Review Article

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Dentistry Section

Oral and Periodontal Manifestations of COVID-19 and its Plausible Association with Periodontal Disease

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ABSTRACT

The coronavirus disease 2019 (COVID-19), has caused a significant and urgent threat to the global health. It has markedly affected the delivery of healthcare services all over the world. Early diagnosis of the disease is imperative to contain the spread of the viral infection. The virus can also lead to potential systemic complications such as lungs involvement, skin, and oral manifestations. The presence of oral lesions is emerging evidence that may indicates the presence of COVID-19 infection. Since, the virus has affinity for Angiotensin Converting Enzyme (ACE2) receptors present in the respiratory tract, oral mucosa, tongue and salivary glands; therefore, the oral cavity serves as a major habitat for invasion of the virus. This review aimed to discuss the oral and periodontal manifestations of COVID-19. Articles between December 2019 and April 2021 were searched for this narrative review in Pub Med, Scopus, Science Direct related to COVID-19 and its oral manifestations, using the following terms: “Corona virus,” “COVID-19,” and “SARS-CoV-2” in combination with “Stomatognathic diseases,” “Oral manifestation,” and “Mouth diseases” and "Periodontal diseases". The oral manifestations commonly associated with COVID-19 are salivary gland disorders, xerostomia, alteration of taste and smell and lesions in oral mucosa. The appearance of these oral manifestations during the asymptomatic phase of disease helps in early identification of the disease. The recent COVID-19 infection has been strongly associated with the appearance and establishment of cytokine storm. It is found that many components of the cytokine storm are common with the cytokine expression found in periodontitis. This narrative review aims at exploring the association between COVID-19 and periodontal disease through their cytokine profiles.

Keywords: Angiotensin converting enzyme-2 receptors, Coronavirus disease 2019, Cytokine, Early diagnosis

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is an infectious disease affecting the respiratory tract. The SARS-CoV-2 is mainly transmitted through respiratory droplets and close contact with the infected routes. Most of the infected people present with fever, cough and difficulty in breathing; some develop severe pneumonia, renal and multiorgan failure and some may remain asymptomatic [1].

The novel coronavirus disease 2019 (2019-nCoV) has been found to be a serious threat to global health. Current researches showed that coronavirus invades human cells via the receptor ACE2 through single-cell RNA sequencing (scRNA-seq) data analysis [2]. Hence, it is found that cells with ACE2 receptor may become the host cell for the coronavirus. Studies have identified the organs that are at risk and are vulnerable to COVID-19 infection (e.g., lung; Zou X et al., 2020) [3], tongue mucosa (Wang W et al., 2020) [4], salivary gland mucosa (Xu J et al., 2020) [5], epithelial cells of oral mucosa (Xu H et al., 2020) [6]. The SARS-CoV-2 interaction with ACE2 receptors may also impair taste bud sensitivity, which could induce dysfunctional gustatory responses [7].

The COVID-19 presents with a wide range of oral signs and symptoms that includes taste disorders, unspecific oral ulcerations, desquamative gingivitis, petechiae, and co-infections such as candidiasis [8]. There is uncertainty in these oral manifestations whether they are following a typical clinical pattern resulting from the direct SARS-CoV-2 infection or due to systemic deterioration, given the possibility of co-infections, impaired immune system, and adverse reactions of medical treatment [9,10]. Since, there is lack of clarity in the prevalence of clinical manifestations, the range of COVID-19 oral manifestations has been considered of broad and current interest. Hence, the present review focused on oral and periodontal manifestations in COVID-19 and its assosciation with periodontal disease.

LITERATURE SEARCH

The most relevant contributions related to oral and periodontal manifestations of COVID-19 were chosen based on the nature, in this narrative review article. The search was conducted using six MeSH keywords including, “Corona virus,” “COVID-19,” “SARS-CoV-2”, “Stomatognathic diseases,” “Oral manifestation,” and “Mouth disease”, “Periodontal manifestation” in Pub Med, Scopus, and Science Direct databases among articles between December 2019 and April 2021.

The review of literature showed that most of the studies were on systemic manifestations, therefore we focused more on oral related symptoms and periodontal health and possible disease mechanisms which may provide new clinical information and new vistas for early diagnosis of COVID-19.

