Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies ***NLM ID:*** *101716117*

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Index Copernicus value = 85.10

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

How Chronic Periodontitis associated with Systemic Diseases increases the case fatality rate among COVID-19 Patients

Anil Sharma[1], Rupali[2], Shiva Chauhan[3], Rohit Sharma[4], Vidushi Jindal[5], Poonam Rajput[6], Vikas Jindal[7]

[1]Post Graduate, Department Of Periodontics, Himachal Dental College, Sundernagar, H.P. India;
[2]Post Graduate, Department of Roga Nidana, Shri JG Cooperative Society's Ayurvedic Medical College and Hospital, Ghataprabha, RGUHS, Karnataka, India;
[3]Senior Lecturer, Department Of Periodontics, Himachal Dental College, Sundernagar. H.P., India;
[4]Reader, Department Of Periodontics, Himachal Dental College, Sundernagar, H.P. India;
[5]Third year Student, Universida Catolica San Antonio (UCAM, Murcia, Spain);
[6]Post Graduate, Department Of Periodontics, Himachal Dental College, Sundernagar, H.P., India;
[7]H.O.D. Department Of Periodontics , Himachal Dental College, Sundernagar, H.P., India

***ABSTRACT*:**
Chronic inflammations are increasingly considered as a potential trigger for COVID-19 disease. Infectivity activation of different inflammatory cascades of the host and dysbiotic events by chronic periodontitis negatively affects oral mucosa, bone, and all other periodontal tissues and could have systemic implications. Any chronic infection of the oral cavity like periodontitis is a constant potential source of infection and a separate risk factor for various systemic diseases like diabetes, CVS, respiratory diseases, etc. These preexisting systemic diseases have been widely associated with the progression of severe COVID -19 disease and it's ill effects. Since systemic health was affected by inflammatory cascades, dysbiotic factors, and comorbidities, these possibilities also related to the periodontal status of the patients which ultimately considered the risk of complication of COVID-19 disease. However periodontal status like PPD, CAL, etc has not been reported yet. Only based on oral dental and medical history is taken from the COVID-19 patients we reached on the conclusion that chronic periodontitis and COVID-19 disease relation could help us for identifying the risk groups and for the establishment of pertinent recommendations. By identifying these risk groups of chronic periodontitis with underlying systemic diseases we can control the CFR among COVID-19 patients.

Key words: Chronic inflammation, Chronic Periodontitis , Systemic diseases and COVID-19.

Received: 02/07/2020 **Modified:** 23/07/2020 **Accepted:** 24/07/2020

Corresponding Author: Dr. Rohit Sharma, Reader, Department Of Periodontics, Himachal Dental College, Sundernagar, H.P. India

This article may be cited as: Sharma A, Rupali, Chauhan S, Sharma R, Jindal V, Rajput P, Jindal V. How Chronic Periodontitis associated with Systemic Diseases increases the case fatality rate among COVID-19 Patients. J Adv Med Dent Scie Res 2020;8(8):71-77.

INTRODUCTION:

Chronic periodontitis is an chronic infectious inflammatory disease mainly caused by the bacteria's present in the dental plaque, leading to the progressive destruction of the supporting tissues of the tooth (i.e. gingiva, cementum, periodontal ligament and alveolar bone)[1]. Periodontal disease is characterized by the periods of exacerbation interspersed with the periods of remission and presents a local microbial burden which initiates local inflammation and destruction of that tissue locally. Periodontal diseases are a group of chronic inflammatory diseases including gingivitis and

