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The Mouth-COVID Connection: Il-6 Levels in Periodontal Disease — Potential Role in COVID-19-Related Respiratory Complications

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Abstract

Researchers are combining efforts to better understand SARS-CoV-2 and recent findings point to the importance of cytokine storms. Elevated IL-6 levels can predict COVID-19 pulmonary complications. Dental professionals play a significant role, since periodontitis can increase IL-6 levels locally and systemically. Periodontal treatment have positive effects in systemic inflammation and the importance of oral hygiene and periodontal health for respiratory conditions and COVID-19 should not be underestimated.

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Abstract

Researchers around the world are combining efforts to increase our understanding on SARS-CoV-2, and recent findings point to the potential role of cytokine storms in the severity of this viral infection. High IL-6 levels have been linked to significantly higher risk for pulmonary complications and increased need for mechanical ventilation in COVID-19 patients. As dental professionals try to establish a new normal in their practices, they play a significant role in decreasing transmission of the coronavirus disease and decreasing inflammation and IL-6 levels because periodontitis has been shown to increase cytokine levels locally and systemically. Periodontitis has been previously associated with increased risk for respiratory conditions, such as chronic obstructive pulmonary disease (COPD), pneumonia and lung function, hence there is biological plausibility for a link between periodontitis, IL-6 levels and COVID-19-related pulmonary problems. The potential mechanisms behind this association include systemic inflammation, bacterial load, gut dysbiosis and endothelial function. Genetic variations in the

IL-6 gene can also be a relevant risk factor for exacerbated inflammatory response. Findings from pneumonia studies showing lower rates of infection and mortality associated with plaque control suggest that dental care can have a major impact in the coronavirus disease course. Furthermore, for systemically healthy patients and for those who have systemic conditions, periodontal treatment can decrease the burden of systemic inflammation, thus decreasing the risk for pulmonary complication due to COVID-19. Despite the lack of studies on this topic, the importance of oral hygiene and periodontal health for respiratory conditions and COVID-19 infections should not be underestimated. Dentists should promote screening, plaque control and periodontal treatment because a healthy periodontium can help decrease the severity and complications related to COVID-19.

Introduction

The global COVID-19 outbreak has caused a public health emergency crisis, as declared by the World Health Organization in January 2020.[1] While up to 80% of patients infected by SARS-CoV-2 recover after mild cold-like symptoms with no major complications, 20% can develop serious respiratory complications that can develop into acute respiratory distress syndrome due to the virus' ability to infect human respiratory epithelial cells. Around 5% of COVID-19 patients require intensive care and mechanical ventilation.[2]

As researchers from different countries try to shed light on potential treatments and vaccines against the coronavirus, recent findings point to the potential role of cytokine storms in this viral infection, particularly interleukin-6 (IL-6).[3–5] A recent study from Germany suggested that high IL-6 levels can be a powerful predictor of respiratory failure and need for mechanical ventilation in hospitalized COVID-19 patients.[4]

Dental professionals have suffered the impact of COVID-19 in profound ways, which is directly related to the importance of the oral cavity as a transmission route, the potential for salivary glands to function as reservoirs for COVID-19, the infectivity of saliva and occupational health issues due to the nature of dental treatments. With the reopening of dental practices during the pandemic, dental professionals are faced with challenges that range from strict infection control measures to a decrease in the number of patients willing to undergo dental treatments.[6]

In these extraordinary times, dental professionals might need to shift their focus to a general health and systemic inflammation approach. In this context, periodontitis has been linked to increased levels of proinflammatory cytokines, including IL-6, which is a recognized mediator in the periodontal destruction process.[7] The ability of nonsurgical periodontal treatment to lower cytokine levels has been highlighted in the dental literature.[8,9] Thus, lower IL-6 levels and inflammation resulting from periodontal treatment can potentially protect COVID-19 patients against life-threatening respiratory complications.

In fact, previous studies have linked periodontitis to respiratory conditions, with increased risk for complications and higher mortality rate in hospitalized patients.[10] The impact of a connection between periodontal treatment, IL-6 levels, respiratory conditions and COVID-19 can be powerful considering the high prevalence of periodontal disease in adults, the high transmission rate of SARS-CoV-2, the limited access to periodontal treatment during the pandemic and the shortage of health care resources related to hospitalized COVID-19 patients who require mechanical ventilation.[14]

The proposed biological mechanisms behind the link between periodontitis and increased risk for COVID-19 complications are presented in the FIGURE. In this review, the current state of

knowledge on the scientific foundation for the connection between IL-6 levels and periodontitis, COVID-19 and respiratory diseases is presented, including the importance of this cytokine for periodontitis, viral infections and COVID19, the effect of periodontal treatment in IL-6 levels, the biological link between periodontitis, respiratory problems and coronavirus disease. The clinical importance of this review lies in the awareness that dental professionals can have a major impact on the COVID-19 pandemic through promotion of periodontal health, considering the benefits of prevention and treatment of periodontal disease on overall health, including the prevention of complications resulting from the coronavirus disease.

IL-6 in Relation to Periodontitis

Periodontitis is characterized by an inflammatory process that results in destruction of the periodontium triggered by mediators derived from the adaptive and innate immune response to microorganisms in the biofilm.[12] Cytokines are soluble proteins that attach to cell surfaces through specific receptors, regulating cell function and mediating complex cell interactions involved in periodontal destruction. In periodontitis, cytokines cause intracellular cascades and phenotypic changes that regulate the amplitude and severity of the host response with interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α) and IL-6 being the most extensively investigated.[13]

IL-6 is a well-known proinflammatory cytokine secreted by a multitude of cells, including monocytes, macrophages, endothelial cells, epithelial cells, B and T cells. In periodontitis, IL-6 is crucial for regulation of the host response to infection, injury and alveolar bone resorption.[14] The participation of IL-6 in periodontal inflammation has been well described in the literature through genetic studies on IL-6 polymorphisms and studies evaluating IL-6 expression levels in serum, saliva, gingival crevicular fluid (GCF) and gingival tissues. Each of these categories is

discussed below.

