types to diagnose COVID-19 are oropharyngeal and nasopharyngeal swabs. Nevertheless, gathering these specimen types involves direct interaction between health workers and patients, presenting a high risk of virus transmission. Moreover, collecting oropharyngeal or nasopharyngeal specimens comes with pain and can lead to bleeding, particularly in thrombocytopenia patients. Thus, oropharyngeal or nasopharyngeal swabs cannot be suitable for serial controlling of viral load. Specimens of saliva can be conveniently given by telling patients to spit into a sterile container [5].

The aim of this study is to gather all the information about saliva and its association with COVID-19 for the whole health care professionals across the world.

Human saliva

Human saliva is a distinctive body fluid that is produced by the salivary glands. Saliva mostly consists of water (94–99%) with organic molecules accounting for nearly 0.5% and inorganic ones for 0.2%. It plays an important role in digesting food, lubricating oral mucosa, cleaning and preserving the oral cavity, and influencing the homeostasis of the oral cavity. A normal adult usually generates about 600 ml of saliva every day. Besides salivary gland excreta, saliva also includes food particles, serum elements, oral microorganisms and their metabolites, white blood cells, and exfoliated epithelial cells.

By now, over 700 microbial species have been detected in saliva, many of which are linked to oral and systemic diseases. Not only does

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https://doi.org/10.1016/j.oraloncology.2020.104821
Received 21 May 2020; Accepted 24 May 2020
Available online 27 May 2020
1368-8375/

saliva offer an ecological niche for the colonization and development of oral microorganisms, but it also prevents the overgrowth of particular pathogens to preserve the homeostasis of the oral cavity. In addition, saliva may serve as a gatekeeper, and prevent pathogens from spreading to the gastrointestinal and respiratory tract [6].

SARS-CoV-2 has at least three separate routes to present in saliva. SARS-CoV-2 in the lower and upper respiratory tract reaches the oral cavity along with the liquid droplets; SARS-CoV-2 in the blood may enter the mouth through the gingival crevicular fluid; and major and minor infection of the salivary gland, with the ensuing release of particles into the saliva through salivary ducts [7].

Hyposalivation

Human saliva is a complicated fluid and plays a crucial role in preventing from a viral infection, especially through the innate immune system, which is a notable first-line defense [8]. Iwabuchi et al. proposed that hyposalivation could result in severe respiratory infection. Two possible explanations for enhancing the incidence rate of this infection are as follows:

- Lowered saliva secretion can disrupt the oral and airway mucosal surfaces as a physical barrier, thereby enhancing the viral colonization and adhesion.
- This decrease may also hinder the secretion of antimicrobial peptides and proteins [8,9].

Considering the existence of various proteins with established antiviral characteristics in saliva such as lysozyme, mucins, cathelicidin (LL-37), lactoferrin, peroxidase, sIgA SLPI, salivary agglutinin (gp340, DMBT1), alpha-defensins, beta-defensins, and cystatins, some of which may potentially impede virus replication especially SARS-CoV-2. Besides, antiviral activity in saliva can be due to salivary microvesicles including at least 20 microRNA's, which may restrict the replication of some types of viruses. This provides the idea that these salivary proteins can have the same defensive impact against SARS-CoV-2. A possible risk factor for severe respiratory infection could be hyposalivation. It can leave patients at a significant risk of getting COVID-19 [8].

Salivary glands as potential reservoirs for COVID-19

ACE-2 is a critical COVID-19 receptor. Liu et al. studied SARS-CoV and showed that epithelial cells of salivary gland having elevated ACE-2 expression were infected [10]. The ACE-2 expression in minor salivary glands was greater than that in the lungs, indicating that a target for COVID-19 may possibly be salivary glands. Furthermore, before lung lesions emerge, SARS-CoV RNA can be found in the saliva. This could account for asymptomatic infections. For SARS-CoV, the salivary gland is a significant reservoir of the virus in saliva. The positive rate of COVID-19 in the saliva of patients can exceed about 92%, and the live virus can also be cultivated through saliva samples. This proposes that COVID-19 spread through asymptomatic infection may come from the contaminated saliva. Consequently, the source of asymptomatic infection could be salivary glands [11].