periodontitis.[2]According to World Health Organization severe periodontal disease which may result in tooth loss, is very common and it affect almost 10 % of the global population.[3.]According to F.D.I. almost 11 % of population affected by the severe periodontal disease globally.[4] Various risk factors like poor oral hygiene, stress, aging, alcohol consumption, depression, tobacco chewing, smoking and numbers of systemic diseases such as diabetes mellitus, respiratory diseases, peripheral arterial diseases, obesity, pregnancy and cardiovascular diseases have relation with periodontal diseases.[5]Some of these conditions may in turn increases the incidence and severity of periodontal disease by modifying the body's immune response to periodontal plaque bacteria's and their by products.[6] Common bacterial pathogens associated with the chronic periodontitis are Porphyromonas gingivalis,tenerella forsythia and treponema denticola (red complex bacterias),but more pathogenic bacterias like provetella species, Aggregatibactor Actinomycetecomitans etc. Evidence showed a bi-directional relationship between periodontitis and systemic diseases. The possible mechanisms or pathways linking oral infections to secondary systemic effect are: metastatic spread of infection from the oral cavity as a result of transient bacteremia , metastatic injury from the effect of circulating oral microbial toxins, and metastatic inflammation caused by immunological injury induced by oral microorganisms.[7]Host factors such as nutritional diet and immune response are the determinant by the emergence and persistence of microbial dysbiosis which ultimately lead to the growth of these pathogens and their virulent toxins in chronic periodontitis[8].This Chronic periodontitis disease which is a continuous inflammatory condition increases the Case Fatality rate (CFR) among COVID-19 patients.

The outbreak of corona virus disease 2019 (COVID-19) in the region of Wuhan, China has evolved rapidly in to public health crises and spread rapidly to other parts of the world[9].The novel corona virus belongs to a family of single stranded RNA viruses known as Coronaviridae.[10] This family of viruses are known to be zoonotic in origin means transmitted from animal to humans. These include severe acute respiratory syndrome corona virus (SARS-CoV),first identified in 2002 and Middle East Respiratory Syndrome corona virus (MERS-CoV),first identified in 2012.[11.]Since the published genome sequence for this novel corona virus has a close resemblance with other beta-corona viruses such as SARS CoV and MERS-CoV ,the corona virus study group of International Committee on Taxonomy of Viruses has given its specific name as SARS CoV-2,even though it is popularly COVID-19 virus.[12]On 30th January 2020,the World Health Organization (WHO) declared the outbreak of SARS CoV -2 and its associated disease COVID-19 a public health emergency and on March 11,declared it as pandemic.[13]The SARS CoV-2 virion is crown shaped with a diameter of 50-200 nm ,having four structural proteins :spike (S), envelop (E),membrane (M) and nucleocapsid (N).The S and M proteins are responsible for viral envelope generation and the N protein carries the RNA genome (30kb).Oral mucosa and nasal mucosa are the primary contact epithelium through which SARS CoV-2virus enters the host cells.[14]Oral mucous membrane has three epithelium namely oral epithelium, sulcular epithelium and junction epithelium through which virus enters the gingival crevice and periodontal pockets in periodontal diseases. Intact epithelium is a primary barrier who prevent the entery of any type of antigen which may be virus or bacteria,whenever there is breach in above said epitheliums due to chronic disease like periodontitis it becomes very easy to the spike protein (S) which is glycoprotein in nature that facilitates SARS COV-2 attachment, fusion, entry and transmission in to the host cells by binding with human angiotensin converting enzyme 2 (hACE2) receptors, which are expressed by epithelial cells of the oral mucosa, nasal mucosa, lungs alveoli, intestine , kidney, blood vessels etc[15].Due to SARS CoV-2 virus penetration there is increase in gingival crevicular fluid secretion flow inflammatory cytokines levels increased in GCF and antibodies against SARS CoV-2 virus levels also raised in GCF.