COVID-19 AND CLINICAL MANIFESTATIONS

COVID-19 shows varied clinical presentation, ranging from asymptomatic state to acute respiratory distress syndrome along with multiorgan dysfunction. The clinical presentation of COVID-19 includes fever, cough, sore throat, fatigue, headache, myalgia, breathlessness and conjunctivitis [11]. It is found that COVID-19 is associated with increase in inflammatory cytokines such as Interleukin (IL)-IL2, IL7, IL10, Interferon-gamma inducible protein 10 kD (IP-10),Granulocyte colony-stimulating factor (G-CSF or GCSF), Monocyte chemotactic protein-1 (MCP-1), Macrophage inflammatory protein-1 alpha (MIP-1α/CCL3); Tumor Necrosis Factor alpha (TNFα) which can progress to pneumonia, respiratory failure and death in some cases by the end of first week [12]. Acute lung injury, Acute Respiratory Distress Syndrome (ARDS) , shock and acute kidney injury are the complications associated with severe COVID-19 disease. Elderly and those with underlying co-morbidities are associated with more adverse outcomes and death. The case fatality rate associated with this disease was found to be between 2% and 3% [11].

The high transmissibility of SARS-CoV-2 may be attributed to the unique virological features of SARS-CoV-2. Transmission of SARS-CoV-2 occurred mainly after illness onset and peaked following disease severity. However, the SARS-CoV-2 viral load in upper respiratory tract samples was already highest during the first week of symptoms, and thus the risk of pharyngeal virus shedding was very high at the beginning of infection. Transmission of COVID-19 takes place through viruses in liquid droplets during speech from COVID carrier [13]. However, much smaller particles, aerosols are also attributed to the spread of the virus [14]. Coronavirus pose a risk of prolonged infection such as the case of SARS-CoV-2 due to their persistence on inanimate surfaces for days. These findings explain the rapid geographic spread of COVID-19, and to reduce the risk of transmission of this disease, a public health intervention provides benefits to mitigate the pandemic [15].

ORAL MANIFESTATIONS OF COVID-19

The oral manifestations commonly associated with COVID-19 are salivary gland disease, xerostomia, dry mouth and burning sensations, oral ulcerations and blisters, taste and smell alterations, and oral mucosal lesions. In addition to the above symptoms erosion, bulla, vesicle, pustule, fissured/depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, haemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding were also noted in patients with COVID-19 [4,5,8,16-27]. The sites of involvement of these oral manifestations were tongue, labial mucosa, palate, gingival, buccal mucosa, oropharynx and tonsil [16-27]. Most of the oral lesions were symptomatic. The oral lesions had a latency time of 4 to 12 weeks with the onset of systemic symptoms [16-27]. These oral manifestations could be due to the direct viral infection or they are aggravated by COVID-19, linked to immunocompromised system or long term pharmacotherapy [28].

Therefore, the range of oral manifestations of SARS-CoV-2 has been considered of broad and modern day interest. COVID-19 additionally could also jeopardise the oral health leading to a variety of opportunistic fungal infections, recurrent oral Herpes Simplex Virus (HSV-1) infection, oral unspecific ulcerations, fixed drug eruptions, dysgeusia, xerostomia, ulcerations [29].

Salivary Gland Disease

The SARS-CoV-2 expression has been detected in the oral epithelium and sputum, swabs of human saliva. This expression in saliva is being considered a tool for diagnostic strategies. Patients with COVID-19 infection are found to have salivary gland involvement. ACE2 has been reported as an important receptor for COVID-19. Xu J ., demonstrated that ACE2 expression in minor salivary glands compared to lungs was higher, thereby suggesting that COVID-19 could potentially target salivary glands [5]. In accordance to these findings, Chen N et al., evaluated the expression of ACE2 receptor of 2019-nCoV in the epithelial cells of salivary gland and demonstrated the possibility of 2019-nCoV infection of the salivary glands [12]. They also mentioned that higher positive saliva detection rate of 75% in critically ill patients was due to virus invasion caused by high viral loads or infected salivary glands in the last stage of the disease. The same results have been also reported by Wang W et al., and Kotfis K and Skonieczna-Żydecka K [4,17]. It is important to know that only salivary detection of COVID-19 was seen and the presence of it in the nasopharynx had no evidence. Additionally, analysis of ACE2 in human organs showed a high expression of ACE2 in minor salivary glands [5].

Xerostomia

A relatively high number of COVID-19 patients presented with dry mouth [30]. The factor that controls salivary gland secretion includes temperature, circadian rhythm and intensity, type of taste [31]. It is noted that hyposalivation in COVID-19 patients is attributed to the use of medication and psychological processes such as depression, anxiety, stress through pathways in the amygdala, hypothalamus and brainstem [20].

