Potential Link between COVID-19 and Periodontitis: Cytokine Storm, Immunosuppression, and Dysbiosis

Gisele Maria Campos Fabri

Dental School of Universidade Federal de Juiz de Fora, Brazil

Abstract

Aim: Investigate the theoretical scientific evidence about biological mechanisms between periodontitis and COVID-19.

Results: As well as in periodontal disease, in COVID-19 the host immune response appears central to delineate the course of the disease. However, the severity and outcome of the COVID-19 might be associated with the excessive production of proinflammatory cytokines "cytokine storm" leading to an acute respiratory distress syndrome. In this sense, it is plausible to reflect on the possibility of a summation effect generating a hyper inflammatory phenotype that could worsen the prognosis. The periodontitis are able to cause adverse systemic inflammation and bacteremia that could impact in severity of systemic disease. Thus, is plausive to study the progression of COVID-19 in periodontal patients and, too, the periodontal alterations by immune dysregulation in COVID-19 patients.

Conclusion: Despite of lack of clinical studies about interrelationship associating PD and COVID-19, there is evidence suggesting possible biological pathways evidencing two-way relationship among periodontal disease and COVID-19. The provided rationale could be used to design an observational study. Thus, the phenomenon of immune dysregulation, inflammaging and dysbiose needs to be more fully understood in this era of pandemic.

Key Words: Coronavirus, COVID-19, Periodontal disese, Inflammation, Cytokines, Dysbiosis

Abbreviations: ACE2: Angiotensin Converting Enzyme II; AD: Alzheimer's Disease; Anti-S-IgG: Antibodies Against Spike Protein; ARDS: Acute Respiratory Distress Syndrome; COVID-19: Coronavirus Disease; CRP: C Reactive Protein; CSS: Cytokine Storm Syndrome; IL: Interleukin; INF- Gamma: Interferon Gamma; PD: Periodontal Disease; RANKL: FactorκB–Ligand; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2 of the Genus Betacoronavirus; sHLH: Secondaryunder-Recognised Haemophagocytic Lymphohistiocytosis; TNF-α: Tumor Necrosis Factor-Alpha

Introduction

Periodontitis is a prevalent chronic inflammatory disease with local and systemic consequences. There is an increase of systemic circulating cytokines and chemokines that are similar with then released in Coronavirus disease (COVID-19) such as C Reactive Protein (CRP), acute phase proteins, TNF-α (Tumor necrosis Factor- Alpha), IL (Interleukin)-1β, IL-2 and IL-6 and Interferon gamma (INF-gamma). It is indicative to reflect about chance of periodontitis contribute to hyperinflammation.

Therefore, the initiation and progression of periodontal disease occurs through a dysbiosis of oral microbiota which interacts with the host's immune defenses, leading to inflammation and tissue damage. Thus, it is suggestive to consider about the probability of preexisting periodontal disease to affect the severity of COVID 19 rather than viral pathogenesis alone. Experimental studies demonstrated that pre-exposure of airway epithelial cells to bacteria aggravates the release of cytokines in response to subsequent viral infection and, also, promote biofilm growth on airway epithelial cells.

Despite of lack of studies about interrelationship between Periodontal Disease (PD) and COVID-19, there is potential biological plausibility. Our team has been studied different aspects involving PD and systemic condition, with interesting results. It is crucial that the health care professionals be aware about this possibility and to assessment oral health of patients, since, periodontal disease is treatable condition. Besides, it is mandatory to stimulate the oral care procedures and oral hygiene to reduce the risk of local and systemic complications during the pandemic.

Cytokine Storm Syndromes (CSS) and Immunosuppression: Potential

Speculative link between COVID-19 and periodontitis

Cytokine Storm Syndrome (CSS) is a systemic inflammatory reaction that can be triggered by a multiplicity of factors such as some medications and infections [1]. This is a proposed path mechanism of severe viral infections such as corona virus that cause Coronavirus disease (COVID-19), characterizing a pandemic [2]. On the order hand, chronic periodontitis, one of the most prevalent chronic inflammatory diseases of human is characterized by cytokine hyper-reactivity, with influence on systemic inflammatory-immune responses [3].

