

Episode #31 – Periodontal Disease and COVID-19 February 26, 2021

Global prevalence of periodontal disease[1]
Periodontal diseases are prevalent both in developed and developing countries and affect approximately 20-50% of the global population. About 10% suffer from severe periodontal disease worldwide. Incidence and prevalence of periodontal disease have constantly increased during the past 3 decades, making it the 12th most prevalent pathology globally. [1] [2] [3]

Global prevalence of COVID-19
According to the World Health Organization, as of February 2021, there have been over 110,000,000 confirmed cases of COVID-19 and over 2,455,000 deaths. [4]

Association between periodontitis and severity of COVID-19 infection[2]
Marouf et al. (2021) conducted a case-control study to investigate the association of periodontitis with COVID-19 complications. The study, entitled 'Association between periodontitis and severity of COVID-19 infection: A case-control study', was published in the *Journal of Clinical Periodontology*. The investigators utilized the State of Qatar's national electronic health records to select adult patients diagnosed with COVID-19 between February and July 2020. Participants also had to have at least one dental appointment between March 2019 to March 2020 and dental radiographs to assess their periodontal conditions. Patients without dental radiographs in their records were excluded because the presence of periodontitis could not be objectively confirmed. The utilized electronic database holds both the medical and dental records for the country's publicly funded health and dental services.

A total of 568 participants (≥18 years old) were included in the analysis. Among these, 40 patients had experienced COVID-19 complications (i.e., death, intensive care unit [ICU] admissions, or assisted ventilation). The control group was comprised of 528 patients with COVID-19 that were discharged from hospital without major complications.

Periodontal conditions were assessed using posterior bitewing and panoramic radiographs to measure the percentage of bone loss from the most affected posterior teeth using criteria from the AAP classification of periodontal and peri-implant diseases. Periodontitis was defined as bone loss detected at two or more nonadjacent teeth, after

[1] Refer to Episode #5 – The global epidemic of periodontal disease for additional information on the incidence and prevalence of periodontal disease.
[2] Refer to Episode #13 – Oral health and COVID-19 for additional information on periodontal disease and COVID-19.

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

excluding factors such as cracked and fractured roots, caries, and impacted third molars.

Participants were then categorized as either:

- Periodontally healthy or initial periodontitis (Stages 0-1) with bone loss less than the coronal third of the root length (15%) in panoramic, or ≤2 mm in bitewing radiographs, or
- Periodontitis (Stages 2-4) with bone loss more than the coronal third of the root length (>15%) in panoramic, or >2 mm in bitewing radiographs.

Out of the 568 participants, 258 (45%) presented with periodontitis.

Demographic information was obtained (e.g., sex, age) as well as other relevant risk factors associated with COVID-19 complications, such as body mass index (BMI), smoking, asthma, other chronic respiratory diseases, cardiovascular disease (CVD), diabetes, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus), immunosuppressive conditions, cancer, and hypertension.

Blood parameters relevant to the course of the disease such as concentrations of D-dimer, C-reactive protein (CRP), HbA1c, vitamin D, white blood cells (WBCs), and lymphocytes were also collected from the electronic records. Both the initial parameters measured upon diagnosis as well as the parameters measured prior to discharge were collected. Associations between periodontitis and COVID-19 complications were analysed using logistic regression models adjusted for demographic, medical, and behaviour factors. [5]

Significance of various blood parameters

D-dimer is the principal breakdown fragment of fibrin and is used as a biomarker of fibrin formation and degradation. Numerous studies have shown that D-dimer is a valuable marker of activation of coagulation and fibrinolysis. Healthy individuals have low levels of circulating D-dimer, whereas elevated levels are found in conditions associated with thrombosis. D-dimer has been extensively investigated for the diagnosis, monitoring, and treatment of venous thromboembolism for which it is used routinely. D-dimer levels are also elevated in conditions of chronic inflammation, such as active malignancy, rheumatoid arthritis, sickle cell disease, and asthma. Elevated D-dimer has been frequently observed in patients at hospital admission with COVID-19 and was associated with higher incidence of disease severity, thrombotic events, acute kidney injury, and death. [6] [7]