It was also noted that in patients with hyposalivation, there is an increased risk of getting COVID-19. The possible explanation is that the proteins with antiviral properties such as Cathelcidin (LL-37), lactoferrin, lysozyme, mucins, peroxidase, salivary agglutinin (gp340, DMBT1), sIgA SLPI, α, β-defensins, cystatins in saliva are found to be decreased [32]. The severity of SARS-CoV-2 infection is higher in middle aged population and in patients with co-morbidities. Dry mouth has been attributed to the psychological changes in the patient, poor oral hygiene, or adverse reactions due to medications. According to Dos Santos JA et.al., xerostomia occurring in COVID-19 patients and decreased salivary flow are interlinked [8].

Taste and Smell Alterations

The two genes, namely ACE2 and Transmembrane Serine Protease 2 (TMPRSS2) expressed in the olfactory epithelial support cells, stem cells, and nasal respiratory epithelium are mainly involved in the transport of SARS-CoV-2 into the cell, and these may be potential mechanisms whereby this infection can lead to anosmia. The virus penetrates into the CNS through peripheral trigeminal and olfactory nerves following intranasal inoculation. Keyhan SO et al., described that the damage of the olfactory nerve and trigeminal nerve causes dysosmia and dysgeusia due to virus invasion or excessive exposure to chemicals and disinfectant agents that are used by people due to the viral epidemic [20]. A previous study also suggested that complications of demyelination and T-cell mediated autoimmune reactions were noticed in the path of the infection which causes nerve injuries leading to the occurrence of dysosmia and dysguesia [20]. Recently, another mechanism has been proposed which states that the sustentacular cells, the supporting cells of olfactory neurons, have the highest number of ACE2 receptors. These cells transfer odour from air to neurons. The mature olfactory neurons do not express ACE2 while sustentacular cells do. The sense of scent in these patients appears to be lost, due to the fact that these cells aid neurons in sensing odours, possibly by processing odour binding proteins [29].

Oral Mucosa

Oral manifestations associated with COVID-19 includes blisters in labial mucosa, recurrent herpetic stomatitis, small multiple painful ulcers in palate and desquamative gingivitis. In addition to this, other findings include geographic tongue, petechiae, recurrent oral HSV-1, candidiasis, traumatic ulcers and thrush-like ulcers [33].

Chaux Bodard AG et.al., reported a case of 45 year old female patient with an irregular ulcer on the dorsal side of the tongue on intraoral examination. The oral lesion was followed by an erythematous plane lesion on the big toe on the third day. Further on day 8, the patient tested positive for COVID-19 [27]. The irregular ulcer was found to occur after the expression of the macular erythematous lesion, which could be attributed to vasculitis. The vascular inflammation is due to variable inflammatory response associated with COVID-19. The occurrence of the erythematous rash could be due to inflammatory reaction. Thereby the acute, irregular, solitary oral ulcer could be considered as an inaugural symptom of 2019-nCoV infection [29]. In another case report by CM Carreras-Presas et al., they showcased three cases where oral vesiculobullous lesions were seen associated with SARS-CoV-2 infection. In the first case, the lesions resembled a herpetic recurrent stomatitis on the hard palate in a 56-year-old healthy male. The second case was a diabetic, 58-year-old male with multiple small ulcers on his palate with unilateral affection and the last case was a 65-year-old female with blisters in her internal lip mucosa as well as desquamative gingivitis [9]. It was interesting to note that all the three cases had pain with oral ulcers and blisters before seeking medical advice. In less than 2% of the case, stomatitis, oral ulcers, and dry mouth were seen which was due to side effects of antiviral drugs such as interferon-alpha and

beta. Treatment of these conditions included hyaluronic acid and chlorhexidine mouth wash. Thus, it was encouraged that intraoral examinations should be performed in patients with suspected SARS-CoV-2 [34]. As the oral findings are still relatively new in the literature, their occurrence and presentation may vary significantly among COVID-19 patients. Therefore, the associated systemic diseases and/or poor oral health may act as a contributory factor to the oral symptoms [10].

