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REVIEW ARTICLE

Saliva in early detection of COVID- 19 infection

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ABSTRACT:
Saliva is secreted from the salivary glands and has multiple functions, including mouth cleaning and protection, antibacterial effects and digestion. With the rapid advancement in salivaomics, saliva is well recognized as a pool of biological markers. Saliva, as a non-invasive and safe source, could be a substitute for blood in the diagnosis and prognosis of diseases. This review summarizes the latest advancements in saliva-related studies and addresses the potential value of saliva in the early diagnosis of oral diseases, such as dental caries and periodontal disease, as well as cancer, diabetes and other systemic disorders. Recently with the outbreak of COVID- 19 in world, saliva again gained its importance because it is capable of diagnosing cases in early stages. The present review article highlights the diagnostic value of saliva in early detection of COVID- 19 infection.
Key words: COVID, diagnosis, saliva.

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INTRODUCTION

Saliva is a hypotonic fluid in nature. The major salivary glands such as the parotid glands, submandibular glands and sublingual glands secrete approximately 90% of saliva. The salivary glands have high permeability and are surrounded by abundant capillaries, blood and acini, which can exchange molecules. Hence, biomarkers in the blood circulation can infiltrate acini and ultimately secreted into the saliva.[1] Every day, 600 ml of serous and mucinous saliva is secreted from the human salivary glands which contains minerals, electrolytes, buffers, enzymes and enzyme inhibitors, growth factors and cytokines, immunoglobulins such as immunoglobulin A (IgA), mucins and other glycoproteins. Saliva has been studied thoroughly as a potential diagnostic tool and it is expected to become a substitute for other biological fluids such as serum or urine in disease diagnosis.[2]

An outbreak of coronavirus disease (COVID-19) is emerging and rapidly spreading worldwide. A public health emergency of international concern was declared over COVID-19, which is the sixth time WHO has declared a PHEIC since the International Health Regulations took effect in 2005. This new strain of disease was firstly reported in the late December of 2019 and has not been previously identified in human.[3] The novel coronavirus isolated by researchers afterward was named as 2019 novel coronavirus (2019-nCoV). Coronaviruses are enveloped RNA viruses, and two strains of them—severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)— are zoonotic in origin and known to cause fatal respiratory diseases as 2019-nCoV.[4] Due to wide distribution and genomes recombination of coronaviruses, 2019-nCoV is the successive but novel coronavirus and shown to have a higher rate of infection. Early diagnosis of coronavirus and effective prevention of transmission are core tasks in control of 2019-nCoV epidemic.[5]

Human diseases such as cancer, cardiovascular, metabolic, infectious and neurological diseases, have global impact. Diagnosis of these conditions is very demanding and needs supplementing clinical analysis with laboratory testing. Saliva is a complex fluid comprising of proteins, enzymes, hormones, antibodies, cytokines and antimicrobial constituents.[6] The process of entry of these constituents from the blood into the saliva is by transcellular, passive intracellular diffusion and active transport, or paracellular routes by extracellular ultrafiltration within the salivary glands or through the gingival crevice. Saliva is colourless, odourless and has a relative density of 1.004-1.009 and a pH of 6.6-7.1. Salivary fluid is an exocrine secretion comprising of approximately 99% water, containing a variety of electrolytes and proteins, represented by enzymes, immunoglobulins and other antimicrobial factors which are of importance to oral health.[7]

Diagnostic value of saliva for 2019-ncov

The officially pathogen detection is the confirmation of 2019-nCoV nucleic acid from throat swabs. Throat swabs are relatively invasive, induce coughing and cause bleeding occasionally, which may increase risks of healthcare workers infection. Saliva stands at the entry of respiratory system and was also found 2019-nCoV nucleic acid positive. With the nature of non-invasion and less hazard to healthcare workers, saliva specimen collection has the advantages of being more acceptable for patients and more secured for healthcare workers for diagnosis of coronavirus.[8] Till now, three approaches have been reported to collect saliva—coughing out, saliva swabs, and directly from salivary gland duct. In two studies on coughed out saliva, 11 cases out of 12 (91.67%) and 20 cases out of 23 (86.96%) COVID-19 patients were 2019- nCoV RNA positive in saliva, respectively. In one study of saliva swabs, half of 15 (50%) COVID-19 patients were 2019-nCoV RNA positive in saliva. In one study of saliva directly from salivary gland duct, four cases of 31 (12.90%) COVID-19 patients were 2019- nCoV RNA positive in saliva, three of which were critically ill. Early diagnosis of 2019-nCoV is still difficult, diagnostic value of saliva specimens for 2019-nCoV nucleic acid examination remains limited but promising, which we should still be cautious but expected about.[9]

