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Saliva as a Diagnostic Tool for Detection of Coronavirus-A Review

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ABSTRACT

We aimed in this literature review to demonstrate the association and potential of detecting novel coronavirus in saliva of patients and how its implication in future can aid in diagnosis as a non-invasive diagnostic modality. The specimen can be easily obtained and tested from suspected individuals. Review of available literature in PubMed, Google Scholar, EBSCO, and Semantic Scholar was carried out using keywords and combination of "Coronavirus", "saliva" and "diagnosis". Of 1846 articles found, 110 were screened and included in this literature review. Currently, nasopharyngeal swab is the standard diagnostic tool as it has been reported to be accurate and sensitive towards detection of coronavirus. Testing of saliva specimens is now being considered to aid rapid detection, because saliva collection and its testing are relatively simple, cheap, and safe for both patients as well as healthcare professionals. Further research on this will be beneficial to control and contain the virus.

Key words: Coronavirus pandemic, Diagnostic tool, Salivary specimen

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Introduction

In December 2019, an unknown number of pneumonia cases were reported from Wuhan, China which were later categorized as cases of novel coronavirus.[1] As the disease started to spread rapidly throughout China, this generated stress, panic, and anxiety among the individuals. Later on, healthcare authorities-imposed protection guidelines and protocols to contain this virus and prevent its further spread. Although this notion is still being debated upon, the possible origin of coronavirus is thought to be from bats.[2] On 11 March 2020, the World Health Organization (WHO) categorized novel coronavirus 2019 as a pandemic, providing guidelines to the world community for their protection.[3] Coronavirus is known to infect the respiratory, hepatic, and nervous systems of human beings as well as animals.[4] The current rapid spread of coronavirus mandates the identification of effective diagnosis as well as treatment of the patients.

The genome of the novel coronavirus consists of 4 genera (alpha, beta, gamma, and delta), with single-stranded positive-sense RNA. Once inside the body, SARS-CoV-2 uses ACE2 receptor for entry into the cell. This process is facilitated by a serine protease, TMPRSS2 which also cause viral activation by cleavage of S glycoprotein.[5] Zhou et al., proved further that novel coronavirus does not use any other receptors to initiate its action.[2] All tissues and organs of the body that expresses ACE2 receptors are prone to face coronavirus invasion and may present with various symptoms.[6] Large number of ACE2 receptors have been detected in Type II alveolar cells, cholangiocytes, upper esophagus and myocardial cells, respectively.[7]

The mode of transmission for COVID-19 is primarily through respiratory droplets, by direct human-to-human contact and touching objects that have been contaminated by an infected person. Characteristic clinical features of coronavirus mainly include fever, sore throat, dry cough and myalgia with some patients also experiencing stomach upset and disturbed smell sensation.[8]Moreover, the elderly and those with underlying co-morbidities tend to suffer more severe infection as well as mortalities from the pathology.[9] Symptomatic individuals are identifiable, but one of the major hurdles in tackling this pandemic are the asymptomatic individuals who unknowingly transmit the disease.[10] Moreover, severe infections and deaths have been reported in healthy individuals without any co-morbidities.[11] Handwashing, wearing a mask, social distancing and quarantine are some important preventive steps conveyed by WHO and Centers for Disease Control and Prevention (CDC).

Recently it has been reported that male gender tends to contract the virus more frequently as compared to the female gender.[12] Additionally, some professions are particularly prone to contract the virus such as Dental Surgeons**.**[13] Understanding the etiology, mode of transmission, and diagnostic tools can help in the rapid treatment as well as diagnosing the patients for timely interventions.

Presently, the novel coronavirus pandemic is a major dilemma worldwide, where governments, healthcare authorities, and individuals are striving to control its further spread. Most of the countries in the grip of this virus are pressurizing the medical community for coming up with treatments, vaccinations, and rapid and effective diagnostics modalities to control and contain it. Various studies have been carried out regarding the detection of coronavirus as indicated in the literature. Many studies report a positive correlation between coronavirus and its presence in saliva. The introduction of saliva as one of the diagnostic modalities for coronavirus can aid in the rapid testing of individuals whether at home or hospital. Review of available literature in PubMed, Google Scholar, EBSCO, and Semantic Scholar was carried out using keywords and combination of "Coronavirus", "saliva" and "diagnostic tool". Of 1846 articles found on the subject, 110 were screened independently by contributing authors to determine suitability for inclusion in this literature review.