CRP is a protein made by the liver. CRP levels in the blood increase when there is a condition causing inflammation in the body. A CRP test measures the amount of CRP in the blood to detect inflammation due to acute conditions or to monitor the severity of disease in chronic conditions. For example, higher levels of CRP may be a predictive marker in determining which patients with mild COVID-19 will progress to a severe case. [8] [9]

HbA1c (hemoglobin A1c) measurements reflect serum glucose levels over the preceding three months. HbA1c is glycated hemoglobin and its value is measured in

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

percentage of all hemoglobin. The range of results are categorized as normal, prediabetes, and diabetes. [10]

Vitamin D[3] deficiency has been strongly associated with various health outcomes, including all-cause mortality. Vitamin D plays a role in reducing inflammation, regulating adaptive (acquired) and innate immune responses, and helping to prevent overexpression of inflammatory cytokines. Accumulating evidence has shown that insufficient vitamin D levels may lead to dysregulation of immune responses, and thus contribute to autoimmune diseases. Vitamin D deficiency has also been linked to an increase in the risk of initiation and development of viral and bacterial infections. [11] [12] [13] [14]

Murai et al. (2021) conducted a multicentre, double-blind, randomized placebo-controlled trial in two sites in Sao Paulo, Brazil to investigate the effect of a single high dose of vitamin D_3 on hospital length of stay for patients with COVID-19. The study included 240 hospitalized patients with COVID-19 who were moderately to severely ill at the time of trial enrollment from June 2020 to August 2020. Patients were randomly assigned to receive a single oral dose of 200,000 IU of vitamin D_3 (n = 120) or a placebo (n = 120). The study found that a single high dose of vitamin D_3, compared with placebo, did not significantly reduce hospital length of stay. The authors concluded that the findings do not support the use of a high dose of vitamin D_3 for treatment of moderate to severe COVID-19. [15]

WBCs (leukocytes) are made in the bone marrow and found in the blood and lymph tissue and are part of the body's immune system. Types of WBCs include granulocytes (neutrophils, eosinophils, and basophils), monocytes, and lymphocytes (T cells and B cells). Measuring the number of WBCs in the blood is usually part of a complete blood count (CBC) and is used to screen for conditions such as infection, inflammation, allergies, and leukemia. [16]

Lymphocytes are a type of WBC responsible for immune responses. The two main types of lymphocytes are B lymphocytes and T lymphocytes. B lymphocytes make antibodies, and T lymphocytes help kill tumor cells and help control immune responses. A retrospective study of 52 patients with COVID-19 by Han et al. (2020) found that asymptomatic patients hosted viral loads comparable to those of symptomatic patients, but asymptomatic patients showed higher levels of lymphocytes, cleared the viral particles faster, and had lower risks of long-term complications. Further analyses suggested the interaction between the virus and the immune system likely played a role in that process. [17] [18]

Results of Marouf et al. study

Individuals with COVID-19 complications were older (mean age 53.5 participants vs 41.5 controls) and had more comorbidities than those without any complications.

[3] Refer to Episode #22 – Vitamin D's role in systemic health, oral health & COVID-19 for more information on vitamin D.

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

Further, 82% of all patients who had COVID-19 complications had periodontitis (33 out of 40) compared to only 43% of those without COVID-19 complications.

After adjusting for potential confounders (e.g., age, sex, BMI, smoking), periodontitis was associated with at least a 3 times increased risk of overall COVID-19 complications, death, ICU admission, and need for ventilation. For example, those with COVID-19 and who had periodontitis were 3.5 times more likely to be admitted to the ICU, 4.5 times more likely to need assisted ventilation, and almost 9 times more likely to die than those without periodontitis. Similarly, blood levels of WBCs, D-dimer, and CRP (blood markers indicating inflammation) were significantly higher in patients with COVID-19 and periodontitis.