According to WHO situation report July 7, 2020 globally 1,19,64,505 cases and 5,46,964 (4.6%) deaths and recovered 69.12,820 (57.8%) cases reported, In India total cases 7,44,006,deaths 20,653 (2.8%) and 4,57,058 (61.43%) recovered from COVID-19 disease [16], and this numbers continues to increase, therefore measures for prevention, identification and management must be in place for appropriate mitigation of further spread. Worldwide of all infected patients, only a small percentage of patients developed critical state, considering the presence of any comordity or condition, which can be diabetes, hypertension, obesity, asthma, pregnancy, lung diseases liver diseases, oral dysbiosis, aging and gender.[17]Case Fatality Rates are the total number of cases and the total number of deaths from COVID-19 disease outbreak. The overall case fatality rate (CFR) among COVID-19 patients increased in the presence of a preexisting systemic condition, such as cardiovascular disease(CFR,10.5%),diabetes (7.3%),chronic respiratory disease (6.3%),hypertension (6 %) and cancer (5.6 %).[18]The data was also indicative of an age related trend in CFR, which revealed patients aged 80 years or above had 14.8 % CFR,70-79 years of age had an 8 % of CFR. Also no fatal cases were observed in patients aged 9 years or younger. These findings have been referenced by the American Association of Clinical Endocrinologists and by the

American Diabetes Association in their COVID-19 recommendations for diabetic patients.[19]
This review article proposes to evaluate why chronic periodontitis is a risk factor for developing severe COVID-19 illness because of above shared risk factors and lead to increased Case Fatality Rate (CFR) among COVID-19 patients.

Hypothesis : Relation of fhronic periodontitis disease with systemic diseases and their combined impact on the Case Fatality Rate (CFR) among COVID -19 diseased patients:
Chronic periodontitis disease could be related with the case fatality rate (CFR) among severe COVID-19 illness.On the basis of oral dental and medical history taken from the chronic periodontitis patients could be a characteristic to identify a risk group to severe COVID-19 fatalty rate.The suggested relationship between chronic periodontitis and CFR in severe COVID-19 illness could be connected to closely shared risk factors among these affections. Most of the risk factors which are reported in COVID-19 disease patients are.also aggrevates the development of chronic periodontitis disease. Till now only information on the basis of oral history taking but no periodontal status of severe COVID-19 patients yet recorded.

Assessment of Hypothesis :
Examining some of these evidences from another angle, it may be reasonable to assume that periodontal infections could influence the overall health and the course of some systemic diseases. In fact there is accumulating evidence that this may be the case that effect of periodontal diseases may have adverse effects on cardiovascular diseases (atherosclerosis, hypertension, myocardial infarction, stroke, coronary artery diseases), smoking or tobacco abuse (oral cancer and lung cancer), chronic respiratory diseases (COPD, Bronchiectases) genitourinary tract infections (chronic kidney diseases), diabetes mellitus etc.
As the periodontal disease is generally slowly progressing, with age the chronic disease of supporting structure of tooth and their prevalence has continuously increasing. The three pathways for dental infection resulting in systemic dissemination were proposed by Appleton 8 in 1944 : A).Metastasis of the infectious organism by active transport in blood vessels or lymphatic channels. B). Passive diffusion into the blood or lymph enabling the bacterias to reach the most remote areas of the body. C). The products of Bacterial autolysis may in turn to be a potential allergen dispersing into the blood or lymph. The possible routes of infection from periodontal pockets : 1). Lymph and Blood 2). Direct extensions within the tissue 3). Aspiration and Swallowing of the infective organisms enabling passage through pulmonary tract and GIT (gastrointestinal tract) respectively .All these studies showed that chronic periodontal disease may lead to the development of these above said chronic systemic diseases which ultimately leads to increase in overall Case Fatality Rate (CFR) among COVID-19 Patient.

Aging: Aging is a continuous process that causes various degenerative changes at cellular level and sometimes leads to the development of various diseases that can be autoimmune ,infectious and inflammatory including chronic periodontitis. According to WHO elderly population are most commonly affected by chronic periodontitis disease because they have additional risk factors during their life time like poor oral hygiene habits, presence of some other chronic systemic diseases, use of different medications ,environmental factors like smoking and not taking timely dental treatment ,that causes the increased accumulation of dental plaque and leads to alteration in gingival microbiota ,which ultimately leads to the development of periodontitis disease. This periodontitis disease can lead to the complications on various systemic conditions [20].People above 65 years are at higher risk group for severe COVID-19 illness. SARS CoV-2 virus very easily attack these age groups because immunity level of these age groups are lowered as compared to young adults. So the Case Fatality Rate is higher in people above 65 years.[21] Therefore, it is clear from above discussion that aging is a most determining risk factor in linking periodontitis and severe COVID -19 illness since they share the associated risk factors that can lead to complications and increases the CFR. Thus allows to identify this risk group to severe COVID-19 illness.