DIAGNOSTIC METHODS

The detection of SARS-CoV-2 is mandatory for managing COVID-19 which is enabled by real-time Reverse Transcription–Polymerase Chain Reaction (RT-PCR). The RT-PCR detects SARS-CoV-2 nucleic acids. SARS-CoV-2 is found to spread through respiratory droplets, aerosols or fomites. Nasal or oropharyngeal samples are helpful in detection of SARS-CoV-2. It is also noted that samples from bronchoalveolar lavage, tracheal aspirates and pleural fluids and/or urine, blood and faeces contain virus. Saliva is considered as an alternative source for SARS-CoV-2 and virus specific antibodies [35].

Saliva can be used as a viable diagnostic fluid for the detection of COVID-19. The sensitivity of saliva for SARS-CoV-2 detection in COVID-19 patients was higher in comparison to nasopharyngeal swabs. Due to the plethora in disease biomarkers, saliva is considered as a potential diagnostic tool for monitoring general health and disease [29]. It has added advantages of being an easy, safe, economic and non invasive diagnostic approach [36]. Greater than 90% of nasopharyngeal specimens detected respiratory viruses, including coronavirus genera. It was found that ACE2 expressing cells were higher in number in minor salivary glands than that in lungs [36]. The limitations of nasopharyngeal or oropharyngeal swab includes a risk to healthcare workers through sneeze or cough and transmission of virus particles by aerosols. The presence of coagulation disorders or thrombocytopenia can precipitate bleeding which is also one of the limitations of nasopharyngeal swabs [35]. Saliva collection being a non invasive procedure extensively minimises the exposure of healthcare workers to COVID-19. It is noteworthy that the saliva of infected patients was identified with and saliva as a diagnostic fluid adds value to be a potential diagnostic tool for early detection of coronavirus and minimising its spread [29].

COVID-19 AND PERIODONTAL DISEASE

Currently, host and microbial signature states are being examined and studied to possibly identify any potential correlations. Recently, the correlation between periodontitis and COVID-19 has been studied [37].

SARS-CoV-2 results in periodontal manifestations such as inflammation of oral tissues resulting in gingival bleeding. Elevation of the cytokine and interleukin levels is attributed to these manifestations. The periodontal manifestation also included generalised erythematous and edematous gingiva with necrosis of interdental papilla without significant clinical attachment loss [34].

Periodontitis is a chronic inflammatory disease with increase in local and systemic cytokines and chemokines. Presence of bacterial pathogen in the oral cavity acts as a potent risk factor for COVID-19 due to the possibility of bacterial super infection [12]. Pathogenic bacteria present in the oral cavity are Prevotella, staphylococcus and periodonthopathic bacteria such as Prevotella intermedia, fusobacterium, treponema, and vellionella were also noted in patients with severe COVID-19 infections [12].

It was found that SARS-CoV-2 infection might occur as a co-infection of P.intermedia which is a major pathogenic bacteria leading to periodontal disease along with fusobacterium and treponema species [38]. It is also noteworthy that P.intermedia along with fusobacterium species constitutes a large proportion of microbiota present on necrotising periodontal diseases [39]. The SARS-CoV-2 can predispose to necrotising ulcerative periodontitis through co-infection propagated by P.intermedia [40]. Immunocompromised patients such as HIV and those with autoimmune disease were found to be prone to these co-infections [34]. Apart from this, diabetes, hypertension and cardiovascular disease are three main co-morbidities associated with increased risk of complication of COVID-19. These comorbidities are also associated with altered biofilms and periodontitis [40].

Oral microbiota is diverse and complex. In health, it consists of mainly streptococci and viridans group and in periodontal disease state, it consists of gram negative anaerobic bacteria including the red complex bacteria namely Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia [41]. These bacteria are organised into complex community called dental biofilm which is a survival strategy for most of the bacteria, viruses and fungi. The initiation and progression of periodontal disease occurs due to a dysbiosis of commensal oral bacteria with host immune response [42].

It is also noted that apart from viral pathogenesis, periodontal dysbiosis also plays a significant role in the severity of COVID-19. Studies by Kiedrowski MR et al., and Bellinghausen C et al., have also shown that there is an exacerbation of release of pro-inflammatory cytokines in response to viral infection with pre-exposure of airway epithelial cells to common respiratory bacteria such as Haemophilus influenzae, Pseudomonas aeruginosa and Streptococcus pneumonia [43,44]. This is suggestive of microbial interactions on pulmonary inflammation with pleiotropic effects [34]. Taking this into consideration, the bacteriologic status of patients with severe viral infections helps the clinicians to categorize the risk status of the patients [45].