Saliva as a physiological requirement for Oral Health

Saliva is a secretion produced in the oral cavity by major salivary glands which include parotid, submandibular and sublingual glands along with numerous minor salivary glands distributed throughout the mouth. Normally, a person produces around 600 ml of saliva, of which 90% is produced by major salivary glands with the remaining 10% by minor glands.[14] Many functions are performed by saliva including cleansing and protection of teeth, digestion, buffering, antimicrobial effect, and phonation along with other functions as well. Saliva consists of various molecules including electrolytes, carbohydrates, proteins, enzymes, and antibodies that are vital for oral cavity protection.[15]

Saliva as a Source of Virus Spread

Saliva has been known to harbor many viruses, presence of which aid in detection of many pathologies. Previously, viruses such as Zika virus has also been inoculated from saliva of the infected patients, indicating interaction of various salivary biochemicals with the virus.[16] As previously stated, ACE2 receptor is the primary site of action for coronavirus and salivary glands have an abundant number of these receptors. Apart from novel coronavirus, many other viruses have been detected in saliva such as Epstein-Barr virus, Herpes Simplex virus, Chikungunya virus and Ebola virus.[17] Lastly, extrapulmonary sites have also been reported to harbor coronavirus in both patients who have recovered from the infection as well as those who were asymptomatic.[18]

Pathogenesis of COVID-19

Angiotensin-converting enzyme 2 (ACE2) is an important receptor, through which SARS-CoV-2 mainly initiate its action. In previous experimental studies, ACE2 receptors were highly expressed in the salivary glands as compared to the lungs.[19] Sites in the oral cavity which have abundant number of ACE2 receptors include tongue and floor of the mouth.[20] In Rhesus Macaques, the epithelial cells lining the salivary glands were early targets of SARS-CoV-2.[21] Particular emphasis has been given to the induction of cytokine storm by SARS-CoV-2, whereby increased cytokine levels (IL-6, IL-10, and TNF-α), lymphopenia, and decreased IFN-γ expression in CD4+ T cells has been associated with severe COVID-19 infection.[22] This can lead to respiratory distress in the affected individuals which might even require need for ventilator support. In addition to the presence of coronavirus in human saliva, animals infected with coronavirus, have also shown the presence of the virus in their saliva.[23] Moreover, the presence of ACE2 receptors in salivary glands indicate that these glands are a potential target for inflammation by SARS-CoV-2.[24] Regarding human coronavirus replication, recently discovered Cystatin D, a salivary cysteine protease inhibitor has been found to be a potent inhibitor of replication of the novel coronavirus.[25] Xu et al. also report that saliva is a reservoir for coronavirus in asymptomatic patients, who can also transmit the virus to other healthy individuals.[19]

Current Diagnostic Modalities for Coronavirus

Currently, nasopharyngeal and oropharyngeal swabs are collected for detection of coronavirus from suspected patients. These specimens are tested using real-time RT-PCR.[26] Both nasopharyngeal and oropharyngeal swabs are regarded as sensitive for SARS-CoV-2 detection, but the collection of specimens at the right time is particularly emphasized.[27] By using this method, the healthcare workers are in close proximity with the suspected individuals posing a potential risk of being infected e.g. patient sneezing at the time of sample collection either due to discomfort or bleeding especially with patients suffering from thrombocytopenia. The recent development of detecting biological markers in saliva has aided in diagnosing various pathologies caused by an array of bacteria, viruses, and fungi. There has been a tremendous potential of using saliva as a potential diagnosing modality as this offers an edge over other diagnostic tools as the collection of saliva is relatively non-invasive and easy to collect.[28]

Method for Saliva Collection

Saliva is relatively easy to collect and the procedure can be performed at a hospital as well as homes, keeping the convenience of patients in mind.[29] The patient is asked to cough so that saliva is derived from their throat and spit in the sterile container. Viral medium is then added to the container as reported in the studies.[30]

Advantages of using Saliva as a diagnostic tool

Limitations of collecting and using nasopharyngeal and oropharyngeal swabs have been studied which includes the risk of nosocomial infection, a risk to the healthcare professional during sample collection and causing patient discomfort.[31] While collecting the nasopharyngeal sample, it is known that the method can cause sneezing and cough in patients thereby generated aerosols with an increase in the risk of transmission of the virus.[32] Saliva is relatively easy to collect, economical and multiple samples can be collected from the patient without any unnecessary discomfort, even at home.[33] Moreover, since the method is non-invasive, healthcare workers are safe from cross-infection when collecting saliva for diagnosis. Storage and shipping can also be carried out more easily.[34] Furthermore, no additional trained medical staff is required to perform the collection process.[35] Saliva does not clot like blood, so it can be manipulated easily and disposed of as well.[36]

Saliva, as a potential diagnostic tool for COVID-19

Keeping in mind how rapidly the pandemic has been spreading, quick and accurate diagnosis of Coronavirus is a must to control undesired effects on the global community. A study by To et al. reported that molecular testing of saliva compared with a nasopharyngeal swab, leads to an improved detection of respiratory viruses. [30] In a cohort study at two hospitals in Hong Kong, high levels of coronavirus were reported in the posterior oropharyngeal saliva samples of COVID-19 infected patients, especially during the first week after the presentation of the symptoms.[37] Additionally, a previous study by Wang et al. also reported detecting SARS-associated coronavirus in the saliva of the infected individuals.[38] It has been reported that initially the saliva sample detected high viral load, but with serial samples, the load declined eventually to the negative status of both saliva viral load and nasopharyngeal swab.[39] Virus was detected in saliva of an infected individual, but the difference of viral load was observed in those with mild and severe infections.[40] Furthermore, studies point out that coronavirus has also been found in the saliva of neonates and their mothers infected with SARS-CoV-2.[41] Additionally, countries with less resources can be benefited by the potential low-cost and non-invasive method of using saliva for diagnosis.

