Review Article

Proposed Mechanisms for the Relationship between Periodontal Diseases and the Severity of Covid-19: Common Pathogens, Inflammatory Mediators, and Risk Factors

Elham Keykha[1], Leila Khodadadifard[2], Mahdieh-Sadat Moosavi[3], Yaser Fathi[4], Samira Hajisadeghi[5,6]

[1]Department of Oral and Maxillofacial Medicine, Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran, [2]Department of Periodontology, School of Dentistry, Qom University of Medical Sciences, Qom, Iran, [3]Dental Research Center, Dentistry Research Institute, Department of Oral Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran, [4]Department of Oral and Maxillofacial Medicine, School of Dentistry, Alborz University of Medical Sciences, Alborz, Iran, [5]Department of Oral and Maxillofacial Medicine, School of Dentistry, Baqiyatallah University of Medical Sciences, Tehran, Iran, [6]Department of Oral and Maxillofacial Medicine, Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran

Abstract

Periodontal disease (PD) is a chronic inflammatory disease with some cytokine involvement, associated with several risk factors such as diabetes, obesity, etc., Corona Virus Disease 2019 (COVID-19), a new viral infection, also appears to be related to cytokine storm and similar risk factors. In this review, we intend to evaluate the possible relationship between PD and COVID-19. For data collection, English literature was searched in databases including PubMed and Google Scholar. The keywords searched were COVID-19, SARS-CoV-2, PD, respiratory *Impact of Oral pathogens on respiratory diseases:* Epidemiological studies indicated that oral pathogens are related to acute and chronic lung disease, and dental plaque is a likely reservoir for respiratory pathogens. *Viral presence in the periodontal pocket:* SARS-CoV-2 may be released from infected periodontal cells into periodontal pockets. *Common inflammatory mediators:* Several studies showed that the serum levels of interleukins (IL)-1, 6, 17, etc., increase in most patients with severe COVID-19. C-reactive protein (CRP) and endothelin 1(ET-1) may also be related to COVID-19 progression, and these mediators also increase in periodontitis. *Common risk factors:* Due to studies, diabetes mellitus (DM), obesity, aging, and male sex are the most important risk factors common between PDs and COVID-19 and may affect treatment outcomes and prognosis. PD seems to play a significant role in exacerbating COVID-19 and even affects the mortality rate of disease.

Keywords: COVID-19, oral health, periodontal disease, risk factor

Address for correspondence: Prof. Samira Hajisadeghi, Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran - 435916471, Iran.
E-mail: dr.s.hajisadeghi@gmail.com
Submitted: 01-Apr-2023; **Revised:** 13-Sep-2023; **Accepted:** 17-Sep-2023; **Published:** 27-Apr-2024

Introduction

Periodontal diseases (PDs), which are considered a silent pandemic, affect about 10% of the world's population and assent to a multifactorial and immune-mediated disease with some cytokines involvement.[1] On the other hand, the oral cavity is a considerable source of pulmonary pathogens. Poor oral hygiene may develop post-viral complications, especially in individuals prone to biofilm changes such as diabetics, smokers, elderly, hypertensive, and cardiovascular patients.[2]

Corona Virus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in late 2019 and rapidly became a global pandemic.[3] It is a viral infection and in severe cases is

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_116_23

How to cite this article: Keykha E, Khodadadifard L, Moosavi MS, Fathi Y, Hajisadeghi S. Proposed mechanisms for the relationship between periodontal diseases and the severity of Covid-19: Common pathogens, inflammatory mediators, and risk factors. Adv Biomed Res 2024;13:28.

expected to cause bacterial superinfection which leads to some complications including pneumonia.[2] The symptoms of COVID-19 appear to have intercommunication with cytokine storms which contain increased levels of some cytokines in serum.[4] There are also some risk factors linked with severe COVID-19 and a higher risk of complications and death like obesity, diabetes, old age, male gender, and some of them.[5]

The case-control studies have shown the relationship between PDs and the severity of COVID-19.[6-8] Therefore, this review will investigate the relation between COVID-19 and PDs in three sections: the importance of oral microbiomes and PDs in respiratory diseases including COVID-19, common inflammatory mediators affecting periodontitis and COVID-19, and common risk factors between the two diseases and suggest that poor periodontal status may worsen the prognosis of COVID-19. Considering the periodontal status may help physicians identify patients with a higher risk of disease progression and prompt timely invention and may decrease morbidity and mortality rates.

