REVIEW ARTICLE

Understanding COVID-19 through the Dental Lens

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ABSTRACT

Corona virus Disease-19 (COVID-19) is a global health pandemic that has affected life of every individual in the world. It is caused by a novel Corona virus strain that has caused seventh Corona virus infection that has affected human population, named as "COVID-19" virus by the World Health Organization. Previously, six Corona virus infections have affected humans but those caused by SARS-CoV and MERS-CoV have proved to be more lethal. Angiotensin Converting Enzyme 2 (ACE2) has been found as the receptor for COVID-19 through which cellular entry of the virus is mediated into the body. These receptors are abundantly present in the oral cavity especially on the epithelial cells of the tongue, oral mucosa and the gingiva. Saliva is an oral bio-fluid of the oral cavity in which high titres of the virus have been identified during early and later stages of infection. Saliva collection is a non-invasion method and can act as a diagnostic tool for COVID-19 disease. Common oral symptoms of the disease include transient loss of taste, smell and dryness of mouth. Precautionary measures must be taken by dentist before carrying out any dental procedure for safety of the health care professional, staff and also the patient. Dental community must think of the "new normal" regarding clinical dental care in light of post-COVID-19 situation.

KEYWORDS: COVID-19, Dentistry, Angiotensin Converting Enzyme 2 (ACE2), Dental practice.

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INTRODUCTION

Today the entire world faces a pandemic caused by the Corona virus, however, this happening is not something new. In November 2002, an unknown causative agent led to outbreaks of an atypical pneumonia having high fever and mild respiratory symptoms that rapidly progressed to pneumonia within few days and was first reported in humans in Guangdong province of Southern China. The disease was severe with human-to-human transmission.[1] The disease was labelled as a new clinical entity by World Health Organization (WHO) and a "Severe Acute Respiratory Syndrome" (SARS) on 15th March, 2003.[2] Later, pandemic of SARS spread in 29 countries in South-east Asia, North America and Europe and gave rise to first pandemic of the 21st century having a fatality rate of about 10% with more than 8000 deaths.[1,3-5] However, WHO declared that SARS outbreak was contained on 5th July 2003.[5]The causative agent of SARS was novel Coronavirus "Severe Acute Respiratory Syndrome Coronaviruses" (SARS-CoV) an enveloped single-stranded-RNA virus, belonging to the family Coronaviridae that include the genus Coronaviruses and Torovirus.[4,6-7]

Previously, six Coronavirus species including HCoV-229E, HCoV-OC43, HCoV-NL63, and CoV-HKU1 caused human infections like common cold symptoms in immunocompetent individuals and two other strains are SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[8]

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Coronavirus can be categorized as into four types, α, β, γ, and δ.[9] Most of these viruses affect animals and seven Corona viruses that are currently known to cause infection in humans belong to types α and β. Both HCoV-229E and HCoV-NL63 belong to type α while HCoV-OC43, CoV-HKU1, MERS-CoV, SARS-CoV, and 2019 novel Coronaviruses (2019-nCoV), belong to type β. The CoV-HKU1, SARS-CoV, MERS-CoV and COVID-19 as the seventh Coronaviruses are found to cause pneumonia in humans.[10,11]The diversity of Coronavirus is mediated by the infidel nature of RNA-dependent polymerase, high frequency of RNA recombination and usual large genome for the RNA virus.[12] These characteristics of Coronaviruses has also facilitated the emergence of these viruses with new traits making it easier for them to adapt to new hosts and ecological niches and sometimes causing to zoonotic events.[13]

Quite similar to the first decade of the 21st century, during which the world witnessed the devastating outbreak of SARS caused by SARS-CoV, the beginning of the second decade of this century was also plagued by the emergence of another novel Coronavirus, the "Middle East Respiratory Syndrome Coronavirus" (MERS-CoV). This zoonotic virus caused human to human infection leading to an outbreak of severe respiratory disease in the Middle East with secondary spread to Europe, Africa, Asia, and North America since 2012.[13,14] Unlike the SARS, MERS-CoV epidemic led to approximately 2494 confirmed cases and 858 deaths across 27 countries with a fatality rate of about 35%.[5]