Gender :
Interestingly ,different studies have showed that periodontitis has a documented higher prevalence in males (57%) compared to females (37%).It was proposed that differences in immune function could be involved, moreover ,probably behavioral and environmental factors could have an important role to explain the differences in gender ,but this is not proven yet[22].It was documented that males are more prone to become seriously fatal by COVID-19 disease than females. Thus ,chronic periodontitis could show the risk of COVID -19 illness, considering its association with gender and possible immunological status.

Diabetes Mellitus :
Diabetes Mellitus (DM) is a chronic disease that leads to increased abnormal level of glucose in blood (hyperglycemia).Around 10% of cases are of type- 1 DM[23] , where the host immune system attacks the cells that produce insulin and destroy them. The remaining 90% of cases are type-2 DM, where either the body

does not produce the enough of insulin or the cells at absorption level of glucose showed lower response to insulin (insulin resistance).There is significant bidirectional relationship between chronic periodontitis and diabetes mellitus.[24]In fact ,aggressive periodontitis is recognized as the sixth complication of diabetes according to Loe who concluded that both type 1 and type 2 diabetes are predictor of periodontal disease. The proposed mechanisms to understand this bidirectional relationship include alteration in vascular cellular and host repair processes.

Various studies supports an association between severe COVID-19 illness and diabetes mellitus, This is supported by chest x-ray and computed tomography (CT) such as ground glass opacities are typically found in chest and other clinical parameters that state alterations in diabetic patients. Many studies showed that severe COVID-19 diseased patients may have affected expression of the angiotensin -converting enzyme 2 (ACE 2) in the lungs. This ACE 2 receptors are present in large numbers in diabetic patients than in non diabetic patients due to treatment with ACE inhibitors and angiotensin 2 type 1 receptors blockers (ARBs)[25].In both chronic periodontitis and severe COVID-19 diseased patients the response of immune system is compromised by various external, internal and host factors.[26]As diabetes is a strong predictor of periodontal disease and severe COVID-19 disease ,so diabetes could be useful to identify risk groups of COVID-19 diseased patients and leads to increased CFR among these diabetic patients.

Atherosclerotic Cardiovascular Diseases And Hypertension : Atherosclerosis is the thickening of the lumen of the artery wall due to the accumulation of calcium and fatty triglyceride materials that form plaques which made the artery wall more stiff and hard. Atherosclerosis can lead to angina ,myocardial infarction, strokes or aneurysm depending on location and complications. Together, cardiovascular diseases are the number one cause of death globally.[27] An estimated 17.9 million people died from CVDs every year, representing 31% of all global deaths.[28] Of these deaths,80% are due to coronary heart disease (eg heart attack) and cerebrospinal diseases (eg strokes) and mostly affect low and middle income countries. Bacteria, central to the initiation and progression of periodontitis, may provide a direct or indirect mechanistic link to the development of atherosclerotic disease. [29]

Hypertension : A condition in which the force of the blood against the artery walls is too high.Usually hypertension is defined as blood pressure above 140/90 mm of hg and is considered severe if the blood pressure is above 180/120 mm of hg. Hypertension is a health disorder that affects most of the population worldwide. High B.P.is considered as a main risk factor for CVD. Various epidemiological studies showed a strong association between hypertension, cardiovascular disease (CVD) and chronic periodontitis disease.[30]Moderate to severe periodontitis was associated with a 22% raised risk for hypertension while severe periodontitis was linked with 49% higher odds of hypertension. In periodontitis patients the arterial blood pressure was higher than without periodontitis according to NCBI.