Comparison between Saliva and Nasopharyngeal Swabs for Coronavirus Detection

Nasopharyngeal swabs are widely used specimen in clinical practice for the detection of respiratory viruses, including coronavirus through PCR.[25] However, the risk of nosocomial transmission of 2019-nCoV is associated with collection of nasopharyngeal specimens, especially if the patient coughs during the procedure. [27,29] Additionally, the collection method of saliva overcomes these issues related to nasopharyngeal swabs. Kim et al. collected paired saliva and nasopharyngeal specimens from patients with suspected acute respiratory viral infections and reported that both samples were equally sensitive for isolation of the viruses.[42] However, a previous study by Jeongs et al. reported more optimal detection of respiratory viruses in sputum as compared with a nasopharyngeal swab.[43] Literature presents conflicting evidence of superiority and sensitivity of one method over the other. Robinson et al. reported saliva as more sensitive for detection of respiratory viruses[44] while Becker et al. noted that nasopharyngeal swab is more sensitive in detecting coronavirus (COVID-19) as compared to saliva specimen.[45] Hence, it can be said that both saliva and nasopharyngeal swab have their own importance as diagnostic modalities, with the conclusion that saliva testing should also be introduced, specifically for healthcare workers at risk of infection with COVID-19.[27]

Table I: Description of COVID-19 articles using saliva and/or other samples as a diagnostic modality in this review					
Type of Study	**Targeted Sample**	**Method of Sample collection**	**Tests Done on Sample**	**Results**	**Reference No.**
Cross-sectional study	530 patients	Tongue, nasal, and mid-turbinate samples collected by patient. Nasopharyngeal collected by healthcare workers	Reverse transcriptase PCR (RT-PCR)	Tongue, nasal, or mid-turbinate samples have more clinical usefulness compared with nasopharyngeal samples for the diagnosis of Covid-19 SARS-CoV.	31
Observational Cohort study	23 patients	Blood, urine, posterior oropharyngeal saliva and rectal swab	Reverse transcriptase quantitative PCR (RT-qPCR)	Salivary viral load highest during 1st week after onset of symptoms. Posterior oropharyngeal saliva samples more acceptable.	37
Epidemiological Surveillance study	12 patients	Saliva collected by coughing out from throat	Nucleic Acid Extraction and Real-time Reverse Transcription–Quantitative PCR for 2019-nCoV	The 2019-nCoV was detected in the initial saliva specimens of 11 patients (91.7%) with highest viral load in 5 patients (83.3%). Serial saliva specimens showed declines in salivary RNA levels after hospitalization.	39
Retrospective Cohort study	96 patients (3497 samples)	Respiratory, stool, serum and urine samples	Real-time PCR	SARS-CoV-2 mean duration of detection longer in stools sample than respiratory and serum samples. Virus persists longer with higher load in respiratory tissue of patients with severe disease.	40
Descriptive study	2 patients (mother & neonate)	Nasopharynx, Oropharynx, stool,	nCoV real-time polymerase chain reaction	Highest RNA copies of the viruses detected in nasopharynx. Stool viral	41

		saliva, plasma, and urine samples.		load remained higher than other samples.	
Prospective study	236 patients	Paired Nasopharyngeal swabs and saliva specimens	Multiplex RT-PCR	Nasopharyngeal swabs and salivary specimens equally effective to detect respiratory viruses.	42
Prospective study	154 patients	Nasopharyngeal swabs and sputum samples.	Multiplex real-time RT-PCR	Detection rates of respiratory viruses from sputum samples were significantly higher than from nasopharyngeal swabs.	43
Comparative study	137 patients	Nasopharyngeal swabs, throat swabs and saliva specimens	Direct fluorescent antigen testing and nucleic acid amplification tests	Throat swabs and saliva specimens are inferior to Nasopharyngeal swabs for detection of respiratory viruses.	44

Conclusion

Coronavirus is transmitted by person-to-person contact through respiratory droplets. Saliva is a potential reservoir for the novel coronavirus. Saliva specimens can be easily collected from the suspected patients with a relatively simple, cheap and comfortable method. Saliva diagnostics is an evolving field that can be incorporated as part of the disease diagnosis process, along with other diagnostic modalities. To analyze the potential of detecting coronavirus in salivary samples, more research is required to develop rapid testing methods which can be beneficial for the healthcare professionals, scientists and virologist for early and easy detection.

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