It has been generally thought that SARSr-CoV, which is mainly found in bats, and owning to previous two outbreaks caused by SARS-CoV and MERS-CoV that are highly transmissible and pathogenic.[15] Coronaviruses with genetically diversity related to both these disease being discovered in bats worldwide and it was highly likely that future SARS- or MERS-like Coronavirus outbreaks could originate from bats having an increased probability of occurrence in China.[16]

Therefore, 19 years later to the first Coronavirus pandemic and approximately in third decade of the 21st century, on 31st December 2019, clusters of unexplained pneumonia cases were announced in Wuhan city of Hubei province in China by Health Commission of Hubei province, China. Along with symptoms of pneumonia, patients also had radiographic ground-glass lung changes, normal or lower than average white blood cell lymphocyte and platelet counts, hypoxaemia and deranged liver and renal function. These patients tested positive for another type of novel Coronavirus that belonged to *Beta Coronavirus* genus lineage B, and was phylogenetically closely related to bat SARS-like Coronaviruseses.[8,17] The virus was tentatively named by WHO as the 2019-novel Coronavirus (2019-nCoV).[18] Later the infection was also describedas Severe Acute Respiratory Syndrome Coronaviruses2 (SARS-CoV2). On 11th February, the novel pneumonia was named as "Corona Virus Disease-19" (COVID-19) by the WHO.[19] On 11th March 2020, WHO declared the epidemic of this novel Coronavirus as pandemic and as of 16th May 2020, there were 4,425,485 confirmed cases of COVID-19 with 302,959 deaths and hasa spread over 216 countries or territories of the world. At a genome level, this novel Coronavirus was found to be 88-96% identical to bat-derived Severe Acute Respiratory Syndrome (SARS)-like Coronaviruses previously detected in China. The sequence was however found to be more distant from SARS-CoV (resembling about 79%) and MERS-CoV (resembling about 50%).[18,20] The disease has a onset through virus-induced pneumonia and human-to-human transmission. The clinical symptoms of COVID-19 include fever, fatigue, dry cough, myalgia, and dyspnea (breathing difficulties). In some cases headache, dizziness abdominal pain, diarrhea, nausea, and vomiting is also reported.[21] In severe cases, the disease can lead to a progressive respiratory failure due to alveolar damage and even can lead to death.[15,18] The oral symptoms of the disease are variable ranging from anomia to taste disorders (Table-1).

Table-1: Oral symptoms of SARS-CoV and COVID-19.

Type of Coronaviruses Infection	Clinical Features
SARS-CoV	Anosmia[55] Changes in color of the tongue[56] Early stage: Pink or red in tongue tip, with thin-white, white-greasy or yellow-greasy coating; Middle stage: Red, with white-greasy or yellow-thick-greasy coating Recovery stage: Mostly pink or red in tongue tip, few as dark purple, with thin-white or white-greasy, occasionally yellow-greasy coating Swollen Tongue[57]

COVID-19	Smell Disorders[58] Anosmia[59] Hyposmia[60] Dysosmain[30] Amblygeustia Taste Disorders[30] Ageusia, Hypsogeusia, Dysgeusia Pain in Tongue[61] Ulcers Desquamative gingivitis Blisters on inner lip mucosa Dry mouth [30]

It has been reported that COVID-19 has a fatality rate of 2.3%, while being higher in elderly patients and patients with co-morbidities.[5] Although SARS-CoV and MERS-CoV infections had a higher mortality rate (10% and 35% respectively) as compared to COVID-19, the number of deaths are higher due large number of infected cases.[5] This makes the disease of an utmost importance for understanding its pathophysiology, prevention and for finding its treatment modalities and ultimate cure.