Importance of oral microbiomes in respiratory tract infections including COVID-19

Impact of oral pathogens on respiratory diseases

Some studies claimed that one of the possible reasons for such severe symptoms in some COVID-19 patients is bacterial superinfection and complications such as pneumonia and acute respiratory distress syndrome (ARDS). Bacterial superinfection following viral infections causes more serious conditions and increased mortality and morbidity. Bacterial superinfection was reported in more than 50% of COVID-19 deaths.[2] It was shown that bacterial superinfection is very common in severe COVID -19 patients.[9] On the other hand, antibiotics are necessary in many patients with COVID-19, emphasizing the major role of bacterial infection to exacerbate disease symptoms.[2] Evidence-based studies have shown that SARS-CoV-2 can be present in saliva in three ways: transmission through the respiratory tract by the respiratory droplet, by gingival crevicular fluid (GCF), and by salivary glands infection, with subsequent release of particles in saliva via salivary ducts.[10] Respiratory pathogens isolated from dental plaque and bronchoalveolar lavage fluid from patients with pneumonia are similar. They indicate that dental plaque is a likely reservoir for pulmonary pathogens, so saliva aspiration can cause anaerobic lung infection.[11,12] Some mechanisms have been suggested to clarify the possible role of oral pathogens in respiratory tract infection including: Aspiration of oral pathogenic bacteria into the lung; PD-associated enzymes may facilitate oral bacterial colonization, change salivary pellicles and interfere with oral bacterial clearance; and respiratory epithelium alterations (due to the periodontal cytokines) that increase the risk of respiratory infection. A key point about COVID-19 patients is that disease risk factors (age, gender, and comorbidities) are likely to affect the formation and alteration of the oral microbiome. Studies have shown that periodontal pathogenic bacteria are found in the metagenome of patients with severe COVID-19 infection.[2]

On the other hand, many patients with COVID-19 require mechanical ventilation in the Intensive Care Unit (ICU), and the plaque score is higher in ventilated patients than in other patients. These patients have a higher rate of potential respiratory pathogens (especially *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter cloacae*) in dental plaque and oral mucosa.[13] In general, oral health status is likely to affect bacterial superinfection in COVID-19 patients and thus influence disease severity and prognosis.[14] Studies showed that using chlorhexidine mouthwash in ventilated patients reduces the incidence of ventilator-associated pneumonia, the need for systemic antibiotics, and the period of mechanical ventilation in ICU.[13]

Viral presence in the periodontal pockets (PPs)

Microorganisms like the Herpes family of viruses, Cytomegalovirus, Epstein Barr Virus-1, Papillomaviruses, Human Immunodeficiency Virus, Hepatitis B Viruses, Hepatitis C Viruses, and even *Helicobacter Pylori* exist in PPs.[15-18] The following may be potential routes through which viruses initially infect periodontal tissues: directly infected gingival epithelial cells exposed to the oral cavity, migration of virus via the circulation, or presence of immune cells, which are infected by viruses, in the periodontal inflammatory infiltration.[19] Pocket depth was greater in virus-positive sites than in virus-negative sites.[15,16] These findings suggest that PPs are suitable environments for viruses to infect and survive. By polymerase chain reaction (PCR) test, viruses were discovered in several locations of PPs: GCF, subgingival plaque, and gingival tissues.[20] GCF is a blood filtrate and an exudation of inflamed periodontal tissue. As GCF comprises the majority of the humoral and cellular immune factors present in serum, it may indicate systemic diseases.[21] GCF may contain SARS-CoV-2, which is released from infected periodontal cells or terminal capillary complexes in periodontal tissues. The virus could arrive in the oral environment by entering PPs and mixing with saliva that was shown to contain visible SARS-CoV-2.[20,22] Furthermore, periodontal treatments can markedly reduce subgingival numbers of viruses, and this can lead to a reduction in the number of viruses in saliva.[23] It may be concluded if the SARS-CoV-2 is in the PPs, periodontal treatments can play an effective role in reducing the risk of survival of this disease. This virus may also play a role in worsening PDs and causing a destructive cycle (PDs could be worse by the virus, and more severe PDs can hurt COVID-19 disease). So, periodontal therapy could be deemed a factor of care to manage COVID-19-positive patients around the world clinically. These issues need further investigation.