It was also shown that 80% of patients with severe COVID-19 had high bacterial load. Staphylococcus aureus, Streptococcus pneumoniae, and Streptococcus pyogenes are most commonly isolated bacteria [5,40]. It has also been noted that the COVID-19 affected patients with higher severity had increased levels of inflammatory markers. These patients reported in higher neutrophil count and lower lymphocyte count, it is common for a bacterial super infection that implies in severe activity disease of COVID-19 [34].

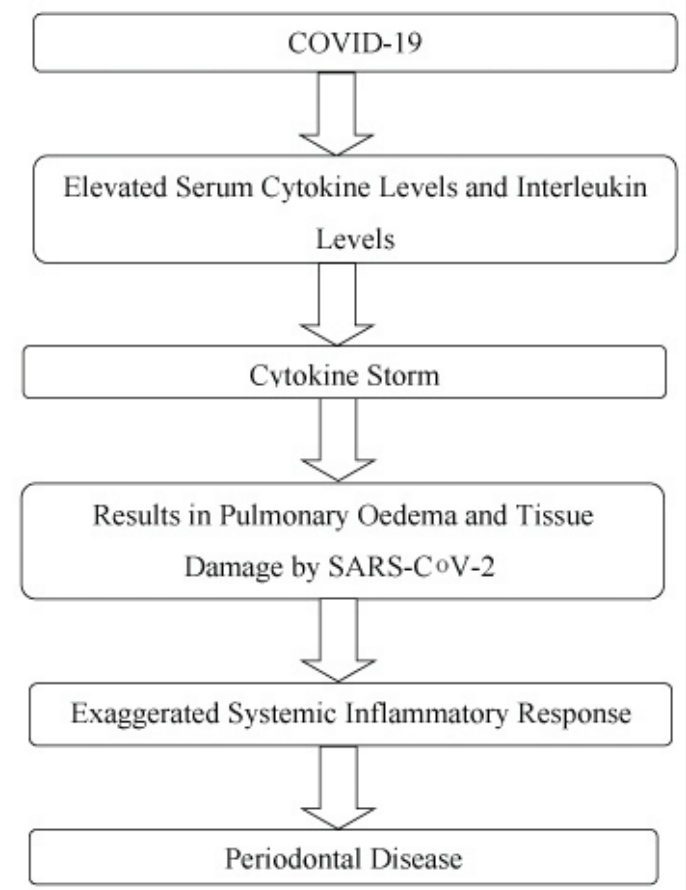
It has been found that host immune response plays an important role in COVID-19 patients [46]. It was found that COVID-19 and periodontal disease have a two way relationship. Studies by (Ruan Q et al., 2020; Zhou F et al., 2020) have shown that periodontitis shares common risk factors with most chronic inflammatory diseases known to influence COVID-19 severity [47, 48]. Periodontitis, in association with Cardiovascular Diseases (CVD), cancer, Coronary Heart Diseases (CHD) and cerebrovascular diseases has been found to have high mortality rates (Scannapieco FA et al., 2003) [49]. These associations are attributed to genetic and environmental risk factors, and also through common chronic inflammatory pathways (Schenkein HA et al., 2020) [50].

Systemic increase in the inflammatory responses during periodontitis shows similarity with the cytokine storm in COVID-19 patients. The SARS-CoV-2 infection results in increased inflammatory response which could possibly cause periodontitis. It is also worth, mentioning that periodontitis might be a predisposing factor for COVID-19 [33,34].

In a study by Takahashi Y et.al., 2020 it was shown that COVID -19 was aggravated by the aspiration of periodontopathic bacteria as a result of the expression of ACE2, which is a receptor for SARS-CoV-2, and inflammatory cytokines in the lower respiratory tract. It was also found that the cleaving of S glycoproteins attributed to the virulence of SARS-CoV-2 by the periodontopathic bacteria [51]. In a study by Marouf N et.al., 2021 it was found that periodontitis is associated with increased fatal outcomes of COVID-19 such as higher risk of ICU admission, assisted ventilation and increase blood concentration of D-dimer, WBC and CRP [52]. Thus, it can be proposed that maintaining periodontal health might become integral for patients associated with increased adverse outcomes of COVID-19.

The association between periodontal disease, oral hygiene and COVID-19 needs further exploration [34].

[Table/Fig-1] It shows the plausible mechanism of association between periodontal disease and COVID-19 [53].



[Table/Fig-1]: Periodontal disease and COVID-19-Plausible Mechanism [53].