In Chronic periodontitis. the accumulation of various bacterial species in the subgingival biofilm and bacterias in plaque and calculus of deep pockets initiates the chronic inflammatory response by inducing the production of cytokines (IL-1,IL—6,IL-8,PGE-2 and TNF-alpha) that regulate and increase the levels of C-reactive protein (CRP). Detection of high concentration of CRP in gingival crevicular fluid (GCF) as a biomarker of CVD , hypertension and also the increased level of CRP in chronic periodontitis showed a evidenced based link between these diseases.[31]

Hypertension is one of the main comorbidities in COVID-19 infection. Hypertensive patients treated with Angiotensin 2 type- 1 receptor inhibitors (ARBs) drugs increases the huge expression of ACE 2 receptors and FURIN mRNA in oral mucosal epithelial cells. Therefore, the expression of ACE 2 in hypertension , CVD and chronic periodontitis may represent the major risk factor for severe COVID-19 disease and also increases the CFR among these COVID-19 patients.[32]

Obesity :

In 2016 more than 1.9 billion adults , 18 years and older , were overweight . Of these over 650 million were obese. After smoking. obesity is the second highest risk factor to cause chronic periodontitis disease .Various studies showed the relationship between obesity and chronic periodontitis since 1977 by Perslein and Bissada. Obesity can alter the composition of periodontal microflora and related with increased periodontal pathogenesis. The main complication of obesity is a continuous systemic inflammatory state. The adipose tissue in obese patients secretes low levels of proinflamatory cytokines (IL-6,IL-8,PGE2,TNF - α) , adipokines like leptine and adiponectine. These cytokines increases the host inflammatory response and may lead to the development and progression of chronic periodontitis disease. Obesity and their systemic complications increases the risk to develop severe COVID-19 illness. The expiratory reserve volume , functional capacity of lungs and respiratory system compliance all are decreased in obese patients. Additionally, altered host inflammatory response reported in obese patients could contribute to aggravate the response of the patients to develop more fatal

COVID -19 disease.[33] The CFR among the obesity and chronic periodontitis patients for COVID-19 disease increased worldwide.

Pregnancy :

During pregnancy mother faced various psychological and physiological changes which leads to the suppression of the mother's immune system.Various studies showed that there is a significant relationship between chronic periodontitis and poor pregnancy outcomes due to an altered inflammatory host response triggered by increased progesterone levels which initiates gingival response causing dysbiosis[34].Studies showed that the bacterias present in plaque results in the activation of cell mediated immune system and subsequent production of pro-inflamatory cytokines like IL-1,IL-6,PGE-2,TNF- α which have been implicated in the mechanism of labour.[35]As the outbreak of SARS-CoV 2 virus occurred worldwide, some cases of COVID-19 were also noticed in pregnant females. The levels of progesterone and esterogen increases many times in pregnancy which leads to the immunosuppression and this predispose the pregnant female to respiratory infectious diseases, less than 10% developed severe COVID-19 disease.[36]Combined infection of SARS-CoV 2 virus in pregnant female with chronic periodontitis could complicates the pregnancy outcomes like preeclampsia , premature low birth weight baby, even death.

Chronic Respiratory Diseases :

Previous studies showed that there is a association between chronic respiratory diseases (COPD ,bronchiectasis) and chronic periodontitis . With poor oral hygiene the chronic respiratory diseases increases by five fold. A good evidence found that improved oral hygiene and regular oral health care by the professionals decrease the rate of progression or stops the occurrence of chronic respiratory diseases among the high risk elderly patients. According to Scannapieco et al with increasing clinical attachment loss in chronic periodontitis patients leads to decreased lung functions. In chronic periodontitis patients with poor oral hygiene the incidence of pulmonary infection ,especially nosocomial pneumonia episodes in high risk patients[37].

Chronic Obstructive Pulmonary Disease (COPD) :

COPD is a chronic inflammatory disease of lungs caused by the exposure of noxious substances or gases. Smoking is the main risk factor of COPD in developed countries. Various studies showed the relationship between COPD and chronic periodontitis, however, this association could be blasted by various factors like age and smoking and this leads to increased mortality rate in older patients. In COPD patients there is a increased risk of aggravation of COVID -19 fatality rate. The pre-existing COPD patient have a four- fold increased risk to develop severe COVID-19 illness .COPD patients present increased expression of ACE-2 receptors on type 2 alveolar cells of lungs.[38]Thus the association of chronic periodontitis with COPD could be helpful to identify the CFR among COVID -19 patients.