Conclusions of Marouf et al. study

The authors concluded that periodontitis was significantly associated with a higher risk of complications from COVID-19, including ICU admission, need for assisted ventilation, and death, and with increased blood levels of biomarkers linked to worse COVID-19 disease outcomes such as D-dimer, WBCs and CRP, and lower concentrations of lymphocytes. [5]

Additional research

Takahashi et al. (2021) suggested that aspiration of periodontopathic bacteria owing to poor oral hygiene might aggravate COVID-19 by inducing the expression of angiotensin-converting enzyme 2 (ACE2), a receptor for SARS-CoV-2, and the production of inflammatory cytokines in the lower respiratory tract. Further the protease of periodontopathic bacteria may promote infectivity of SARS-CoV-2 by degrading the spike protein of SARS-CoV-2. During infection with SARS-CoV-2, it is necessary that the spike protein of SARS-CoV-2 is cleaved by proteases, such as TMPRSS2 and furin in order for adsorption and fusion with the host cells. Although ACE2, TMPRSS2, and furin are expressed in the oral cavity, spike protein may also be cleaved by the proteases produced by periodontopathic bacteria. The reduced chance of receiving professional oral care owing to long-term hospitalization of patients with COVID-19 may increase the aggravation of infection in the lower respiratory tract. Therefore, it can be hypothesized that the management of good oral hygiene can potentially prevent COVID-19 aggravation. [19]

Madapusi Balaji et al. (2020) also suggested in their research that periodontopathic bacteria might enhance SARS-CoV-2 virulence by cleaving the virus's spike proteins. [20]

Badran et al. (2020) hypothesized that periodontal pockets could be an anatomical niche for SARS-CoV-2 virus infection. Numerous studies have detected viruses in periodontal pockets (e.g., herpesviruses, Epstein-Barr virus, human cytomegalovirus) illustrating that periodontal pockets are compatible environments for viral infection and survival. Similarly, SARS-CoV-2 may find periodontal pockets a favourable environment for replication. Periodontal pockets would then act as a reservoir for continuous flow of the virus into the oral cavity via gingival crevicular fluid and mix with saliva. Further, the virus could potentially migrate systemically using the capillary periodontal complex and

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

subsequently infect distant organs and generate focal infections. The authors continue to collect gingival crevicular fluid and subgingival plaque from periodontal pockets of individuals infected with COVID-19 for their research to test their proposed hypothesis. They also suggested that periodontal therapy should be considered a parameter of care in the global clinical management of patients with COVID-19. [21]

Bao et al. (2020) in their review described the large number of COVID-19 cases coinfected with other viruses, fungi, and bacteria, some of which originate from the oral cavity. The authors suggested that risk factors such as poor oral hygiene, cough, increased inhalation under normal or abnormal conditions, and mechanical ventilation provide a pathway for oral microorganisms to enter the lower respiratory tract and thus cause respiratory disease. The authors recommended that oral hygiene in patients with COVID-19 be a concern as co-infection is critical to prognosis. [22]

Botros et al. 2020 proposed that improving oral health could decrease the severity of COVID-19 symptoms and reduce the associated morbidity. They rationalized that most patients with severe complications from COVID-19 have underlying conditions such as obesity, diabetes, and hypertension. Plus, periodontitis increases the risk of developing the same medical conditions. Furthermore, the oral cavity is a reservoir for respiratory pathogens, and people with periodontal disease are more likely to develop hospital-acquired pneumonia than healthy individuals. Therefore the authors concluded that improving oral health in individuals of any age, by reducing their risk of developing non-oral systemic diseases, may reduce the morbidity of COVID-19. However, they did acknowledge that more research is needed to demonstrate the association empirically. [23]

Sahni & Gupta (2020) explored the connection between COVID-19 and periodontal disease through their cytokine connection. For example, periodontitis has long been attributed to having its pathophysiology rooted in a cytokine response. Similarly, the COVID-19 infection has been reported to have adverse outcomes related to the establishment of a cytokine storm, many of the components of which are common with the cytokine expression profile of periodontitis. This common pathway of inflammatory response points towards a possible association between periodontitis and COVID-19 related adverse outcomes. Understanding this association underscores the importance of keeping periodontal disease under control and the value of maintaining meticulous oral hygiene in the COVID-19 era. It also points towards the possibility of the presence of periodontal disease as a predisposing factor towards COVID-19 related adverse outcomes. [24]

Larvin et al. (2020) conducted a study to quantify the impact of periodontal disease on hospital admission and mortality during the COVID-19 pandemic. Data from the UK Biobank cohort was used in this analysis. The study extracted UK Biobank participants who had taken a COVID-19 test between March and June 2020 (n = 13,253), of which 1,616 were COVID-19 positive (12%) and 11,637 were COVID-19 negative (88%). Self-reported oral health indicators of painful or bleeding gums and loose teeth were used as surrogates for periodontal disease, participants who did not report any of the aforementioned indicators were used as controls.