SARS-CoV-2 receptors in the mouth

Coronaviruses (CoVs) have a glycoprotein called spike (S), which is responsible for various CoVs and host tropism, mediating CoVs coupling with surface-specific receptors of

host cells and fusing viral cell membrane.[24] SARS-CoV-2 interacts with the angiotensin-converting enzyme 2 (ACE2) on the surface of human cells via S, leading to the infection of human respiratory epithelial cells.[25] On the other hand, Furin, a proprotein convertase is involved in viral infection via the cleavage of viral envelope glycoproteins. There is a well-known Furin-cleavage site in the spike protein of SARS-CoV-2, possibly facilitating the virus-cell fusion, which may be an explanation for the viral transmission.[26] Available data suggest the expression of ACE2 with a variety of cells, including lung tissue cells, nasal tissue cells, and salivary gland cells, and a high expression of ACE2 was reported by cells from the oral cavity.[27] In addition to ACE2, oral epithelial cells (lip, gingiva, buccal mucosa, palate, and tongue) express Furin as well. Significant expression of Furin and ACE2 on oral epithelial cells may facilitate the efficiency of SARS-CoV-2 entry.[28,29] ACE2 is also reportedly expressed in gingival and periodontal ligament fibroblasts in rats, and human tissues and blockade of angiotensin II 1 receptor (AT1R) and renin could remarkably prevent periodontal bone loss in rats.[30]

SARS-CoV-2 was capable of infecting cells with the help of its S for binding to CD 147 on cell membranes and not essentially ACE2.[31] CD 147 is expressed in oral epithelial cells, constituting the buccal and subgingival components of PP cells, spindle-shaped periodontal ligament fibroblasts, and epithelial cells.[32] Moreover, CD 147 was increasingly expressed in the gingival epithelium in cells collected from patients suffering from PDs.[29,33] It was established that the blockage of CD 147 led to a significant decrease in osteoclasts, improvement of alveolar height, and trabecular microstructure in the interdental periodontium.[34] So, severe periodontitis is associated with an increased CD147 and an increased risk of infection by SARS-CoV-2.

Common inflammatory mediators in severe COVID-19 and PDs

Several markers were identified that are common between PDs and severe COVID-19. These include some Interleukins (IL), C-reactive protein (CRP), Endothelin-1 (ET-1), and Galectin-3 (Gal-3). Inflammatory cytokine storm elevates the severity of COVID-19 which could result in severe adverse effects and death. Tissue injury can be induced extensively by cytokine storms, particularly in the lungs' connective tissue. Among the various cytokines, such as IL-1, 6, and 17 appear to be common between COVID-19 and PDs, described in detail in the following sections [Table 1].

Neutrophil extracellular traps (NETs)

Neutrophil-intermediated defensive mechanisms, named NETs, putatively function to retain and kill bacterial, fungal, viral, and protozoan pathogens.[35] NETosis has been attributed to a possible function in the pathophysiology of PDs with mediators, including interferon alpha, involved in the induction of releasing NET, which is reportedly at greater concentrations in periodontitis patients. An abundance of NETs in pus exudate collected from PP in association with the PPs epithelium of chronic periodontitis patients was reported.[36] Viral stimulated NETs are capable of circulation uncontrollably, giving rise to an excessive bodily systemic response by producing immune complexes, chemokines, and cytokines and eventually in favor of inflammation.[37] NETs have been shown to increase bronchoalveolar lavage fluid in patients suffering from ARDS and those with acutely exacerbated chronic obstructive pulmonary disease (COPD).[35] Arcanjo *et al*. were the pioneers to demonstrate that SARS-CoV2 was actually capable of activating NETosis in human neutrophils. These data refer to elevated levels of NETs in patients with COVID-19 and periodontitis. It proposes that patients affected by PDs may be at a high risk of COVID-19 linked harmful consequences, which, following proper clinical confirmation, will likely add to the present record of situations that predispose to the development of severe types of diseases.[38,39]

Common risk factors between severe COVID-19 and PD

One of the things which can help examine the relationship between PDs and COVID-19 is through close common risk factors of these two diseases, some of which will be mentioned and discussed below. Studies have shown that diabetes and some other systemic diseases may alter oral biofilms associated with higher amounts of Fusobacterium nucleatum, Prevotella intermedia, and *Porphyromonas gingivalis* and an increased rate of periodontitis. Periodontal pathogenic bacteria are found in the metagenome of patients with severe COVID-19 infection.[2]

Diabetes mellitus (DM)

DM is a hyper-inflammatory situation that appears to increase susceptibility to Covid-19 independently of other underlying diseases.[40] Several biological mechanisms have illustrated the association between periodontitis and DM. Periodontitis causes glycemic levels to get out of control, and poor glycemic control increases the risk of developing periodontitis.[41] Some reports showed that elderly patients with chronic diseases such as DM are at higher risk for severe COVID-19 and mortality.[42] Many biomarkers are common between PDs, DM, and COVID-19 such as IL-6, IL-1, and TNF-α. Elevated levels of these biomarkers are associated with poor glycemic control, the severity of COVID-19, and the extent of the severity of periodontitis, and also blocking them was suggested as a possible treatment option.[43,44] On the other hand, it showed that initial nonsurgical periodontal therapy could reduce the levels of the aforementioned biomarkers. Furthermore, DM is associated with increased lung ACE2 expression and in severe COVID-19 cases, ACE2 in the lung may also be affected.[45]

Aging

Aging creates destructive changes in individual cells which can lead to different autoimmune, infectious, and inflammatory diseases including periodontitis. The following are some of the causes which can increase periodontal problems in old age: loss of dexterity which leads to plaque accumulation, systemic effects of diseases, poor nutritional status, low number of teeth that exist in the mouth or edentulous which can lead to malnutrition, use of medication, and lack of timely dental visits.