The contemporary pathogenesis of periodontitis highlights the complex interfaces among dental biofilm, the acquired environmental stressors and genetic elements of host [4]. Genomic, proteomic, and metabolomic aspects are determinant to developing of periodontal diseases, since that the individual reaction, comprising lipid and cytokines mediators, released by the host, as well as modifications in periodontal structures like bone and connective tissue, can be visibly categorized by a specific gene arrangement, metabolite and protein expression [5].

Therefore, it is important to note that chronic periodontal disease is a persistent intense inflammatory infiltrate in the connective tissue with activation of T and B cells through cytokine discharge and determine the progression of the disease. There is a dysregulation of T cells in the periodontitis with activation of subtypes Th1, Th2, and Th17 cells with production of a variety of pro-inflammatory cytokines, such as IL-1β, IL-17E (IL-25) and IL-17, that trigger other immune cells such as neutrophils, dendritic cells and B cells [6]. Then, T cells and B cells stimulated can induce the release of the receptor activator of nuclear factorκB-Ligand (RANKL), which prompt osteoclasts and cause alveolar bone resorption, resulting in tooth loss [6]. Moreover, the activation of B cells by T cells can result in clonal activation of B cells, with antibodies production against bacterial components; though, production of auto antibodies to fibronectin, collagen, and

Corresponding author: Gisele Maria Campos Fabri, Dental School of Universidade Federal de Juiz de Fora, Brazil, E-mail: gisele.fabri@ufjf.edu.br

laminin with gingival tissue damage. Also, B cells stimulate secretion of IL-8 and IL-1β and could contribute to chronic systemic inflammation [6,7]. Then, it is important to note that this immune response is associated with intense cytokine discharge, chronically. Our teams have found that chronic periodontal disease is more frequent in Alzheimer Disease (AD) patients [8], may hamper Rheumatoid arthritis of anti-TNF therapy response [9], impact glycosylated hemoglobin levels in diabetes patients [10] and that there is a possible influence of periodontal disease, as a comorbidity, in refractory craniofacial pain patients and in their pain levels [11]. Furthermore, our previous study showed that there was an association between IL-6 and tumor necrosis factor-α (TNF-α) in patients with AD and periodontitis [12].

In this sense cytokines are produced in acute phase of periodontitis by fibroblasts, epithelial cells and by phagocytes (neutrophils and macrophages). And, in established and advanced lesions of periodontal disease the cytokines are produced by immune cells (lymphocytes) [13]. The first stage of inflammatory response, with cytokine secretion, against periodontal bacteria occurs by activation of pattern recognition and its downstream signaling. The Cytokines associated by this answer is interleukin-1 (IL-1), the IL-6 and Tumor Necrosis Factor (TNF). These cytokines are pro-inflammatory cytokines and leads to activation of the signaling pathways and the differentiation of some cells that will secret additional cytokines, which might act as a direct effector or positive feedback which activates and recruits specific immune cell subgroups and triggers tissue damage [14]. Furthermore, despite these local effects there is an increase of systemic circulating cytokines and chemokines. In the presence of periodontitis there are an increased systemic levels of C Reactive Protein (CRP), acute phase proteins, plasma antibody levels, coagulation factor, total white blood cell count, neutrophils, and cytokines such as TNF-α (Tumor Necrosis Factor- Alpha), IL (Interleukin)-1β, IL-2 and IL-6 and INF-gamma (Interferon gamma) [15]. Importantly, it has been proposed that the prolonged exposure of the periodontium to bacterial attack is associated to effects of aging on these structures, consistent with the alterations associated with immunosenescence and expression of inflammaging in periodontal disease.