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

The authors concluded that their study demonstrated an increased risk of mortality following COVID-19 infection in people with periodontal disease. The findings suggested that while periodontal disease might not increase risk of COVID-19 infection directly, it may be associated with COVID-19 pathology and increase the risk of death. This indicates the importance of good oral hygiene and periodontal disease management. [25]

Siddharthan et al. (2020) conducted a literature review to assess the association between periodontal disease and COVID-19. The similarity seen in the inflammatory response pathways suggested that there is a potential relationship between COVID-19 and periodontitis. It was found that individuals with periodontal disease had a higher risk of developing COVID-19 associated adverse outcomes. The authors concluded that considering the relationship between periodontal disease and COVID-19, significant importance should be given to maintain good oral hygiene and periodontal health during the SARS-CoV-2 pandemic. [26]

Aquino-Martinez et al. (2021) conducted a review to elucidate the potential role of pre-existing periodontal disease on the severity of COVID-19 in older people. The authors highlighted how translocated *Porphyromonas gingivalis*, a prominent periodontal pathogen with highest prevalence in older adults, may facilitate SARS-CoV-2 replication in lung cells through different mechanisms. Further, they illustrated how the inoculation of oral pathogens into the respiratory tract during invasive mechanical ventilation may aggravate SARS-CoV-2-mediated lung inflammation and immune response.

The authors rationalized that the aspiration of oral fluids or food represents a plausible route for the translocation of oral pathogens into the lungs, especially in geriatric patients. Essentially, aspiration pneumonia is one of the most common long-term complications of poor oral hygiene in elderly people, and adequate oral health care can decrease the risk of dying from that condition. Considering that aspiration pneumonia is often caused by *P. gingivalis*, and that oral bacteria have been identified in bronchoalveolar lavage samples from patients with COVID-19, the authors proposed three interconnected mechanisms that might facilitate SARS-CoV-2 replication in lung cells as a consequence of pre-existing pulmonary infection by periodontal bacteria.

The three mechanisms were as follows:
1. *LPS-induced senescence and SARS-CoV-2 replication*
The dissemination of periodontal bacteria into lung tissues may cause lipopolysaccharide-induced senescence[4], which facilitates SARS-CoV-2 cell attachment, entry, and more efficient viral replication. Prolonged exposure to lipopolysaccharide (LPS)[5] causes accelerated senescence in different cell types, including pulmonary epithelial cells. Accumulation of senescent cells in lungs is a

[4] Senescence is a process by which a cell ages and permanently stops dividing. The cell remains active and does not die. Over time, large numbers of old (or senescent) cells can build up in tissues throughout the body. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/senescence
[5] LPS is the major component of the outer membrane of gram-negative bacteria (e.g., *P. gingivalis*). LPS is found to be an important pathogenic factor among many periodontopathic bacteria and plays a role in the disruption of the innate immune system. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4746253/

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

normal event during the process of aging. It has been demonstrated that cells that survive *P. gingivalis* infection display features of accelerated aging. Also, research has found that primary human bronchial epithelial cells that undergo replicative senescence were more susceptible to viral infection and enhanced replication than nonsenescent cells. Thus, periodontal bacteria that colonize lung tissues could aggravate age-related accumulation of senescent cells, which may facilitate more efficient viral replication and attachment.