Table 1: Common inflammatory mediators in severe COVID-19 and PDs

Mediator	Effect	In PDs		In Covid-19 disease	
		Author	Results	Author	Results
IL-6	Proinflammatory cytokine	Machado *et al*.[67]	Serum levels of IL-6 in transplanted patients with periodontitis were higher than transplanted patients without periodontitis	Yang *et al*.[68]	Peripheral blood IL-6 concentrations utilized as a factor to predict Covid-19 development
				Aziz *et al*.[58]	Elevations of IL-6 could predict prolong staying in ICU and mortality
		Cardoso *et al*.[41]	IL-6 levels increase in chronic periodontitis	Ulhaq and Soraya[69]	Significant increases in IL-6 concentrations in severe Covid-19 patients compared to those with non-severe condition
		Almehmadi and Alghamdi[70]	Il-6 can act as a diagnostic marker for areas of active periodontitis and is capable of bone resorption		
		Corbella *et al*.[71]	High levels of IL-6 diminished by periodontal treatment		
IL-17	proinflammatory cytokine	Batool *et al*.[72]	Salivary levels of IL-6 and IL-17 increased in chronic periodontitis patients and the progression of chronic periodontitis increases these levels	Pacha *et al*.[73]	Elevated serum levels IL-17 observed in cytokine storm
		Jayakumar Sunandhakumari *et al*.[74]	Plasma levels of IL-17 decreased following non-surgical periodontal therapy in chronic periodontitis patients	Huang *et al*.[75]	Levels of IL-17 increased in SARS-CoV-2 infection
IL-1	proinflammatory cytokine	Papathanasiou *et al*.[76]	IL-1 family contains the major signaling molecules which stimulate and perpetuate periodontal inflammation.	Van de Veerdon and Netea[77]	Highly upregulation of IL-1/ IL-6 happen in patients with severe disease and blocking of IL-1 inhibit respiratory failure in Covid-19 patients
		Fu *et al*.[78]	IL-1 level expression increased in the periodontitis group and inhibiting IL1 and TNF-α pathways can suppress inflammation and alveolar bone loss in periodontitis.		
CRP	acute inflammatory protein	Montenegro *et al*.[79]	Periodontal therapy can decrease IL-6, IL-8 and, CRP levels in cardiovascular patients with elevated CRP levels	Liu *et al*.[80]	Developing severe COVID19 was more probable in patients with CRP >41.8 mg/L
		Swaroop Chandy *et al*.[81]	Serum CRP levels in patients with chronic and aggressive periodontitis were higher than healthy controls	Tan *et al*.[82]	CRP was related to disease progression and predicted early severe Covid-19
ET-1	A vasoconstrictor and strong mediator of vascular inflammation	Isola *et al*.[83]	Salivary and serum ET-1 levels in patients with coronary heart disease (CHD) and periodontitis plus CHD were higher than patients with periodontitis and healthy controls.	Farhangrazi and Moghimi[49]	ET-1 levels can be a biomarker that predicts patients at high risk to develop the severe type of Covid-19
		Kadhim *et al*.[84]	The Serum level of ET-1 is considered as a biomarker that links between periodontitis and risk of endothelial dysfunction	Badagliacca *et al*. [85]	Blocking of ET receptors affected SARS-CoV-2 pathogenesis in experimental models and ET-1 receptor antagonists is a treatment option in this disease
		Khalid *et al*.[50]	ET-1 levels in patients with chronic periodontitis were significantly higher than healthy controls		
Gal-3	Proinflammatory protein	Velicovic *et al*.[86]	Possible role of Gal-3 in development of periodontal diseases by modulation of the key players in periodontitis pathogenesis	Caniglia *et al*.[87]	An important area in the S protein of Covid-19 is almost the same as the morphology of Gal-3
		Kara *et al*.[88]	Increased level of Gal-3 is associated with the severity of PDs		

These can alter the subgingival plaque and cause periodontal problems.[45] For COVID-19, there are strong indications for age relation in an increased number of cases, the severity of disease, and mortality, so that subclinical infections over the age of 70 are rare.[46] In severe cases, COVID-19 can increase inflammation, compromise lung tissue integrity and function, and cause pneumonia.[47] The onset of pneumonia is related to the aspiration of some bacteria from oral and nasal cavities including periodontal bacteria. Aspiration pneumonia is especially common in the elderly. The oral cavity is a great reservoir for pulmonary pathogens, and dental plaque can provide nutrition for respiratory route pathogens mainly in bad plaque control.[48] A biomarker that may unite PDs and aging is endothelin.[14] Elevated ET-1 levels also may be used as a possible biomarker to identify people at high risk for severe COVID-19.[49] Also, elevated levels of ET-1 in the serum of patients with periodontitis are observed which reduces after periodontal therapy.[50]

Obesity

Obese people are more prone to have PDs than normal-weight people, and this relationship is independent of gender and age.