Deep throat saliva

A study from To et al.[10] showed that deep throat saliva has high diagnosis rate of 2019-nCoV. Twelve positive patients were confirmed based on epidemiological history, clinical criteria, and laboratory detection of 2019-nCoV in nasopharyngeal or sputum specimens, and saliva were collected by coughing out a few days after hospitalization. Using real-time reverse transcription quantitative polymerase chain reaction by testing the S gene of 2019-nCoV, saliva specimens were positive for 2019-nCoV out of 12 patients (91.67%). Those 33 patients who are negative for laboratory test of 2019-nCoV were all negative in saliva examination. In addition, six patients offer serial saliva, and five out of them showed a declining trend of virus as hospitalization is going on. Live virus was detected in three patients of the above six patients by viral culture.

Expression of ACE2 in oral tissues

Xu et al.[11] assessed public bulk RNA-seq from paracarcinoma normal tissues and found expression of ACE2 in oral buccal and gingiva tissue. This group also analyzed data of single-cell RNAseq from patients' oral tissue and found that ACE2 were highly enriched in epithelial cells of tongue, and also in epithelial cells, T cells, B cells, and fibroblasts of oral mucosa. Saliva is generated in salivary glands and flow through ducts into oral cavity.

Liu et al.[12] analyzed rhesus macaques and found ACE2 were also expressed in epithelial cells lining on minor salivary gland ducts, which could be found in sinonasal cavity, oral cavity, pharynx, larynx, trachea, and lungs, amounting to 800–1000 individuals in total and contributing nearly 1% of saliva a day.

Saliva in oral cavity

Oral swabs are probably applicable in early detection. By harvesting oral swabs and testing RNA among 15 COVID-19 patients, Zhang et al.[13] found that half of them (50%) were 2019- nCoV RNA positive in oral swabs, four (26.7%) had positive anal swabs, six (40%)

had positive blood test, and three (20%) were serum positive.

Salivary glands

To rule out contamination of respiratory secretion, Chen et al.[14] collected saliva directly from the opening of salivary gland and found 2019-nCoV nucleic acid, suggesting that salivary glands were 2019-nCoV infected. Thirteen cases who were nucleic acid positive by oropharyngeal swab among COVID-19 patients were included, and four of them (12.90%) were positive in saliva. Three cases of these four were critically ill patients in need of ventilator support, suggesting 2019-nCoV nucleic acid positive in salivary-gland-originated saliva as an indicator of severity of COVID-19.

Saliva versus Blood

Like saliva, blood is a complex bodily fluid known to contain a wide range of molecular components, including enzymes, hormones, antibodies, and growth factors. While cells, tissues, stool, and other alternatives are routinely pursued, blood serum or plasma is traditionally and most frequently the source of measurable biomarkers. Although life-saving in many instances, the procedures required to collect and eventually analyze blood samples can often be expensive, problematic, and physically intrusive. Employing salivary fluids as a medium for biomarker development and evaluation alleviates subject/patient discomfort through the provision of a noninvasive method of disease detection.[15]

Comparatively, saliva carries many advantages over blood, including the following:[16]

1. Collection is undemanding. While blood sampling requires highly trained personnel, saliva procurement can be done by anyone, including self-collection.
2. The procedure is noninvasive. Sample procurement is painless, reducing the discomfort most individuals endure from biopsies and repeated blood draws, while encouraging others to participate in timely medical evaluations and screenings.
3. Samples are safer to handle. Salivary secretions contain factors that inhibit the infectivity of HIV, resulting in extremely low or negligible rates of oral transmission.
4. Samples are easier to ship and store. Saliva does not clot and requires less manipulation than blood.
5. The procedure is economical. Saliva is easily collected, shipped, and stored, resulting in decreased overall costs for patients and health care providers.

COMPARISON OF SALIVA 2019-NCOV AND SARS-COV[17]

Items	2019-nCoV	SARS-CoV
Diagnostic value of saliva	(1) Early detection of viral RNA in saliva. (2) Viral peaks at onset of symptoms. (3) Salivary gland originated virus RNA is associated with severe COVID-19.	(1) Early detection of viral RNA in saliva. (2) Viral peaks 10 days after symptoms. (3) A high initial SARS-CoV load was associated with death
Direct invasion to oral cavity	(1) ACE2 receptor on host cells of tongue and salivary gland. (2) A furin-like cleavage site is peculiar in the S protein of 2019-nCoV.	ACE2 receptor on host cells of tongue and salivary gland.
Infectious saliva droplets	Possible opportunistically airborne transmission	Opportunistically airborne transmission.

CONCLUSION

Saliva is a best diagnostic fluid. Saliva, a biological fluid serves as the diagnostic tool in health and disease. Saliva play an important role in early detection of 2019-nCoV.

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