Periodontal Tissue as COVID-19 Reservoir

It is found that the risk for oral mucosa mediated SARS-CoV-2 is found to increase in patients with chronic periodontitis as it is associated with increased protease levels. Oral mucosa and gingiva and periodontal pocket act as potential reservoir for SARS-CoV-2 due the presence of ACE2 receptors. Human Virus such as human papilloma virus and Herpes Simplex Viruse (HSV) are present in the periodontal pocket. These viruses may enter systemic circulation from periodontal pocket via GCF [54]. In a study by Gupta S et al., it was found that periodontal pockets may act as a potential aid in virus replication. The virus gains entry via saliva to the systemic circulation as the viral load in GCF increases. Thus, it can be speculated that GCF could represent a mode of transmission [55]. Studies by (Badran Z et al., 2020, Matuck BF et al., 2020) showed that periodontal pocket epithelium could act as focal point of infection for SARS-CoV-2 [54, 56]. Recently, it has been established that the spike proteins of the SARS-CoV-2 infects cells by binding to the Cluster of Differentiation 147 (CD 147) on cell membranes. [57] The distant organs were infected with viruses from PP apart from bacterial challenge generating focal infections and thus, to minimize the systemic spread of viral pathogens, periodontal therapy could benefit in such situations [55].

Chronic periodontitis exhibits higher levels of osteopontin, stimulates p38 and NF-kB, pathways and increases the level of proteases. IL-6 and caveolin 1 through JNK–AP-1 signalling pathway is induced by proteases [58]. Furthermore, higher expression of CD 147 is noticed in gingival epithelial cells harvested from periodontitis patients [59]. It was found that furin and cathepsin influences SARS-CoV-2 to infect the host cells. Increased proteases resulted in an increase in the expression of ACE2 and CD147 in gingival and periodontal ligament fibroblasts in rat and human tissues. Therefore, periodontitis could serve as a potential reservoir of SARS-CoV-2 infection and vice versa [34].

Inflammatory oral cavity manifestations are triggered by persistent inflammatory response. In periodontal tissue, there is increased fibrinogen degradation confirming that COVID-19 has an impact on periodontal tissue [38].

CONCLUSION(S)

Coronavirus disease presents with various combinations of signs and symptoms. It can present with many oral manifestations such as xerostomia, oral mucosal lesions, taste and smell alterations, thus providing a new perception to the clinical prevention, diagnosis and treatment of SARS-CoV-2. Saliva have an important role as a diagnostic tool in detection of COVID-19 infection. Periodontal impact of COVID-19 infections has also been studied. The possible biological pathway evidencing two-way relationship among periodontal disease and COVID-19 has been explored. The SARS-CoV-2 infection results in increased inflammatory response which could possibly cause periodontitis. It is also worth, mentioning that periodontitis might be a predisposing factor for COVID-19.

Albeit association between periodontal findings and COVID-19 infection can be drawn, further studies are needed to establish oral and periodontal manifestations as early symptoms of COVID-19.