On the order hand, have been proposed a crucial role of cytokine storm in the pathogenesis of severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus (SARS-CoV-2) human infection. The virus can attack the targeting organs that express Angiotensin-Converting Enzyme II (ACE2), such as the lungs, heart, renal, gastrointestinal tract after access lungs and peripheral blood [16,17]. During the infection process, T cells, B cells were decreased, while inflammatory cytokines persistent to increase [18]. Thus, the COVID-19 trigger a respiratory failure from Acute Respiratory Distress Syndrome (ARDS) and, secondary under-recognised Haemophagocytic Lymphohistiocytosis (sHLH) with a hyper inflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia with multi organ failure. The sHLH is related with COVID-19 disease severity, described by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α [2]. Furthermore, IL-6, increased in patients with COVID-19, can suppress normal T cell activation, and could justify the lymphopenia. And, is critical that ICU patients had lower CD4+ and CD8+ T cell counts, and high concentrations of TNF-α and IL-6 [19].

These immune dysregulation is not completely understood. One proposed hypothesis is that there is an important relation to cell pyroptosis (cell apoptosis with intense discharge of inflammatory cytokines and chemokines) [20], and too, antibodies against spike protein (anti-S-IgG) that induce accumulation of monocyte/macrophage in the lungs [21]. Study of Zhou et al. showed that the Angiotensin-Converting Enzyme II (ACE2) is probable the cell receptor of 2019-nCoV. Have been identified high ACE2 expression in alveolar cells of lung, epithelial cells of esophagus, myocardial cells, kidney cells between others [22]. And, those organs should be considered as likely high risk for COVID-19 [22]. Regarding this finding, a recent study revealed that the oral mucosa could express the ACE2 and was higher in tongue than other oral sites. They also demonstrated that oral epithelial cells are ACE2-positive, indicating that oral cavity might provide possible routes of entry for the coronavirus [23]. Interestingly, have been demonstrated that the ACE2 is expressed in lymphocytes within oral mucosa, like found in lungs, and SARS-cov-2 attacks the lymphocytes, consecutively reduce the immune defense [23].

The finds about inflammatory pathways on COVD-19 and DP are similar. There is overexpression of the cytokines such as TNF-α (Tumor Necrosis Factor-Alpha), IL (Interleukin)-1β, IL-2 and IL-6 and INF-gamma (Interferon gamma), same increased systemic levels of C Reactive Protein (CRP), acute phase proteins, coagulation factor and aspects related to inflammaging. Accordingly, is plausible to been hypothesized that alterations in the function of immune cells in periodontal disease could contribute to immune dysregulation and higher fragility of periodontal sick to SARS-cov-2?

Therefore, is relevant to consider that systemic effect of periodontitis followed by SARS-CoV-2 infection could lead to an aggravated inflammatory response? And the opposite: is possible that immune dysfunction observed in COVID-19, with lymphopenia, could modify the periodontal condition? These speculative pathways are detailed in *(Figure 1).*

Dysbiosis Pathway in Periodontitis and COVID-19: Possible Evidences

The oral microbiota is very diverse and does not exist anywhere else on the body. In the Human Microbioma Project, more than 1,200 different types of microbes were identified in the human mouth [23]. In health conditions, the indigenous oral flora consists, mainly, of streptococcus of the viridans group, in the presence of PD the prevalent bacteria comprise a group of gram-negative anaerobic microorganisms; among the most important, we find the so-called “red complex” pathogens, especially *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* [24,25]. These bacteria are organized into a complex community: dental biofilm. Biofilm formation is a survival strategy for bacteria, viruses, and fungi