2. *Periodontal bacteria and exacerbation of lung inflammation*

Periodontal bacteria may exacerbate lung inflammation caused by SARS-CoV-2 infection. For example, the SARS-CoV-2 spike protein can interact with lipid A, a component of LPS, and result in significant upregulation of the inflammatory reaction compared with the individual effect of LPS. Also, research recently proposed that the connection between periodontitis and COVID-19 could be through a common proinflammatory cytokine expression profile; that is, patients with severe symptoms of COVID-19 have increased serum IL-1β, IL-7, IL-10, IL-17, IL-8, TNF-α, and MCP-1 levels, among others. The secretion of many of these cytokines is increased in periodontal tissues of patients with periodontal disease compared to healthy controls. For instance, IL-17 seems to play an important role in exacerbating lung inflammation, and this proinflammatory cytokine can serve as a biomarker of COVID-19 severity. Notably, IL-17 plays an important role in periodontal disease pathogenesis, and it is secreted by senescent alveolar bone osteocytes. Thus, pre-existing gram-negative bacterial infection and the associated presence of LPS might exacerbate local lung inflammation as result of SARS-CoV-2 spike protein binding by enhancing NF-κB[6] activation.

3. *Impaired immune surveillance caused by periodontal bacteria*

Periodontal bacteria may impair immune surveillance and facilitate SARS-CoV-2 replication in lung cells. For example, during the early stages of invasion, *P. gingivalis* can delay the recruitment of neutrophils by inhibiting the expression of IL-8, a key chemokine that guides these immune cells into the site of infection. This absence of an IL-8 gradient severely affects local immune defense and promotes the overgrowth of these pathogens. This mechanism is called local chemokine paralysis. However, periodontal pathogens depend on inflammation for source nutrients. Subsequently, once pathogenic bacteria increase in number and form a biofilm, they proactively induce inflammation. Other periodontopathic bacteria such as *T. forsythia* and *A. actinomycetemcomitans* also have the ability to decrease immune recognition. Thus, the combination of impaired host immune surveillance caused by advancing age and the bacterial mechanisms of immune evasion may promote bacterial overgrowth and facilitate SARS-CoV-2 replication in the lungs.

[6] Nuclear factor kappa B (NF-κB) is protein transcription factor and is considered a regulator of innate immunity. The NF-κB signaling pathway links pathogenic signals and cellular danger signals thus organizing cellular resistance to invading pathogens.
https://www.frontiersin.org/articles/10.3389/fcell.2019.00154/full

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

Periodontal disease and ventilator-associated pneumonia (VAP)

Intubation and invasive ventilation are sometimes required to provide respiratory support for patients experiencing respiratory failure caused by COVID-19 infection. The inoculation of periodontal pathogens, bacteria from the dorsal surface of the tongue, and contaminated upper airway secretions have been directly implicated in the pathogenesis of VAP. A higher risk of oral bacteria inoculation exists when advanced periodontal disease is present in patients that require invasive mechanical ventilation. Thus, in older patients with neglected oral care, a greater number of oral bacteria can be attached to the endotracheal tube, translocated into the respiratory tract, and contribute to exacerbated SARS-CoV-2-mediated inflammation.

The authors concluded that considering that poor oral hygiene and the aspiration of periodontal bacteria could aggravate COVID-19 lung infection, appropriate oral care is crucial to prevent the exacerbation of lung inflammation. [27]

Take home messages

Complications of COVID-19 are caused by a severe inflammatory reaction that share some common signals with periodontitis. Research has demonstrated that periodontitis can affect systemic health and has been independently associated with increased risk of most chronic non-communicable diseases such as CVDs, diabetes, hypertension, chronic renal disease, pneumonia, and cancer. Research has demonstrated that periodontitis could be a risk factor for COVID-19 complications and highlights the importance of periodontal health in the prevention and perhaps even the management of COVID-19 complications. Future research is necessary to examine the influence of periodontitis and periodontal treatments on COVID-19 infection to better understand the relationships.

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

References

[1] M. Nazir, "Prevalence of periodontal disease, its association with systemic diseases and prevention," *International Journal of Health Sciences,* vol. 11, no. 2, pp. 72-80, April-June 2017.

[2] World Health Organization, "Oral health," 25 March 2020. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/oral-health. [Accessed 20 February 2021].