Relationship of COVID-19 Virus Receptor with Oral Mucosal Tissues

The Coronavirus S-protein is the structural protein responsible for the crown-like shape of the CoV viral particles, from which the original name "Coronavirus" has been coined. This protein belongs to class-I viral fusion protein and contributes to cell receptor binding, tissue tropism and pathogenesis. The SARS-CoV S1-protein contains a conserved Receptor Binding Domain (RBD), which recognize Angiotensin-Converting Enzyme 2 (ACE2) as receptor for the SARS-CoV virus.[22] The ACE2 protein expresses on the oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain.[23]

Similarly, it has been reported that COVID-19 virus binds to ACE2 receptors for cellular entry of and does not require other Coronaviruses receptors, such as aminopeptidase N (APN) and dipeptidyl peptidase 4.[18] It has been shown that receptor binding domain (RBD) of COVID-19 virus mediates strong interactions with human ACE2 receptor.[24] Thus cells that express ACE2 receptors can act as target cells and are susceptible to 2019-nCoV infection.[25] Recent studies have indicated that ACE2 expression has been found on type-II alveolar cells of lungs, striated epithelial cells of esophagus, absorptive enterocytes from ileum and colon, myocardial cells, renal tubular duct cells, cholangiocytes, bladder urothelial cells, leydig cells and cells in seminiferous ducts in testis.[25-28]

It has also been documented that ACE2 expression has been found in the epithelial cells of the oral mucosa and tongue as compared to the epithelial cells of buccal and gingival tissues. The ACE2 expression was also found on the T cells, B cells and fibroblasts. This suggested that mucosa of the oral cavity is a potentially high-risk route for the COVID-19 virus infection.[29] Expression of ACE2 in the salivary glands cells of patients infected with COVID-19 has also been reported indicating a possibility of COVID-19 infection in the salivary glands.[30] Previously it has also been shown that salivary gland epithelial cells act as target for SARS-CoV in Rhesus Macaques.[31] More recently, through Genotype-Tissue Expression (GTEx) analysis, it has been suggested the higher expression of ACE2 in minor salivary glands than that in lungs indicating that minor salivary glands could be potential targets for COVID-19.[32] Another recent study also reported similar findings through GTEx analysis indicating that ACE2 protein could be present in salivary glands and they can act as invasive tissue for the COVID-19 virus with a possibility of acute and chronic sialadenitis that could be caused in humans by COVID-19 virus.[33]

Furin is a cellular endoprotease, identified in 1990s, that proteolytically activates large number of proteins in secretory pathways and has been implicated in diseases such as anthrax, bird flu, cancer, dementia and Ebola fever.[34] It has also been associated in viral infections through cleaving viral envelope glycoproteins and enhancing infection with host cells.[35] A furin-like cleavage site in the spike protein of 2019-nCoV has been identified which was not found in other SARS-CoVs, and it may account for difference in pathogenicity of COVID-19 and important implications in development of anti-viral drugs.[11,36] Furin expression has been detected in human tongue epithelial cells also therefore combined with ACE 2, it is expected that tongue tissue can be at the highest risk of Coronaviruses infection in oral cavity.[37,38] It is still to be determined how furin-like

cleavage site plays a big role in 2019-nCoV infection.[39]

Relationship of COVID-19 Virus with Saliva

World Health Organization has claimed that COVID-19 disease spreads through saliva droplets from mouth and nasal discharge from the nose.[40] Saliva is an oral bio-mixture secreted from the major and minor salivary glands which is 99% water and 1% comprising of proteins, crevicular fluid, desquamated oral epithelial cells, microbes, and may contain blood, respiratory secretions, gastric acid from reflux, and food debris in pathological occasions.[41] It has been reported that the COVID-19 virus has been detected in saliva of 97% of the infected patients. Saliva was found to contain viral nucleic acids, whereas live virus was detected through viral culture, indicating that saliva can act as a non-invasion tool for diagnosis, monitoring and infection control in patients with COVID-19 disease.[42] Another report suggested 100% detection of COVID-19 virus through saliva samples.[43] A study also found cases where samples tested positive for COVID-19 in saliva while negative for respiratory swabs indicating important of saliva testing for COVID-19 patients.[44] Previously, SARS-CoV has been shown to have a high viral load in saliva that further suggested its possible transmission through oral droplets.[45] COVID-19 viral load in saliva obtained from posterior oropharynx (deep throat) has been found higher during the first week after the onset of symptoms and subsequently declines with time.[46] COVID-19 transmitted by asymptomatic infection may originate from infected saliva.[32]