Transmission of saliva droplets

The size of droplets can determine how far and long they can fly along with the airflow. Huge droplets within a short distance or touching infected surfaces spread majority of transmissible respiratory infections. Huge droplets with a diameter of greater than 60 μm appear to settle rapidly from the air, making the transmission risk minimal for individuals in close vicinity to the source of the saliva droplet. Small droplets with a diameter of less than or equal to 60 μm can cause short-range transmission for individuals with distance less than one meter. In a desirable environment, small droplets are likely to fade away into droplet nuclei with a diameter of less than 10 μm, and then become capable of long-range aerosol transmission.

When speaking, coughing, sneezing, or even breathing, saliva droplets are produced and shaped as particles in a combination of moisture and droplet nuclei of microorganisms. The quantity, distance, and size of saliva droplets vary among individuals, indicating that the infectious intensity and transmission route of saliva droplets differ when the same pathogen is contracted. Each cough can produce about 3000 saliva droplets nuclei, which is approximately equivalent to the quantity generated during a 5-min chat. Each sneeze can produce roughly 40,000 droplets of saliva covering several meters in the air. A regular exhalation may create saliva droplets that exceed one meter in the air. Huge saliva droplets with more mass typically fall to the ground ballistically and small saliva droplets fly by airflow like a cloud over longer distances.

For a susceptible host to develop infectious droplets of saliva, they can enter the mouth, eyes, or be inhaled directly into the lungs. The virus may lead to another individual's respiratory infections by inducing ocular complications. Thus, the SARS-CoV contamination was minimized to a degree by wearing surgical masks and protective eyewear or face shield in vulnerable healthcare workers [2,12].

SARS-CoV-2 may cause acute and chronic sialadenitis

Wang et al. proposed that SARS-CoV-2 might induce acute sialadenitis and associated symptoms, such as pain, discomfort, inflammation, and secretory dysfunction in salivary glands.

SARS-CoV-2 can attach to ACE-2 receptors on the epithelium of salivary glands, fuse with them, replicate, and lyse cells to trigger apparent signs and symptoms, such as discomfort, inflammation, and pain in major salivary glands. After the cytolytic activity of SARS-CoV-2 lyses the acinar cells, salivary amylase is unleashed into the peripheral blood. It can be inferred that the amylase rises in peripheral blood during the early contamination process. Secreted inflammatory cytokines facilitate the inflammatory reaction that destroys the tissue of the salivary glands as the immunopathological process continues. Granulation and fibrogenesis can restore the inflammatory damage by decreasing immunoreaction. After the severe stage, the function of salivary glands can be anomalous due to contamination with SARS-CoV-2, which may induce chronic sialadenitis [13].

Current COVID-19 diagnosis

The main strategy of identification for COVID-19 is Reverse Transcription quantitative Polymerase Chain Reaction (RT-qPCR), which is commonly used to extract viral RNA from oropharyngeal and nasopharyngeal swabs or sputum samples. In addition, a chest X-ray may be an invaluable diagnostic method for identifying bilateral pneumonia, displaying as multi-lobar ground-glass opacities with an asymmetric, peripheral, and posterior distribution [14].

Salivary diagnostics

Saliva is now widely established as a reservoir for biological indicators that range from modifications in nucleic acids, proteins, and biochemicals to the microflora. As a diagnostic fluid, saliva has tremendous potential and advantage over other biological fluids because the sampling process of saliva does not entail an invasive intervention, and it is inexpensive and helpful for controlling the systemic health. In the near future, designing accurate and responsive salivary diagnostic instruments and the implementation of established guidelines following meticulous testing will enable the use of salivary diagnostic as chair-side tests for diversified oral and systemic diseases. The benefits of salivary diagnostic tests are economical, noninvasive, healthier to apply than serum sampling, diagnostic values in real-time, no requirement for specialized healthcare workers, numerous samples are simple to obtain,

Table 1
The most recent clinical findings using salivary diagnostic tests for COVID-19.