[3] R. Nocini, G. Lippi and C. Mattiuzzi, "Periodontal disease: The portrait of an epidemic," *Journal of Public Health and Emergency,* vol. 4, no. 10, pp. 1-6, June 2020.

[4] World Health Organization, "WHO Coronavirus Disease (COVID-19) Dashboard," 21 February 2021. [Online]. Available: https://covid19.who.int/. [Accessed 21 February 2021].

[5] N. Marouf, W. Cai, K. Said, H. Daas, H. Diab, V. Chinta, A. Hssain, B. Nicolau, M. Sanz and F. Tamimi, "Association between periodontitis and severity of COVID-19 infection: A case–control study," *Journal of Clinical Periodontology,* pp. 1-9, 1 February 2021.

[6] J. Berger, D. Kunichoff, S. Adhikari, T. Ahuja, N. Amoroso, Y. Aphinyanaphongs, M. Cao, R. Goldenberg, A. Hindenburg, J. Horowitz, S. Parnia, C. Petrilli, H. Reynolds, E. Simon, J. Slater, S. Yaghi, E. Yuriditsky, J. Hochman and L. Horwitz, "Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19," *Arteriosclerosis, Thrombosis, and Vascular Biology,* vol. 40, no. 10, pp. 2539-2547, 25 August 2020.

[7] Y. Yao, J. Cao, Q. Wang, Q. Shi, L. Liu, Z. Luo, X. Chen, S. Chen, K. Yu, Z. Huang and B. Hu, "D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study," *Journal of Intensive Care,* vol. 8, Article 49, pp. 1-11, 10 July 2020.

[8] Lab Tests ONLINE, "C-Reactive Protein (CRP)," 12 April 2020. [Online]. Available: https://labtestsonline.org/tests/c-reactive-protein-crp. [Accessed 20 February 2021].

[9] G. Wang, C. Wu, Q. Zhang, F. Wu, B. Yu, J. Lv, Y. Li, T. Li, S. Zhang, C. Wu, G. Wu and Y. Zhong, "C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation," *Open Forum Infectious Diseases,* vol. 7, no. 5, 1-5 May 2020.

[10] E. Brutsaert, "Diabetes Mellitus (DM)," Merck Manual Professional Version, September 2020. [Online]. Available: https://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/diabetes-mellitus-and-disorders-of-carbohydrate-metabolism/diabetes-mellitus-dm. [Accessed 20 February 2021].

[11] M. Shojaei, A. Sabzeghabaei, H. Barhagh and S. Soltani, "The correlation between serum level of vitamin D and outcome of sepsis patients; a cross-sectional study," *Archives of Academic Emergency Medicine,* vol. 7, no. 1, pp. 1-6, 10 January 2019.

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

[12] F. Panfili, M. Roversi, P. D'Argenio, P. Rossi, M. Cappa and D. Fintini, "Possible role of vitamin D in Covid-19 infection in pediatric population," *Journal of Endocrinological Investigation,* pp. 1-9, 15 June 2020.

[13] M. Iruretagoyena, D. Hirigoyen, R. Naves and P. Burgos, "Immune response modulation by vitamin D: Role in systemic lupus erythematosus," *Frontiers in Immunology,* vol. 5, Article 513, pp. 1-7, 12 October 2015.

[14] K. Amrein, M. Scherkl, M. Hoffman, S. Neuwersch-Sommeregger, M. Köstenberger, A. Berisha, G. Martucci, S. Pilz and O. Malle, "Vitamin D deficiency 2.0: An update on the current status worldwide," *European Journal of Clinical Nutrition,* vol. 74, p. 1498–1513, 20 January 2020.

[15] I. Murai, A. Fernandes, L. Sales, A. Pinto, K. Goessler, C. Duran, C. Silva, A. Franco, M. Macedo, H. Dalmolin, J. Baggio, G. Balbi, B. Reis, :. C. V. Sntonangelo, B. Gualano and R. Pereira, "Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19," *JAMA,* 17 February 2021.

[16] National Cancer Institute, "White blood cell," [Online]. Available: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/white-blood-cell. [Accessed 20 February 2021].

[17] National Cancer Institute, "Lymphocyte," [Online]. Available: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/lymphocyte. [Accessed 20 February 2021].