Smoking :

Smoking is a major risk factor to develop chronic periodontitis and it affects the progression , severity of disease and response to treatment in periodontal therapy. Smoking promotes microbial imbalance in periodontal tissues and promotes the growth of various periodontal pathogens and their virulence factors which causes the destruction of the periodontal tissues and impair the immune response of the host. On the other side smoking is also a main risk factor of COVID-19 disease progression and aggravates the COVID -19 symptoms 1.4 times. It was suggested that smoking cessation could decrease the risk of developing severe COVID-19 fatality rate.[39]

Asthma :

Asthma is a chronic inflammatory disease of airways. Various studies showed the positive relationship between asthma and chronic periodontitis. It was proposed that asthma could be the risk factor for increasing the CFR among COVID -19 patients. It was noticed that in asthma patients ,there was decreased expression of ACE-2 receptors at cellular level used by SARS-CoV-2 for entry in to the host. However, in asthma patients with diabetes presented increased expression of ACE-2 and Trans Membrane Protease Serine2 (TMPRSS2) for SARS-CoV-2 entry to the host cells.[40]So the chronic periodontitis patients along with these asthma and DM were most susceptible for SARS-CoV-2 infection and increased CFR

CANCER:

Cancer is a malignant disease in which there is a unlimited growth of the cells, not under control and destroy the body tissues. This cause changes in the genome of the normal cells. These mutations in the cells occur due to continuous exposure to chemical ,physical and environmental factors. Previous studies showed that chronic periodontitis is an independent high risk factor for head and neck cancers ,especially in oral cavity cancer s followed by oropharynx and larynx.[41].Michaud et al proven a significant association between history of chronic periodontitis and risk of developing lung, kidney, pancreas and hematological cancers.[42]

There was no specific evidence for proving the mechanism of interaction between cancer and chronic periodontitis. Several studies showed that how microbial imbalance induces inflammation by

regulating the host inflammatory cascades by increasing the recruitment of cytokines and chemokines ,this leads to the destruction of periodontal epithelium and spread of periodontal pathogens in to systemic circulation, which causes systemic immune dysregulation and increased the risk of developing cancer.

Patients with cancer ,especially lung cancer are more susceptible to COVID -19 fatality, because there immune response was suppressed by chemotherapy and radiotherapy treatment given and nutritional deterioration which in turn induces dysbiosis, destruction of host cells and increased possibility of developing respiratory infections. Thus identifying cancer patients with chronic periodontitis could represent a group at risk for severe COVID-19 fatality.[43]

Liver Diseases :

Various studies proved that there was a relationship between chronic periodontitis and liver diseases. Imbalance in microflora of the periodontal tissues of the oral cavity leads to the initiation of inflammation due to the activation various cytokines (IL-IB,IL-6,IL-10, IL-12,TNF-alpha etc.which ultimately leads to the progression of liver diseases like liver cirrhosis, hepato cellular carcinoma and non alcoholic fatty liver disease. Lipopolysaccharide released from P.gingivalis also initiates inflammations in liver.[44] However , studies showed that preexisting liver diseases patients are more vulnerable for COVID-19 fatality because SARS-CoV-2 virus attaches to hepatocytes and chlangiocytes using ACE-2 receptors [45].Thus the patients with chronic periodontitis and underlying liver diseases could increase the Case Fatality Rate (CFR) among COVID-19 patients.