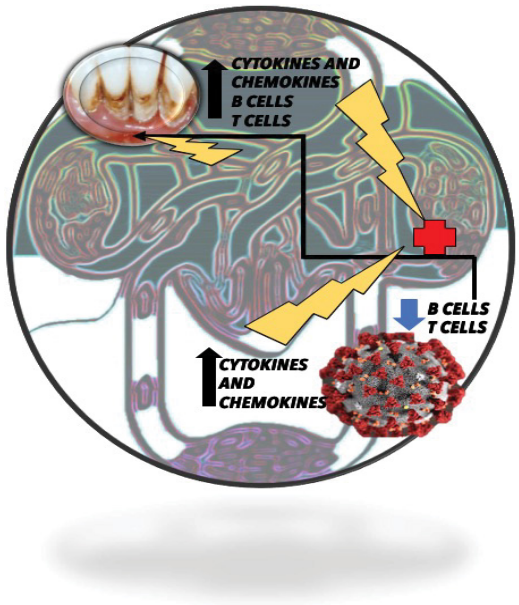

Figure 1. *Periodontal disease leads to persistent production of cytokines and chemokines and could result in systemic inflammation. These process lead to tissue damage and can hit pulmonary inflammation. The systemic effect of periodontitis followed by SARS-CoV-2 infection could lead to an aggravated inflammatory response. The opposite may also factual in that immune dysfunction observed in COVID-19, with lymphopenia, could worsen the periodontal condition.*

reside and interact, especially in the hostile environment. Under the protection of the biofilm, the microbial cells of the biofilm become tolerant and resistant to antibiotics and immune responses, which increase the difficulties for the clinical treatment of biofilm infections [26].

To maintain biofilm homeostasis the metabolic interactions like metabolic syntropy, mutualistic cross-feeding and cross-respiration occurs. These interfaces include mutual metabolite interactions, detoxification of oxidative compounds and increasing of ATP [26].

Therefore, the initiation and progression of periodontal disease occurs through a dysbiosis of the commensal oral microbiota (dental biofilm or dental plaque), which interacts with the host's immune defenses, leading to inflammation and tissue damage. This pathophysiological situation persists through episodes of activity and quiescence, until the affected tooth is extracted or the microbial biofilm is removed therapeutically and the inflammation disappears [27].

Furthermore, this periodontal infection is, directly and indirectly, associated with several systemic diseases due a number of factors, including bacteremia and systemic release of local inflammatory mediators [28].

In this sense, is important to know if periodontal infection could affect the COVID -19 severity and too if COVID-19 can affect periodontal status, particularly in critical patients. There is a lack of studies about viruses as memberships of oral microbiome. A previous study investigated the arrangement of oral viral populations in a periodontally healthy subjects or periodontitis. They demonstrated that viruses present were, majority, bacteriophages. The viruses residing dental biofilm were distinct considering oral health status, while those present in saliva were not. They predicted that dental biofilm viruses in periodontitis seem to be significantly more tending to kill their bacterial hosts than those found in healthy mouths. Also, they hypothesized that viruses have crucial role as drivers of ecosystem diversity to the oral microbiome in disease and health states [29].

Besides, bacterial co-infection with upper respiratory tract viruses is reported [30]. Hence, it is significant to study about the probability of periodontal dysbiosis to affect the severity of COVID-19 rather than viral pathogenesis alone. Experimental studies showed that pre-exposure of airway epithelial cells to bacteria exacerbates the release of pro-inflammatory cytokines in response to subsequent viral infection and too promote biofilm growth on airway epithelial cells, suggesting a microbial interactions on pulmonary inflammation with pleiotropic effects [31,32]. If these data can be translated into the clinical setting, it might enable clinicians to identify patients at high risk for developing more severe viral infections on the basis of their bacteriological status [32].

Moreover, scientific literature related that there is relationship between periodontitis and respiratory diseases such as pneumonia. It was found that periodontitis is associated with respiratory diseases due to poor oral hygiene and low immunity state and oral procedures aimed at control oral infection and oral bacterial count have impact in reduced incidence of respiratory illness [33-35]. This reflects the importance of oral hygiene among patients with respiratory illness.

Another issue to consider is about the risk factors involving COVID-19 and Periodontal disease. Both condition share risk factors such as chronic tobacco smoke exposure and age.

Results and Discussion

As well as in periodontal disease, in COVID-19 the host immune response appears central to delineate the course of the disease. However, the severity and outcome of the COVID-19 might be associated with the excessive production of proinflammatory cytokines “cytokine storm” leading to an acute respiratory distress syndrome. In this sense, it is plausible to reflect on the possibility of a summation effect generating a hyperinflammatory phenotype that could worsen the prognosis. The periodontitis are able to cause adverse systemic inflammation and bacteremia that could impact in severity of systemic disease. Thus, is plausive to study the progression of COVID-19 in periodontal patients and, too, the periodontal alterations by immune dysregulation in COVID-19 patients.