[18] H. Han, Z. Xu, X. Cheng, Y. Zhong, L. Yuan, F. Wang, Y. Li, F. Liu, Y. Jiang, C. Zhu and Y. Xia, "Descriptive, retrospective study of the clinical characteristics of asymptomatic COVID-19 patients," *mSphere,* vol. 5, no. 5, pp. 1-11, October 2020.

[19] Y. Takahashi, N. Watanabe, N. Kamio, R. Kobayashi, T. Iinuma and K. Imai, "Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19," *Journal of Oral Science,* vol. 63, no. 1, pp. 1-3, 2021.

[20] T. Madapusi Balaji, S. Varadarajan, U. Rao, A. Raj, S. Patil, G. Arakeri and P. Brennan, "Oral cancer and periodontal disease increase the risk of COVID 19? A mechanism mediated through furin and cathepsin overexpression," *Medical Hypotheses,* vol. 144, Article 109936, pp. 1-2, November 2020.

[21] Z. Badran, A. Gaudin, X. Struillou, G. Amador and A. Soueidan, "Periodontal pockets: A potential reservoir for SARS-CoV-2?," *Medical Hypotheses,* vol. 143, Article 109907, pp. 1-3, October 2020.

[22] L. Bao, C. Zhang, J. Dong, L. Zhao, Y. Li and J. Sun, "Oral microbiome and SARS-CoV-2: Beware of lung co-infection," *Frontiers in Microbiology,* vol. 11, Article 1840, pp. 1-13, 31 July 2020.

[23] N. Botros, P. Iyer and D. Ojcius, "Is there an association between oral health and severity of COVID-19 complications?," *Biomedical Journal,* vol. 43, no. 4, pp. 325-327, August 2020.

[24] V. Sahni and S. Gupta, "COVID-19 & periodontitis: The cytokine connection," *Medical Hypotheses,* vol. 144, Article 109908, p. 1, November 2020.

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

[25] H. Larvin, S. Wilmott, J. Wu and J. Kang, "Frontiers in Medicine," *The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic,* vol. 7, Article 604980, pp. 1-7, 23 November 2020.

[26] S. Siddharthan, N. Naing and N. Wan-Arfah, "Periodontal disease and COVID-19," *Journal of Pharmaceutical Research International,* vol. 32, no. 32, pp. 88-91, 3 December 2020.

[27] R. Aquino-Martinez and S. Hernández-Vigueras, "Severe COVID-19 lung infection in older people and periodontitis," *Journal of Clinical Medicine,* vol. 10, no. 2, pp. 1-17, 14 January 2021.

Additional Resources

Association between periodontitis and severity of COVID-19 infection: A case-control study, Marouf, N; Cai, W; Said, K; Daas, H; Diab, H; Chinta, V; Hssain, A; Nicolau, B; Sanz, M; Tamimi, F. *Journal of Clinical Periodontology,* February 1, 2021, p 1-9
https://onlinelibrary.wiley.com/doi/full/10.1111/jcpe.13435

Aspiration of periodontopathic bacteria due to poor oral hygiene potentially contributes to the aggravation of COVID-19, Takahashi, Y; Watanabe, N; Kamio, N; Kobayashi, R; Iinuma, T; Imai, K. *Journal of Oral Science*, Volume 63, Issue 1, 2021, 2021, p 1-3
https://www.jstage.jst.go.jp/article/josnusd/63/1/63_20-0388/_article

Oral cancer and periodontal disease increase the risk of COVID-19? A mechanism mediated through furin and cathepsin overexpression, Madapusi Balaji, T; Varadarajan, S; Rao, U; Raj, A; Patil, S; Arakeri, G; Brennan, P. *Medical Hypotheses*, Volume 144, Article 109936, November 2020, p 1-2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7263251/

Periodontal pockets: A potential reservoir for SARS-CoV-2? Badran, Z; Gaudin, A; Struillou, X; Amador, G; Soueidan, A. *Medical Hypotheses*, Volume 143, Article 109907, October 2020, p 1-3
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7833827/