Study	Number of patients	Sample source	Diagnosis efficiency in Saliva
Azzi et al. [17]	25 (17 males, 8 females) with mean age: 61.5±11.2	Drooling saliva	100% viral positive
To et al. [5]	12 (7 males, 5 females) with median age: 62.5	Saliva from the throat by coughing out	91.7% (11/12)
Chen et al. [18]	13 confirmed COVID-19 patients with 4 critically ill	Opening of salivary gland canal	30.7% (4/13) 75% (3/4) in critically ill patients
To et al. [19]	23 (13 males and 10 females) with median age: 62	Posterior oropharyngeal saliva	87% (20/23)
Williams et al. [20]	39 confirmed COVID-19 patients	Spit saliva	85% (33/39)
Azzi Et al. [21]	A 71-year-old man with a negative respiratory swab test	Drooling saliva	100%
	A 64-year-old-man with a negative respiratory swab test	Collected saliva with a pipette	100%

collecting and monitoring are doable at home, minimizing the possibility of cross-infection, better shipping and storage than serum sampling, lesser agitation during the diagnostic process, screening assays are commercially available, and saliva does not clot and can be handled more efficiently than blood. Thus, salivary diagnostic testing can offer a convenient and cost-effective mechanism for early-diagnosis of Covid-19 [15].

It has been documented that three methods capture saliva thus far: saliva swabs, coughing out, and directly from the salivary gland duct. For clinical applications needing a strong positive rate of virus identification, saliva from deep throat provides the strongest positive rate, which could account for early-diagnosis of COVID-19. Saliva extracted from saliva gland ducts is consistent with acute COVID-19 which may likely be a reliable and noninvasive test for acute patients [12].

There are several diagnostic methods that can be conducted before commencing a dental emergency treatment in dental clinics including loop-mediated isothermal amplification (LAMP) tests, antibody testing, and microfluidic RT-PCR devices [7,16].

There are six studies evaluating the diagnosis efficiency of saliva and all the associated information is shown in Table 1.

Evaluation and treatment of patients with salivary gland disease in this pandemic situation.

A three-step guideline to survey patients with salivary gland disease is as follows [22]:

(1) Primary telemedicine examination
   1.1. Recognize patients having touchable or visible lesions, mass presence in the majority of salivary gland region, and neoplasm symptoms
   1.2. Ask the history of skin cancer of the head and neck, lymphoma, etc.
   1.3. Ask the clinical symptoms and history of inflammatory salivary gland disease
(2) Diagnostic examination for patients suspected of having salivary gland neoplasm
   2.1. COVID-19 screening
   2.2. FNA biopsy
   2.3. Ultrasound of salivary gland
   2.4. Extra imaging such as MRI, if needed
   2.5. Make sure of the existence of salivary gland disorder
   2.6. Identify signs and symptoms of non-neoplastic illness
(3) Patient counseling and recommendations for treatment
   3.1. Survey FNA biopsy outcomes
   3.2. Assess treatment options and prognosis
   3.3. Prescribe COVID-19 test before any surgery
   3.4. Pay attention to age comorbidities of the patient
   3.5. Radiation oncology and hematology consultations, if required
   3.6. Considering the outbreak situation

Patients can optimally receive the test for COVID-19 before any surgical procedures. Health professionals need to be conscious about COVID-19 false negatives, and the infeasibility of repeating COVID-19 testing for most patients. In some selected cases, chest CT can be recommended for further assessment and risk stratification to evaluate signs of COVID-19-associated pulmonary activity or metastases.

Surgery will be postponed for any patients with abnormal chest CT results, those either with symptoms of COVID-19 or confirmed cases of COVID-19. If dental surgery is an emergency, dentists must address the possibility of aerosolization. Sinonasal area and pharynx, suitable PPE of the whole operating room team are strongly advised for minor salivary gland tumors of the oral cavity. The number of staff in the operating room must be minimized.

The risk of aerosolized mucosal secretions is only found during intubation and extubation for parotid and submandibular neoplasm surgeries. During intubation and extubation, all the staff in the room must wear suitable PPE while all unneeded staff must leave the room.

Controlling the obstructive salivary gland disease can be remotely conducted in most cases. In rare situations, intraoperative drainage and biopsy or office-based assessment and treatment procedures may be needed for handling an abscess, detecting cancer, relieving acute pain which has not been treated with proper medical care. Due to irrigation and aerosolization, sialendoscopy should be stopped during the outbreak of COVID-19 [22].

In addition, all dentists should know that the use of a mouthrinse and/or local nasal products, which include beta-cyclodextrins in conjunction with flavonoid agents, might provide invaluable adjunctive care to minimize the viral load of saliva and nasopharyngeal microbiota, including SARS-CoV-2 [23]. Therefore, dental professionals can create a safer atmosphere for themselves as well as their patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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