Conclusion

Despite of lack of clinical studies about interrelationship associating PD and COVID-19, there is theoretical evidence suggesting a possible biological pathway evidencing two-way relationship among periodontal disease and COVID-19. The provided rationale could be used to design an observational study. Thus, the phenomenon of immune dysregulation, inflammaging and dysbiosis needs to be more fully understood in this era of pandemic.

It is imperative and urges the need for controlled clinical trials to support this association. However, the periodontitis are able to cause adverse systemic inflammation

and bacteremia that could impact in severity of systemic disease and, probably, the progression of COVID-19 and COVID-19 by immune dysregulation, possibly, could modify the periodontal condition. It is crucial that the health care professionals be aware to assessment oral health of the patients, since periodontal disease is, sometimes, neglected. Besides, it is mandatory to stimulate the oral care procedures and oral hygiene to reduce the risk of local and systemic complications during the pandemic, particularly in patients with higher risk to COVID-19. These additional cares will certainly not be vainly, but will impact the patient's clinical outcomes.

Declarations

Ethics approval and consent to participate
Not applicable
Consent for publication
Not applicable
Availability of data and material
Not applicable
Competing interests
Non-financial competing interests
Funding
No Funding

Authors' Contributions

Fabri GMC conceived of the presented idea, developed the theory and investigated the findings of this work. Further, analyzed and discussed the results and wrote the final manuscript.

Acknowledgment

I would like to offer my special thanks to Prof José Fabri Júnior, Prof José Tadeu Tesseroli de Siqueira, Prof Maria das Graças A M Chaves who inspired and supported me.

References

1. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, et al. Cytokine release syndrome. *Journal for Immuno Therapy of Cancer*. 2018; **6**: 56.

2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020; **395**: 1033-1034.

3. Ling MR, Chapple IL, Matthews JB. Peripheral blood neutrophil cytokine hyper-reactivity in chronic periodontitis. *Innate Immunity*. 2015; **21**: 714-725.

4. Marchesan JT, Girnary MS, Moss K, Monaghan ET, Egnatz GJ, et al. Role of inflammasomes in the pathogenesis of periodontal disease and therapeutics. *Periodontol 2000.* 2020; **82**: 93-114.

5. Kornman KS. Mapping the pathogenesis of periodontitis: A new look. *Journal of Periodontology.* 2008; **79**: 1560-1568.

6. Campbell L, Millhouse E, Malcolm J, Culshaw S. T cells, teeth and tissue destruction-what do T cells doin periodontal disease? *Molecular Oral Microbiology*. 2016, **31**: 445-456.

7. Figueredo CM, Lira-Junior R, Love RM. T and B Cells in periodontal disease: New functions in a Complex Scenario. *International Journal of Molecular Sciences*. 2019; **16**: 3949.

8. De Souza Rolim T, Fabri GM, Nitrini R, Anghiah R, Teixeira MJ, et al. Oral infections and orofacial pain in Alzheimer's disease: A case-control study. *Journal of Alzheimer's Disease*. 2014; **38**: 823-829.

9. Savioli C, Ribeiro AC, Fabri GM, Calich AL, Carvalho J, et al. Persistent periodontal disease hampers anti-tumor necrosis factor treatment response in rheumatoid arthritis. *Journal of Clinical Rheumatology*. 2012; **18**: 180-184.

10. Fabri GM, D'Aleva P, Lotemberg S. Periodontitis and metabolic control: A preliminary study. *International Journal of Odontostomatology*. 2014, **8**: 273-277.

11. Fabri GM, Siqueira SR, Simione C, Nasri C, Teixeira MJ, et al. Refractory craniofacial pain: Is there a role of periodontal disease as a comorbidity? *Arquivos de Neuro-Psiquiatria*. 2009; **67**: 474-479.

12. Cestari JA, Fabri GM, Kalil J, Nitrini R, Jacob-Filho W, et al. Oral infections and cytokine levels in patients with alzheimer's disease and mild cognitive impairment compared with controls. *Journal of Alzheimer's Disease*. 2016; **52**: 1479-1485.