Saliva has been shown as an interesting alternatives as compared to other fluid for detection of viruses as oral shedding is more frequent in saliva than in blood therefore, it has been suggested that saliva can act as a non-invasive detection tool for COVID-19 as compared to nasopharyngeal and oropharyngeal swabs.[47,48] At the moment two types of swabs either nasopharyngeal or oropharyngeal are the recommended upper respiratory tract specimen types for 2019-nCoV diagnostic testing. However, sample collection form both these types require a close contact between health care workers and patients posing a high risk of viral transmission to healthcare workers. In addition, the collection of these swabs can cause discomfort and bleeding, especially in patients with thrombocytopenia. Saliva swabs can be easily obtained by asking patients to spit into a sterile bottle thus minimizing risk of any viral transmission to health care workers.[42]

As saliva also forms a first line of defense against foreign viral infections molecules, it has been suggested that hypo-salivation can add a risk to enhancement of the viral infection in COVID-19 disease.[49] It has been reported that incidence of acute respiratory infection was higher in individuals with hypo-salivation as compared to those without it, thus indicating that hypo-salivation can act as a risk factor for acute respiratory infection by mediating viral colonization and adhesion and decreasing production of anti-viral proteins and peptides.[50] Saliva provides defensive mechanism against viral infections through presence of anti-viral proteins and peptides in it, which include cathelcidin (LL37), lsozyme, mucins, lactoferrin, peroxidase, salivary agglutinin (gp340, DMBTI), α-defensins and β defensins, sIgA and cystatins etc. Salivary gp340 has shown antiviral potential against HIV-I as well as influenza A.[49]

It is believed that COVID-19 infection occurred within indoor space.[17] The COVID-19 RNA is detected in saliva therefore, WHO has claimed that one of the main routes of COVID-19 is through saliva droplets generated by infected people when breathing, talking in close contact of less than 1meter, coughing, or sneezing. One cough can generate about 3000 saliva droplets, 40,000 saliva droplets reach several meters in air generated by one sneeze and one normal exhalation can generate saliva droplets reaching the distance of 1 m in air, thus there can be a possibility of COVID-19 to spread as airborne transmission through saliva droplets.[38]

Safety Measures in Clinical Dental Practice

The nature of spread and transmission by COVID-19 through droplets, sneezes and aerosols has increased the risk of nosocomial infections in a dental setting.[17] A patient with cough or sneeze and receive dental treatment including the use of a high-speed handpiece or ultrasonic instruments

make their secretions, saliva, or blood aerosolize to the surroundings. This would untimely lead to contaminated dental apparatus and practice environment.[50] Hand hygiene has been advocated for ensuring protection against the virus. In addition, thorough disinfection of whole dental clinics should become a regular practice. Dentist should ensure wearing of Personal Protective Equipment including masks, gloves, gowns, and goggles or face shields, to protect facial skin from potentially infected blood or any other secretions. As salivary and respiratory droplets are the main route of COVID-19 transmission, particulate respirators (e.g., N-95, KN95 or FFP2-standard masks) are now recommended for routine dental clinical procedures.[51] Dental clinics should establish routine checks to measure and record staff and patient's temperatures and questions regarding travel and quarantine history must be asked. Patients with fever should be referred to hospital for proper assessment. In areas where COVID-19 spreads, nonemergency dental treatment should be postponed.[51] In case of performing any dental procedure, pre-procedural mouthwash having Chlorhexidine (CHX), Cetylpyridinium chloride (CPC) and essential oils have shown to lead to reduction of 68.4% Colony-Forming Units (CFU) in dental aerosols. It is still not certain how much any mouth wash is effective against COVID-19, however it has been shown that CHX has some antiviral potential. Approximately 0.12%-0.05% CHX mouthwash can be used as a pre-procedural mouthwash. During intraoral imaging, it is recommended to double cover the intraoral sensor. Using rubber dams reduces splatter during endodontic treatment and restorative treatment and wherever possible, should be employed. It is suggested to manually scale and polish instead of using ultrasonic instrument and use of high-speed hand pieces and three-way syringe should be avoid as much as possible during the COVID-19 outbreak.[52] Any medical/dental waste including PPE should be delivered to a labelled temporary storage area. The items that can be re-used such as dental tools or any PPE materials should be clean, disinfect and autoclaved if possible. The medical and domestic waste produced via treatment of any suspected or confirmed COVID-19 patients should be disposed in double-layered yellow bags tied carefully. The surface area of the waste bags should be appropriately labelled and disposed in compliance with requirements of medical waste.[53]