Increased levels of obesity are associated with more extent and severity of periodontitis. Obesity alone can create a destructive pathway in oral health. It can change the microbial composition of the periodontium and increase periodontal pathogens.[51] Adipose tissue secretes low levels of cytokines, including TNF-α and IL-1, 6, and 8. These cytokines could lead to periodontitis by changing bacteria's status in the gingiva. [45,52]

Elevated inflammatory factors in obesity can exacerbate a patient's response and lead to severe COVID-19.[53] Adipose tissue significantly increases viral shedding in obese people with influenza infection, and there is a possibility of increased viral shedding in adipose tissue in obese people with COVID-19. Viral infection can intensify the preliminary response of cytokines in adipose tissue.[54-56] IL-6 is one of the most important of these cytokines and an independent predictor of COVID-19 mortality.[53,57,58] IL-6 inhibition is suggested as a treatment for COVID-19.[52] Also, periodontitis can exacerbate inflammatory status in COVID-19 by spreading microbial productions as a reservoir of inflammatory cytokines. Therefore, obese people with periodontitis may have an increased hazard for severe COVID-19.[45]

Gender

The prevalence and severity of periodontitis are more common in men than women. Various reasons were proposed to explain it, including immune system function and environmental and behavioral factors, which require more detailed and extensive studies to determine.[59]

Due to COVID-19, men have a greater gender distribution than women. Some studies attributed the difference in the prevalence and severity of COVID-19 to the male gender, and men can be associated with fatal outcomes in patients with severe forms of the disease.[60-62] Decreased susceptibility to viral infection in women likewise can be attributed to the protection of sex hormones and X chromosomes, which play a vital role in innate and acquired immunity.[63] On the other hand, the most probable entry point for SARS-COV-2 is ACE2 and the ACE2 encoding gene is located on the X chromosome.[64] Due to gene dosage, men suffer more from X-linked diseases. Men may suffer more from ACE2 related diseases than women probably because of more occurrences of ACE2 on the X chromosome.[65] Therefore, it seems that ACE2 expression is probably higher in men than women, and this gender difference might lead to an increase in morbidity and mortality due to Covid-19 in men than women.[66]

Conclusion

Presumably, PDs play a role in the exacerbation of the Covid-19 disease and even affec this disease's mortality rate. According to this study, there are at least three different connections between PDs and Covid-19. Firstly, the common microbiome and oral environment as a reservoir of SARS-CoV-2. Secondly, inflammatory mediators of PDs can aggravate the condition of COVID-19. Finally, similar risk factors make the underlying condition worse. Therefore, there is a need for further studies to determine the cause-and-effect relationship between these two diseases. By proving this relationship, the need to pay attention to oral hygiene education and pay special attention to PD treatment will become more apparent. On the other hand, considering the periodontal status may help physicians identify patients with a higher risk of disease progression and prompt timely invention and may decrease morbidity and mortality rates.