REFERENCES

[1] Pant BD. Covid-19: Oral manifestations, impact and lessons for the future. Orthod J Nepal. 2020;10(2):52-54.
[2] Amorim dos Santos J, Normando AGC, Carvalho da Silva RL, Acevedo AC, De Luca Canto G, Sugaya N, et al. Oral manifestations in patients with COVID-19: A living systematic review. J Dent Res. 2021;100(2):141-54.
[3] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-92.
[4] Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA [Internet]. 2020 [cited 2021 May 11]; Available from: https://jamanetwork.com/journals/jama/fullarticle/2762997.
[5] Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary glands: Potential reservoirs for COVID-19 asymptomatic infection. J Dent Res. 2020;99(8):989-89.
[6] Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8.
[7] Mariz BALA, Brandão TB, Ribeiro ACP, Lopes MA, Santos-Silva AR. New insights for the pathogenesis of COVID-19-related dysgeusia. J Dent Res. 2020;99(10):1206-06.
[8] Amorim dos Santos J, Normando AGC, Carvalho da Silva RL, De Paula RM, Cembranel AC, Santos-Silva AR, et al. Oral mucosal lesions in a COVID-19 patient: New signs or secondary manifestations? Int J Infect Dis. 2020;97:326-28.
[9] Martín Carreras-Presas C, Amaro Sánchez J, López-Sánchez AF, Jané-Salas E, Somacarrera Pérez ML. Oral vesiculobullous lesions associated with SARS-CoV-2 infection. Oral Dis. 2021;27(S3):710-12.
[10] Mortazavi H, Rezaeifar K, Nasrabadi N. Oral manifestations of Coronavirus Disease-19: A mini-review. Open Access Maced J Med Sci. 2020;8(T1):286-89.
[11] Cao Y, Hiyoshi A, Montgomery S. COVID-19 casefatality rate and demographic and socioeconomic influencers: Worldwide spatial regression analysis based on countrylevel data. BMJ Open 2020;10:e043560. Doi: 10.1136/bmjopen-2020-043560.
[12] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020;395(10223):507-13.
[13] Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141-54.
[14] Stadnytskyi V, Bax CE, Bax A, Anfinrud P. The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission. Proc Natl Acad Sci. 2020;117(22):11875-77.
[15] Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246-51.
[16] Vieira AR. Oral manifestations in coronavirus disease 2019 (COVID-19). Oral Dis. 2021;27(S3):770-70.
[17] Kotfis K, Skonieczna-Żydecka K. COVID-19: Gastrointestinal symptoms and potential sources of SARS-CoV-2 transmission. Anaesthesiol Intensive Ther. 2020;52(2):171-72.
[18] Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z. Olfactory and oral manifestations of COVID-19: sex-related symptoms-A potential pathway to early diagnosis. Otolaryngol Neck Surg. 2020;163(4):722-28.
[19] Sinadinos A, Shelswell J. Oral ulceration and blistering in patients with COVID-19. Evid Based Dent. 2020;21(2):49.