The "*New Normal*" for Dentistry

It has been noted that post-COVID-19 situation has led to the almost complete shutdown of all routine dental work, other than emergency care. It is recognized that the highest risk of viral spread is during any procedure in which upper respiratory aerosols are generated. In such a setting, it is mandatory that all workers involved in such procedures are adequately protected with PPE. This situation is not dissimilar to how the health concerns and stigma surrounding HIV/AIDS disrupted dentistry and threw it into a rapid (and for many, unwanted) evolution. Suddenly, dentists couldn't do things the way they'd always done them. Almost overnight, universal precautions were established and dentists were forced to change in order to protect their own and their patient's health.[51]

Some steps that will be inevitable before dentistry can resume include widespread testing of dentists, clinical staff and patients unless an effective mass vaccine is available soon, or effective ways to suppress or shield workers from aerosols are found. The physical risk due to aerosol generating procedures can be reduced by using PPE, sophisticated air filtration and decontamination systems, high-speed air evacuation systems, and disinfection/antimicrobial procedures for workers, equipment, and patients.[51,52]

But not only are these steps costly and complex, making their implementation much more limited in scale and therefore reducing the number of compliant dental practices, but they increase the timeframe of treatment, and reduce the number of procedures that can be carried out every day. This will have a heavy impact on current dentistry models. However, industrial partnership will become essential to help the profession and industry recover at least in part over the next year. Not only will there be a need to invest in new air-cleaning and product disinfection technologies, but new ways to avoid invasive treatments may be the focus of attention. The greatest challenge will be with respect to orthodontic and endodontic treatments and the provision of dental implants.[53]

Nearly 40 years after the onset of HIV/AIDS, dentistry finds itself in a similar position today with the COVID-19 pandemic. Just like responsible dentist's post-AIDS crisis didn't go back to practicing without gloves or masks, it can be believed that it would be naive to assume things will go back to normal when dental offices are allowed to re-opened. Recent studies suggest that dentistry is one of the most high-risk profession to contract COVID-19 due to the amount of aerosols generated in a dental office.[51,54] After looking into these studies, it can be thought that as dentists, "Why weren't we concerned about this before the Coronaviruses outbreak?" "I can't believe he practiced without gloves," We hope that future dentists look back and think, "Can you believe that dentists used to practice without aerosol controls?" Just like dentists did after the HIV/AIDS crisis, we feel confident that we can move this profession past COVID-19 and into a *new normal* that is safer for us and for our patients.

CONCLUSION

World Health Organization has declared COVID-19 as a public health emergency of an international concern. The disease transmission is human-to-human contact and some underlying mechanisms for disease progression and its pathophysiology are beginning to elucidate, thus enabling scientists and researchers to work towards target therapies for its prevention and cure. The dental profession has especially changed greatly after this pandemic. The introduction of post-COVID safety protocols are expensive and complex and partnerships with industry can help dental profession by investing and fabrication of new air-cleaning and product disinfection technologies and for dentists to formulate procedures for invasion aerosol generating procedures. We hope that current and future dentists should evaluate dental profession can move into a *new normal* that is safer for us and for our patients and for future generations.

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CONFLICT OF INTEREST

None to declare.

FINANCIAL DISCLOSURE

None to disclose.

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Author's Contribution

SG: Conception of study, compilation of data, manuscript writing and final approval of the manuscript.

AJA: Drafting of manuscript, Intellectual input through critical analysis.