Acknowledgement

We highly appreciate Qom School of Dentistry, Qom, Iran, for their sincere technical assistance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sahni V, Gupta S. COVID-19 and Periodontitis: The cytokine connection. Med Hypotheses 2020;144:109908.
2. Sampson V, Kamona N, Sampson A. Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? Br Dent J 2020;228:971-5.
3. Fisher D, Heymann D. Q and A: The novel coronavirus outbreak causing COVID-19. BMC Med 2020;18:57.
4. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect 2020;53:368-70.
5. Jordan RE, Adab P, Cheng KK. Covid-19: Risk factors for severe disease and death. BMJ 2020;368:m1198.
6. Larvin H, Wilmott S, Wu J, Kang J. The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic. Front Med (Lausanne) 2020;7:604980.
7. 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;48:483-91.
8. Gupta S, Mohindra R, Singla M, Khera S, Sahni V, Kanta P, *et al*. The clinical association between periodontitis and COVID-19. Clin Oral Investig 2022;26:1361-74.
9. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, *et al*. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol 2020;17:533-5.
10. Moosavi MS, Aminishakib P, Ansari M. Antiviral mouthwashes: Possible benefit for COVID-19 with evidence-based approach. J Oral Microbiol 2020;12:1794363.
11. Han YW, Wang X. Mobile microbiome: Oral bacteria in extra-oral infections and inflammation. J Dent Res 2013;92:485-91.
12. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, *et al*. Association between periodontal pathogens and systemic disease. Biomed J 2019;42:27-35.
13. Muthu J, Muthanandam S, Mahendra J. Mouth the mirror of lungs: Where does the connection lie? Front Med 2016;10:405-9.
14. Scannapieco FA, Cantos A. Oral inflammation and infection, and chronic medical diseases: Implications for the elderly. Periodontol 2000 2016;72:153-75.
15. Sharma R, Padmalatha O, Kaarthikeyan G, Jayakumar ND, Varghese S, Sherif K. Comparative analysis of presence of Cytomegalovirus (CMV) and Epsteinbarr virus-1 (EBV-1) in cases of chronic periodontitis and aggressive periodontitis with controls. Indian J Dent Res 2012;23:454-8.
16. Das S, Krithiga GS, Gopalakrishnan S. Detection of human herpes viruses in patients with chronic and aggressive periodontitis and relationship between viruses and clinical parameters. J Oral Maxillofac Pathol 2012;16:203-9.