[20] Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due to the 2019 Novel Coronavirus; A hypothesis that needs further investigation. Maxillofac Plast Reconstr Surg. 2020;42(1):9, s40902-020-00254-7.
[21] Yifan T, Ying L, Chunhong G, Jing S, Rong W, Zhenyu L, et al. Symptom cluster of ICU nurses treating COVID-19 pneumonia patients in Wuhan, China. J Pain Symptom Manage. 2020;60(1):e48-53.
[22] Dar Odeh N, Babkair H, Abu-Hammad S, Borzangy S, Abu-Hammad A, Abu-Hammad O. COVID-19: Present and future challenges for dental practice. Int J Environ Res Public Health. 2020;17(9):3151.
[23] Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin Infect Dis. 2020;71(15):889-90.
[24] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. Eur Arch Otorhinolaryngol. 2020;277(8):2251-61.
[25] Vaira LA, Salzano G, De Riu G. The importance of olfactory and gustatory disorders as early symptoms of coronavirus disease (COVID-19). Br J Oral Maxillofac Surg. 2020;58(5):615-16.
[26] Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic- An observational cohort study. J Otolaryngol- Head Neck Surg. 2020;49(1):26.
[27] Chaux-Bodard AG, Deneuve S, Desoutter A. Oral manifestation of Covid-19 as an inaugural symptom? J Oral Med Oral Surg. 2020;26(2):18.
[28] Dziedzic A, Wojtyczka R. The impact of coronavirus infectious disease 19 (COVID-19) on oral health. Oral Dis. 2021;27(S3):703-06.
[29] Katira P, Shah D, Maniyar F. Oral manifestations of COVID-19: Early diagnostic aid? Int J Sci Res. 2020;9(10):01-03.
[30] Chen L, Zhao J, Peng J, Li X, Deng X, Geng Z, et al. Detection of SARS-CoV-2 in saliva and characterization of oral symptoms in COVID-19 patients. Cell Prolif. 2020;53:e12923.
[31] Proctor GB. The physiology of salivary secretion. Periodontol 2000. 2016;70(1):11-25.
[32] Farshidfar N, Hamedani S. Hyposalivation as a potential risk for SARS-CoV-2 infection: Inhibitory role of saliva. Oral Dis. 2021;27(S3):750-51.
[33] Recalcati S. Cutaneous manifestations in COVID-19: A first perspective. J Eur Acad Dermatol Venereol [Internet]. 2020 [cited 2021 May 11];34(5). Available from: https://onlinelibrary.wiley.com/doi/10.1111/jdv.16387.
[34] Gofur NP. Impact of SARS-CoV-2 on periodontal tissue manifestation. J Int Oral Health. 2020;12(8):90.
[35] Kevadiya BD, Machhi J, Herskovitz J, Oleynikov MD, Blomberg WR, Bajwa N, et al. Diagnostics for SARS-CoV-2 infections. Nat Mater. 2021;20(5):593-605.
[36] NIH COVID-19 Autopsy Consortium, HCA Oral and Craniofacial Biological Network, Huang N, Pérez P, Kato T, Mikami Y, et al. SARS-CoV-2 infection of the oral cavity and saliva. Nat Med. 2021;27(5):892-903.
[37] Peng X, Xu X, Li Y, Cheng L, Zhou X, Ren B. Transmission routes of 2019-nCoV and controls in dental practice. Int J Oral Sci. 2020;12(1):9.
[38] Patel J, Woolley J. Necrotizing periodontal disease: Oral manifestation of COVID-19. Oral Dis. 2021;27(S3):768-69.
[39] Herrera D, Retamal-Valdes B, Alonso B, Feres M. Acute periodontal lesions (periodontal abscesses and necrotizing periodontal diseases) and endo-periodontal lesions: Dd56ll Joint EFP-AAP Workshop. J Periodontol. 2018;89:S85-102.
[40] Sampson V. Oral hygiene risk factor. Br Dent J. 2020;228(8):569.
[41] Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL. Microbial complexes in subgingival plaque. J Clin Periodontol. 1998;25(2):134-44.
[42] Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primer. 2017;3(1):17039.
[43] Kiedrowski MR, Gaston JR, Kocak BR, Coburn SL, Lee S, Pilewski JM, *Staphylococcus aureus* et al. biofilm growth on cystic fibrosis airway epithelial cells is enhanced during respiratory syncytial virus coinfection. D'Orazio SEF, editor. mSphere. 2018;3(4):e00341-18, /msphere/3/4/mSphere341-18.atom.
[44] Bellinghausen C, Gulraiz F, Heinzmann ACA, Dentener MA, Savelkoul PHM, Wouters EF, et al. Exposure to common respiratory bacteria alters the airway epithelial response to subsequent viral infection. Respir Res. 2016;17(1):68.
[45] Fabri GMC. Potential link between COVID-19 and periodontitis: Cytokine Storm, Immunosuppression, and Dysbiosis. 2020;19(7):5.
[46] Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: A rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183(1):71-77.
[47] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-48.
[48] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62.
[49] Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. Ann Periodontol. 2003;8(1):38-53.
[50] Schenkein HA, Papapanou PN, Genco R, Sanz M. Mechanisms underlying the association between periodontitis and atherosclerotic disease. Periodontol 2000. 2020;83(1):90-106.
[51] Takahashi Y, Watanabe N, Kamio N, Kobayashi R, Iinuma T, Imai K. Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19. J Oral Sci. 2021;63(1):01-03.
[52] Marouf N, Cai W, Said KN, Daas H, Diab H, Chinta VR, et al. Association between periodontitis and severity of COVID-19 infection: A case-control study. J Clin Periodontol. 2021;48(4):483-91.
[53] Sahni V, Gupta S. COVID-19 & Periodontitis: The cytokine connection. Med Hypotheses. 2020;144:109908. Doi: 10.1016/j.mehy.2020.109908.
[54] Badran Z, Gaudin A, Struillou X, Amador G, Soueidan A. Periodontal pockets: A potential reservoir for SARS-CoV-2? Med Hypotheses. 2020;143:109907. Doi: 10.1016/j.mehy.2020.
[55] Gupta S, Mohindra R, Chauhan PK, Singla V, Goyal K, Sahni V, et al. SARS-CoV-2 detection in gingival crevicular fluid. J Dent Res. 2021;100(2):187-93.
[56] Fernandes Matuck B, Dolhnikoff M, Maia GVA, Isaac Sendyk D, Zarpellon A, Costa Gomes S, et al. Periodontal tissues are targets for Sars-Cov-2: A post-mortem study. J Oral Microbiol. 2021;13(1):1848135.
[57] Wang K, Chen W, Zhou YS, Lian JQ, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein [Internet]. Microbiology; 2020 [cited 2021 May 29]. Available from: http://biorxiv.org/lookup/doi/10.1101/2020.03.14.988345.
[58] Sharma CG, Pradeep AR. Plasma and crevicular fluid osteopontin levels in periodontal health and disease. J Periodontal Res. 2007;42(5):450-55.
[59] Wang J, Yang D, Li C, Shang S, Xiang J. Expression of extracellular matrix metalloproteinase inducer glycosylation and caveolin-1 in healthy and inflamed human gingiva. J Periodontal Res. 2014;49:197-204.

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