13. Ara T, Kurata K, Hirai K, Uchihashi T, Uematsu T, et al. Human gingival fibroblasts are critical in sustaining inflammation in periodontal disease. *Journal of Periodontal Research.* 2009; **44**: 21-27.

14. Pan W, Wang Q, Chen Q. The cytokine network involved in the host immune response to periodontitis. *International Journal of Oral Science*. 2019; **11**: 30.

15. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, et al. Association between periodontal pathogens and systemic disease. *Biomedical Journal.* 2019; **42**: 27-35.

16. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nature Microbiology*. 2020; **5**: 562-569.

17. Wang D, Hu B, Hu C, Zhu F, Liu X, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020; **323**: 1061-1069.

18. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. *Emerging Microbes and Infections*. 2020; **9**: 727-732.

19. Yang M. Cell pyroptosis, a potential pathogenic mechanism of 2019-nCoV infection. *SSRN Electron Journal*. 2020.

20. Liu L, Wei Q, Lin Q, Fang J, Wang H, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight*. 2019; **4**: e123158.

21. Zou X, Chen K, Zou J, Han P, Hao J, et al. The single-cell RNA-seq data analysis on the receptor ACE2expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. *Frontiers of Medicine*. 2020; **14**: 185-192.

22. Xu H, Zhong L, Deng J, Peng J, Dan H, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*. 2020; **12**: 8.

23. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner ACR, et al. The human oral microbiome. *Journal of Bacteriology*. 2010; **192**: 5002-5017.

24. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent

RL Jr. Microbial complexes in subgingival plaque. *Journal of Clinical Periodontology*. 1998; **25**: 134-144.

25. Rautemaa R, Lauhio A, Cullinan MP, Seymour GJ. Oral infections and systemic disease-an emerging problem in medicine. *Clinical Microbiology and Infection*. 2007; **13**: 1041-1047.

26. Wu H, Moser C, Wang HZ, Høiby N, Song ZJ. Strategies for combating bacterial biofilm infections. *International Journal of Oral Science*. 2015; **7**: 1-7.

27. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nature Reviews Disease Primers*. 2017; **3**: 17038.

28. Hegde R, Awan KH. Effects of periodontal disease on systemic health. *Disease-a-Month*. 2019; **65**: 185-192.

29. Ly M, Abeles SR, Boehm TK, Robles-Sikisaka R, Naidu M, et al. Altered oral viral ecology in association with periodontal disease. *mBio*. 2014; **5**: e01133-14.

30. Fouchier R, Rimmelzwaan G, Kuiken T, Osterhaus A. Newer respiratory virus infections: Human metapneumovirus, avian influenza virus and human corona viruses. *Current Opinion in Infectious Diseases*. 2005; **18**: 141-146.

31. Kiedrowski MR, Gaston JR, Kocak BR, Coburn SL, Lee S, et al. *Staphylococcus aureus* biofilm growth on cystic fibrosis airway epithelial cells is enhanced during respiratory syncytial virus coinfection. *mSphere*. 2018; **3**: e00341-e00358.

32. Bellinghausen C, Gulraiz F, Heinzmann AC, Dentener MA, Savelkoul PH, et al. Exposure to common respiratory bacteria alters the airway epithelial response to subsequent viral infection. *Respiratory Research*. 2016; **17**: 68.

33. Muthu J, Muthanandam S, Mahendra J. Mouth the mirror of lungs: where does the connection lie? *Frontiers of Medicine*. 2016; **10**: 405-409.

34. Moghadam SA, Shirzaiy M, Risbaf S. The associations between periodontitis and respiratory disease. *Journal of Nepal Health Research Council*. 2017; **15**:1-6.

35. Hobbins S, Chapple IL, Sapey E, Stockley RA. Is periodontitis a comorbidity of COPD or can associations be explained by shared risk factors/behaviors? *International Journal of Chronic Obstructive Pulmonary Disease*. 2017; **12**: 1339-1349.