17. Salehi MR, Shah Aboei M, Naghsh N, Hajisadeghi S, Ajami E. A Comparison in prevalence of *helicobacter pylori* in the gingival crevicular fluid from subjects with periodontitis and healthy individuals using polymerase chain reaction. J Dent Res Dent Clin Dent Prospects 2013;7:238-43.
18. Rodrigues PM, Teixeira AL, Kustner EC, Medeiros R. Are herpes virus associated to aggressive periodontitis? A review of literature. J Oral Maxillofac Pathol 2015;19:348-55.
19. Miller CS. Viruses: Are they really culprits for periodontal disease? A critical review? J Investig Clin Dent 2014;5:243.
20. Badran Z, Gaudin A, Struillou X, Amador G, Soueidan A. Periodontal pockets: A potential reservoir for SARS-CoV-2? Med Hypotheses 2020;143:109907.
21. Fitzsimmons TR, Sanders AE, Bartold PM, Slade GD. Local and systemic biomarkers in gingival crevicular fluid increase odds of periodontitis. J Clin Periodontol 2010;37:30-6.
22. To KK, Tsang OT, Yip CC, Chan KH, Wu TC, Chan JM, *et al*. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 2020;71:841-3.
23. Zhang Y, Wang X, Li H, Ni C, Du Z, Yan F. Human oral microbiota and its modulation for oral health. Biomed Pharmacother 2018;99:883-93.
24. Lu G, Wang Q, Gao GF. Bat-to-human: Spike features determining 'host jump' of coronaviruses SARS-CoV, MERS-CoV, and beyond. Trends Microbiol 2015;23:468-78.
25. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, *et al*. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457-60.
26. 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;14:185-92.
27. Wu C, Zheng M. Single-cell RNA expression profiling shows that ACE2, the putative receptor of Wuhan 2019-nCoV, has significant expression in the nasal, mouth, lung and colon tissues, and tends to be co-expressed with HLA-DRB1 in the four tissues 2020.
28. Mei Z, Bingpeng L, Hongbin G, Xinhong W, Kaibin W, Mingxiao L, *et al*. Significant expression of FURIN and ACE2 on oral epithelial cells may facilitate the efficiency of 2019-nCov entry. BioRxiv 2020.
29. Baima G, Marruganti C, Sanz M, Aimetti M, Romandini M. Periodontitis and COVID-19: Biological mechanisms and meta-analyses of epidemiological evidence. J Dent Res 2022;101:1430-40.
30. Santos CF, Morandini AC, Dionísio TJ, Faria FA, Lima MC, Figueiredo CM, *et al*. Functional local renin-angiotensin system in human and rat periodontal tissue. PLoS One 2015;10:e0134601.
31. 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. BioRxiv 2020.
32. Feldman M, La VD, Lombardo Bedran TB, Palomari Spolidorio DM, Grenier D. Porphyromonas gingivalis-mediated shedding of extracellular matrix metalloproteinase inducer (EMMPRIN) by oral epithelial cells: A potential role in inflammatory periodontal disease. Microbes Infect 2011;13:1261-9.
33. 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.
34. Yang D, Liu R, Liu L, Liao H, Wang C, Cao Z. Involvement of CD147 in alveolar bone remodeling and soft tissue degradation in experimental periodontitis. J Periodontal Res 2017;52:704-12.
35. Grabcanovic-Musija F, Obermayer A, Stoiber W, Krautgartner WD, Steinbacher P, Winterberg N, *et al*. Neutrophil extracellular trap (NET) formation characterises stable and exacerbated COPD and correlates with airflow limitation. Respir Res 2015;16:59.
36. Gupta S, Sahni V. The intriguing commonality of NETosis between COVID-19 and Periodontal disease. Med Hypotheses 2020;144:109968.
37. Mozzini C, Girelli D. The role of Neutrophil Extracellular Traps in Covid-19: Only an hypothesis or a potential new field of research? Thromb Res 2020;191:26-7.
38. Arcanjo A, Logullo J, Menezes CCB, de Souza Carvalho Giangiarulo TC, Dos Reis MC, de Castro GMM, *et al*. The emerging role of neutrophil extracellular traps in severe acute respiratory syndrome coronavirus 2 (COVID-19). Sci Rep 2020;10:19630.
39. Shamsoddin E. Is periodontitis associated with the severity of COVID-19? Evid Based Dent 2021;22:66-8.
40. Tadic M, Cuspidi C, Sala C. COVID-19 and diabetes: Is there enough evidence? J Clin Hypertens (Greenwich) 2020;22:943-8.
41. Cardoso EM, Reis C, Manzanares-Céspedes MC. Chronic periodontitis, inflammatory cytokines, and interrelationship with other chronic diseases. Postgrad Med 2018;130:98-104.
42. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775-6.
43. Cauchois R, Koubi M, Delarbre D, Manet C, Carvelli J, Blasco VB, *et al*. Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19. Proc Natl Acad Sci U S A 2020;117:18951-3.
44. Mandrup-Poulsen T, Pickersgill L, Donath MY. Blockade of interleukin 1 in type 1 diabetes mellitus. Nat Rev Endocrinol 2010;6:158-66.
45. Pitones-Rubio V, Chávez-Cortez EG, Hurtado-Camarena A, González-Rascón A, Serafín-Higuera N. Is periodontal disease a risk factor for severe COVID-19 illness? Med Hypotheses 2020;144:109969.
46. Davies NG, Klepac P, Liu Y, Prem K, Jit M, CMMID COVID-19 working group, *et al*. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med 2020;26:1205-11.
47. Santesmasses D, Castro JP, Zenin AA, Shindyapina AV, Gerashchenko MV, Zhang B, *et al*. COVID-19 is an emergent disease of aging. Aging Cell 2020;19:e13230.
48. Qian Y, Yuan W, Mei N, Wu J, Xu Q, Lu H, *et al*. Periodontitis increases the risk of respiratory disease mortality in older patients. Exp Gerontol 2020;133:110878.
49. Farhangrazi ZS, Moghimi SM. Elevated circulating endothelin-1 as a potential biomarker for high-risk COVID-19 severity. Precision Nanomedicine 2020;3:622-8.
50. Khalid W, Varghese SS, Sankari M, Jayakumar ND. comparison of serum levels of endothelin-1 in chronic periodontitis patients before and after treatment. J Clin Diagn Res 2017;11:ZC78-81.
51. Suvan JE, Finer N, D'Aiuto F. Periodontal complications with obesity. Periodontol 2000 2018;78:98-128.
52. Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation, and cytokine amplification in coronavirus disease 2019? Obesity (Silver Spring) 2020;28:1191-4.
53. Dietz W, Santos-Burgoa C. Obesity and its Implications for COVID-19 Mortality. Obesity (Silver Spring) 2020;28:1005.
54. Kern L, Mittenbühler MJ, Vesting AJ, Ostermann AL, Wunderlich CM, Wunderlich FT. Obesity-Induced TNFα and IL-6 Signaling: The missing link between obesity and inflammation-driven liver and colorectal cancers. Cancers (Basel) 2018;11:24.
55. Maier HE, Lopez R, Sanchez N, Ng S, Gresh L, Ojeda S, *et al*. Obesity Increases the duration of influenza a virus shedding in adults. J Infect Dis 2018;218:1378-82.
56. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev 2012;76:16-32.
57. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, *et al*. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. Clin Infect Dis 2020;71:1937-42. doi: 10.1093/cid/ciaa449.
58. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol 2020;92:2283-5.
59. Ioannidou E. The sex and gender intersection in chronic periodontitis. Front Public Health 2017;5:189.
60. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, *et al*. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020;146:110-18.
61. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 2020;8:e20.
62. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol 2017;198:4046-53.
63. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, *et al*. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol 2020;92:577-83.