Results of the hypothesis :

There is enough evidence to support that chronic periodontitis acts as a major risk factors for severe COVID-19 fatality. Many studies proved that chronic periodontitis has been widely associated with various systemic diseases like diabetes, cardiovascular diseases, chronic respiratory diseases ,chronic kidney diseases, obesity etc. So the systemic health could be decided on the basis of periodontal status of the individuals. Therefore chronic periodontitis along with these underlying systemic diseases and other environmental factors are the common risk factors in COVID-19 diseased patients. These comorbidities and additional factors increases the Case Fatality Rate (CFR) among COVID-19 patients. Since Periodontal health status of COVID-19 patient was not detected till now, so it is bit difficult to find out the relationship between chronic periodontitis and COVID-19 fatality.

Perhaps dysbiosis means alteration in oral microflora in subgingival periodontal tissues leads to increased number of periodontal pathogens and their toxins leads to the activation of inflammatory cascades and immune response of the host .Combined infection of these pathogens of chronic periodontitis and SARS-CoV-2 virus with other established risk factors and underlying systemic diseases increases the inflammatory response of the host due to increased cytokine storm. This all increases the CFR among COVID-19 patients, Still more studies are awaited to find out the relationship between chronic periodontitis, systemic diseases and their effect on the CFR among COVID-19 patients.

REFERENCES :

1. Newman MG, Takei H, Carranza FA, editors .Carraza's Clinical Periodontology, 10th ed. Philadelphia: WBSaunders Company; 2007. p. 100-129.
2. Armitage GC. Periodontal diagnoses and classification of periodontal diseases.Periodontol 2000 [Internet]. 2004;34:9–21. Available from:http://www.ncbi.nlm.nih.gov/pubmed/14717852.
3. www.who.int/news-room/fact-sheets/detail/oral-health
4. https//www.fdi worlddental..org
5. Albandar JM. Global risk factors and risk indicators for periodontal diseases.Periodontol 2000 [Internet]. 2002;29:177–206. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12102708.
6. Taylor GW,Bidirectional interrelationships between diabetes and periodontal diseases:An epidemiological perspective.Ann Periodontal 2001;6;99-112.
7. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005;76;2016-15.
8. Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions. Nat Rev Microbiol [Internet]. 2018 Dec 9;16(12):745–759. Available from: http://www.nature.com/articles/s41579-018-0089-x
9. Transmission of Coronavirus Disease 2019 (COVID-19) | CDC [Internet]. [cited 2020 Mar 9]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/about/transmission.html
10. Gorbalenya, A.E., Baker, S.C., Baric, R.S. et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol (2020). https://doi.org/10.1038/s41564-020-0695-z
11. Wax RS, Christian MD. Practical recommendations for critical care and anesthesiology teams caring for novel coronavirus (2019-nCoV) patients. Can J Anaesth 2020 Feb 12. doi: 10.1007/s12630-020-01591-x.
12. Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. bioRxiv 2020 Feb 11;2020.02.07.937862.
13. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020 [Internet]. [cited 2020 Mar 11]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---3-march-2020
14. Li, F. Structure, function, and evolution of coronavirus spike proteins. Annu. Rev.Virol. 3, 237–261 (2016).
15. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International Journal of Oral Science. 2020 Feb 24;12(1):1-5.
16. Covid19.who.int/
17. Yang J,Zheng Y,et al. Prevalence of comorbidities and its effect in patients infected with SARS-CoV-2:a systematic review and