Oral microbiome and SARS-CoV-2: Beware of lung co-infection, Bao, L; Zhang, C; Dong, J; Zhao, L; Li, Y; Sun, J. *Frontiers in Microbiology*, Volume 11, Article 1840, July 31, 2020, p 1-11
https://www.frontiersin.org/articles/10.3389/fmicb.2020.01840/full

Is there an association between oral health and severity of COVID-19 complications? Botros, N; Iyer, P; Ojcius, D. *Biomedical Journal*, Volume 43, Issue 4, August 2020, p 325-327
https://www.sciencedirect.com/science/article/pii/S2319417020300810?via%3Dihub

COVID-19 & periodontitis: The cytokine connection, Sahni, V; Gupta, S. *Medical Hypotheses*, Volume 144, Article 109908, November 2020, p 1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7832148/

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA

The impact of periodontal disease on hospital admission and mortality during COVID-19 pandemic, Larvin, H; Wilmott, S; Wu, J; Kang, J. *Frontiers in Medicine*, Volume 7, Article 604980, November 23, 2020, p 1-7
https://www.frontiersin.org/articles/10.3389/fmed.2020.604980/full

Periodontal disease and COVID-19, Siddharthan, S; Naing, N; Wan-Arfah, N. *Journal of Pharmaceutical Research International*, Volume 32, Issue 32, December 3, 2020, p 88-91
https://www.journaljpri.com/index.php/JPRI/article/view/30937

Severe COVID-19 lung infection in older people and periodontitis, Aquino-Martinez, R; Hernández-Vigueras. *Journal of Clinical Medicine*, Volume 10, Issue 2, January 14, 2021, p 1-17
https://www.mdpi.com/2077-0383/10/2/279/htm

SARS-CoV-2 detection in gingival crevicular fluid, Gupta, S; Mohindra, R; Chauhan, P; Singla, V; Goyal, K; Sahni, V; Gaur, R; Verma, D; Ghosh, A; Soni, R; Suri, V; Bhalla, A; Singh, M. *Journal of Dental Research*, Volume 100, Issue 2, November 2, 2020, p 187-193
https://journals.sagepub.com/doi/10.1177/0022034520970536

The intriguing commonality of NETosis between COVID-19 & periodontal disease, Gupta, S; Sahni, V. *Medical Hypotheses*, Volume 144, Article 109968, November 2020, p 1
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7276117/

Is the gingival sulcus a potential niche for SARS-Corona virus-2? Kheur, S; Kheur, M; Gupta, A; Raj, A. *Medical Hypotheses*, Volume 143, Article 109892, October 2020, p 1-2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255245/

SARS-CoV-2 infection and oral health: Therapeutic opportunities and challenges, Coke, C; Davison, B; Fields, N; Fletcher, J; Rollings, J; Roberson, L; Challagundla, K; Sampath, C; Cade, J; Farmer-Dixon, C; Gangula, P. *Journal of Clinical Medicine*, Volume 10, Issue 1, Article 156, January 5, 2021, p 1-19
https://www.mdpi.com/2077-0383/10/1/156/htm

Periodontal pocket and COVID-19: Could there be a possible link? Elisetti, N. Medical Hypotheses, Volume 146, January 2021, p 1
https://www.sciencedirect.com/science/article/pii/S0306987720332461?via%3Dihub

Effect of a single high dose of vitamin D_3 on hospital length of stay in patients with moderate to severe COVID-19: A randomized clinical trial, Murai, I; Fernandes, A; Sales, L; Pinto, A; Goesssler, K; Duran, C; Silva, C; Franco, A; Macedo, M; Dalmolin, H; Baggio, J; Balbi, G; Reis, B; Antonangelo, L; Caparbo, V; Gualano, B; Pereira, R. *JAMA*, February 17, 2021, p E1-E8
https://jamanetwork.com/journals/jama/fullarticle/2776738

Disclaimer: This document is educational and not intended to provide clinical advice nor should it be used as a replacement for professional dental or medical advice. Dental hygienists are encouraged to consult with CDHO practice advisors and refer to CDHO guidelines. Dental hygienists are responsible for the decisions they make and for the consequences associated with those decisions. © ODHA