64. Tukiainen T, Villani AC, Yen A, Rivas MA, Marshall JL, Satija R, *et al*. Landscape of X chromosome inactivation across human tissues. Nature 2017;550:244-8.
65. Sama IE, Voors AA. Men more vulnerable to COVID-19: Explained by ACE2 on the X chromosome? Eur Heart J 2020;41:3096.
66. Majdic G. Could Sex/Gender Differences in ACE2 Expression in the lungs contribute to the large gender disparity in the morbidity and mortality of patients infected with the SARS-CoV-2 virus? Front Cell Infect Microbiol 2020;10:327.
67. Machado V, Botelho J, Lopes J, Patrão M, Alves R, Chambrone L, *et al*. Periodontitis impact in interleukin-6 serum levels in solid organ transplanted patients: A Systematic Review and Meta-Analysis. Diagnostics (Basel) 2020;10:184.
68. Yang P, Ding Y, Xu Z, Pu R, Li P, Yan J, *et al*. Epidemiological and clinical features of COVID-19 patients with and without pneumonia in Beijing, China. Medrxiv 2020.
69. Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect 2020;50:382-3.
70. Almehmadi AH, Alghamdi F. Biomarkers of alveolar bone resorption in gingival crevicular fluid: A systematic review. Arch Oral Biol 2018;93:12-21.
71. Corbella S, Francetti L, Taschieri S, De Siena F, Fabbro MD. Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis. J Diabetes Investig 2013;4:502-9.
72. Batool H, Nadeem A, Kashif M, Shahzad F, Tahir R, Afzal N. Salivary levels of IL-6 and IL-17 could be an indicator of disease severity in patients with calculus associated chronic periodontitis. Biomed Res Int 2018;2018:8531961.
73. Pacha O, Sallman MA, Evans SE. COVID-19: A case for inhibiting IL-17? Nat Rev Immunol 2020;20:345-6.
74. Jayakumar Sunandhakumari V, Sadasivan A, Koshi E, Krishna A, Alim A, Sebastian A. Effect of nonsurgical periodontal therapy on plasma levels of IL-17 in chronic periodontitis patients with well controlled type-II diabetes mellitus-A Clinical Study. Dent J (Basel) 2018;6:19.
75. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
76. Papathanasiou E, Conti P, Carinci F, Lauritano D, Theoharides TC. IL-1 Superfamily members and periodontal diseases. J Dent Res 2020;99:1425-34.
77. van de Veerdonk FL, Netea MG. Blocking IL-1 to prevent respiratory failure in COVID-19. Crit Care 2020;24:445.
78. Fu C, Wei Z, Zhang D. PTEN inhibits inflammatory bone loss in ligature-Induced periodontitis via IL1 and TNF-α. Biomed Res Int 2019;2019:6712591.
79. Montenegro MM, Ribeiro IWJ, Kampits C, Saffi MAL, Furtado MV, Polanczyk CA, *et al*. Randomized controlled trial of the effect of periodontal treatment on cardiovascular risk biomarkers in patients with stable coronary artery disease: Preliminary findings of 3 months. J Clin Periodontol 2019;46:321-31.
80. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, *et al*. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 2020;127:104370.
81. Chandy S, Joseph K, Sankaranarayanan A, Issac A, Babu G, Wilson B, *et al*. Evaluation of C-reactive protein and fibrinogen in patients with chronic and aggressive periodontitis: A Clinico-Biochemical Study. J Clin Diagn Res 2017;11:ZC41-5.
82. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, *et al*. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020;92:856-62.
83. Isola G, Polizzi A, Alibrandi A, Indelicato F, Ferlito S. Analysis of endothelin-1 concentrations in individuals with periodontitis. Sci Rep 2020;10:1652.
84. Kadhim SS, Al-Windy SA, Al-Kuraishy HM, Al-Gareeb AI. Endothelin-1 is a surrogate biomarker link severe periodontitis and endothelial dysfunction in hypertensive patients: The potential nexus. J Int Oral Health 2019;11:369.
85. Badagliacca R, Sciomer S, Petrosillo N. Endothelin receptor antagonists for pulmonary arterial hypertension and COVID-19: Friend or foe? J Heart Lung Transplant 2020;39:729-30.
86. Velickovic M, Arsenijevic A, Acovic A, Arsenijevic D, Milovanovic J, Dimitrijevic J, *et al*. Galectin-3, possible role in pathogenesis of periodontal diseases and potential therapeutic target. Front Pharmacol 2021;12:638258.
87. Caniglia JL, Guda MR, Asuthkar S, Tsung AJ, Velpula KK. A potential role for galectin-3 inhibitors in the treatment of COVID-19. PeerJ 2020;8:e9392.
88. Kara C, Çelen K, Dede FÖ, Gökmenoğlu C, Kara NB. Is periodontal disease a risk factor for developing severe Covid-19 infection? The potential role of Galectin-3. Exp Biol Med (Maywood) 2020;245:1425-7.