metaanalysis Int J Infect Dis Int.2020 May,94:915.Available from :https://linkinghub.elsevier.com/retrieve/pii/S1201971220301363
18. Zunyou Wu and Jennifer M.McGoogan. Characteristics of an important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China.JAMA.February24,2020.
19. The American Diabetes Association.COVID-19 (Coronavirus) Int.2020.Available from :https://www.diabetes.org/diabetes/treatment-care/planning-sick-days/coronavirus.
20. Pihlstrom B. Periodontal risk assessment, diagnosis and treatment planning. J Periodontol 2001;25:37-58.
21. Applegate WB, Ouslander JG. COVID-19 Presents High Risk to Older Persons. J Am Geriatr Soc [Internet]. 2020 Apr;68(4):681–681. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.16426
22. Haytac MC, Ozcelik O, Mariotti A. Periodontal disease in men. Periodontol 200 [Internet]. Feb;61(1):252–65. Available from http://doi.wiley.com/10.1111/j.1600-0757.2011.00410.x.
23. Whiting D R, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; **94**: 311-321.
24. Taylor G W. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. Ann Periodontol 2001; **6**: 99-112.
25. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Metab [Internet]. 2020 May 1;318(5):E736–41. Available from: https://journals.physiology.org/doi/10.1152/ajpendo.00124.2020
26. Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions. Nat Rev Microbiol [Internet]. 2018 Dec 9;16(12):745–759. Available from: http://www.nature.com/articles/s41579-018-0089-x
27. World Health Organisation., World Heart Federation., World Stroke Organisation. Global atlas on cardiovascular disease prevention and control. Mendis S, Puska P, Norrving B, editors. Geneva: World Health Organisation in collaboration with the World Heart Federation and the World Stroke Organisation; 2011.
28. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; **385**: 117-171.
29. Tonetti M S, Van Dyke T E, Working group 1 of the joint EFP/AAP workshop. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol 2013; **40**: S24-29.
30. Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation [Internet]. 2012 May 22;125(20):2520–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22514251
31. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on Creactive protein in relation to periodontitis. J Clin Periodontol [Internet]. 2008 Apr;35(4):277–90. Available from: http://www.ncbi.nlm.nih.gov/ pubmed/18294231
32. 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 [Internet].2020;12(1):8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32094336.
33. Ryan PM, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation and Cytokine Amplification in COVID-19. Obesity [Internet]. 2020 Apr 21; oby.22843. Available from: https:// onlinelibrary.wiley.com/ doi/abs/10.1002/oby.22843
34. Gibbs RS. The relationship between infections and adverse pregnancy outcomes: An overview. Ann Periodontol 2001;6:153-163.
35. Gil L, Mínguez I, Caffesse R, Llambés F. Periodontal Disease in Pregnancy: The Influence of General Factors and Inflammatory Mediators. Oral Health Prev Dent [Internet]. 17(1):69–73. Available from:http://www.ncbi.nlm.nih.gov/pubmed/30793124.
36. Liu H, Wang L-L, Zhao S-J, Kwak-Kim J, Mor G, Liao A-H. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol [Internet].2020 Jun;139:103122. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165037820300437
37. Scannapieco FA. Potential associations between chronic respiratory disease and periodontal disease: Analysis of National Health and Nutrition Examination Survey III. J Periodontol 2000;71:1528-1534.
38. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of Covid-19: A systemic review and meta-analysis. J Med Virol [Internet]. 2020 Apr 15; Available from: http://doi.wiley.com/10.1002/jmv.25889
39. Vardavas C, Nikitara K. COVID-19 and smoking: A systematic review of the evidence.Tob Induc Dis [Internet]. 2020 Mar 20;18(March). Available from: http://www.journalssystem.com/tid/COVID-19-and-smoking-A-systematic-review-ofthe- evidence,119324,0,2.html
40. Jackson DJ, Busse WW, Bacharier LB, Kattan M, O'Connor GT, Wood RA, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. J Allergy Clin Immunol [Internet]. 2020 Apr; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674920305510.
41. Tezal M, Grossi SG, Genco RJ. Is periodontitis associated with oral neoplasms? J Periodontol 2006;77:1465-1482.
42. Meyer MS, Joshipura K, Giovannuci E, Michandi DS. Periodontal disease and cancer. Cancer causes control 2008;19:895-907.
43. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol [Internet]. 2020 Mar; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0923753420363833
44. Hirschfeld M, Weis JJ, Toshchakov V, Salkowski CA, Cody MJ, Ward DC, et al. Signaling by Toll-Like Receptor 2 and 4 Agonists Results in Differential Gene Expression in Murine Macrophages. Moore RN, editor. Infect Immun [Internet]. 2001 Mar 1;69(3):1477– 1482. Available from: https://iai.asm.org/content/69/3/1477
45. Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int [Internet]. 2020 Apr 6; Available from: http://doi.wiley.com/10.1111/liv.14470