Genetic Studies: IL-6 Polymorphisms and Risk for Periodontitis

Polymorphisms deriving from one base change in the genome are known as single nucleotide polymorphisms (SNPs), resulting in different gene versions or alleles. Cytokine SNPs can influence risk and outcomes for certain diseases, such as periodontitis, by influencing secretion of these mediators, immune and inflammatory responses.[15] The diversity in the clinical presentation of periodontitis have been partly attributed to genetic nucleotide variations in the IL-6 gene, localized in chromosome 7.[16] In 2003, the first study associating an IL-6 polymorphism (-174) to periodontitis was published and a protective effect for allele C against periodontitis was reported in a sample from Brazil.[17]

The role of IL-6 polymorphisms in the susceptibility to periodontitis has been explored in several other studies, with different SNPs being investigated (-174, -572, -597, -373, -190, -1363, -6106, -1480, +874). A summary of published studies on IL-6 gene polymorphisms in patients with periodontitis is presented in the TABLE. For the IL-6 gene, SNP -174 (promoter region) and -572 (regulatory region) have been the most investigated, and the majority of studies have found an association between these polymorphisms and the risk for periodontitis,[17–28] which was confirmed in a recent meta-analysis.[29] The SNP -1363 was only evaluated in two studies, which reported a positive association with periodontitis.[20,30] Two studies investigated IL-6 SNP -597, from which one found an association with periodontitis.[31,32] The remaining IL-6 polymorphisms have been investigated to a lesser degree with varying results (TABLE).

Data on IL-6 gene variants suggest that SNP -174 allele C can protect against chronic and aggressive periodontitis, while allele G increases the risk. Likewise, for SNP -572, allele C seems

to have a protective effect for chronic and aggressive periodontitis. The majority of these studies report on data from European, Asian and Brazilian participants, hence further studies on different ethnic groups are warranted. The protective effect of the polymorphisms has been linked to lower serum IL-6 levels.[32,33] The other IL-6 SNPs have been studied to a lesser degree, reasons why their association to periodontitis needs to be further explored.

In Vitro Studies on IL-6 Expression in Periodontitis

High expression of IL-6 has been reported in inflamed gingival tissues, and human gingival fibroblasts are able to produce elevated IL-6 levels when exposed to polysaccharides (LPS) or IL-1.[34,35] The role of IL-6 on periodontal bone destruction has been investigated through in vitro studies, which suggest that this cytokine is involved in osteoclastogenesis, a crucial process in alveolar bone destruction. IL-6 stimulates osteoclast formation and increases expression of receptor activator of nuclear factor-κB ligand (RANKL) in osteoblasts, being an essential mediator for osteoclast function and possibly osteoblast function.[36,37]

Additional in vitro studies have revealed that upregulation of matrix metalloproteinases (MMPs) is one of the mechanisms by which IL-6 causes periodontal destruction.[35] IL-6 stimulates the production of MMP-1 in human gingival fibroblasts, which is a key protease in the process of tissue destruction due its ability to degrade collagen and activate the fibrinolytic protease cascade.[38]

When CD4+ T-cells from gingival tissue and peripheral blood from periodontitis patients were exposed to Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, upregulation of IL-6 levels was observed in comparison to healthy subjects.[39] Similar responses were found in

studies exposing monocytes or whole blood cells from periodontitis patients to LPS and/or

studies exposing monocytes or whole blood cells from periodontitis patients to LPS and/or

periodontal pathogens, where increased levels of IL-6 were consistently observed in cells from periodontitis patients compared to periodontally health patients. The main cellular sources for IL-6 secretion in the periodontium have been identified as macrophages, epithelial cells and T-cells.[40,4]

Collectively, data from in vitro studies have shown that T-cells, gingival fibroblasts, monocytes, and peripheral mononuclear cells from gingiva and blood produce elevated IL-6 levels when stimulated by pathogens, LPS or other cytokines. Cells from periodontitis patients can express a different phenotype, characterized by higher IL-6 expression when compared to cells from periodontally healthy subjects. Once secreted, IL-6 mediates periodontal destruction through upregulation of MMPs and osteoclastogenesis.

IL-6 levels in Gingival Crevicular Fluid (GCF), Saliva, Gingival Tissues and Serum

As soluble proteins, cytokines produced in periodontal tissues can be detected in the GCF. A variety of studies have measured IL-6 levels in GCF, and despite some conflicting results, IL-6 levels seem to be higher in the GCF of periodontitis patients when compared to subjects with a healthy periodontium according to a comprehensive meta-analysis.[42] Doubled IL-6 levels have been reported in sites with refractory periodontitis when compared to stable periodontal sites.[43]

As another potential source for biomarkers, saliva has also been investigated for IL-6 levels, given the higher volume and easier access for sampling in comparison to GCF.[44] Despite the fact that IL-6 salivary levels seem to be low in periodontal health and periodontitis, few studies have detected an increase in salivary IL-6 levels in the presence of periodontitis.[45,46] In a recent clinical study by Batool and co-workers, IL-6 salivary levels increased with increasing severity of

chronic periodontitis.[47] However, several other studies have failed to detect differences in salivary IL-6 levels of periodontitis, suggesting that IL-6 might not be a strong biomarker for periodontitis in saliva.[48,49]

When compared to healthy gingival tissues, inflamed gingival tissues have shown higher IL-6 concentration through immunohistochemistry methods.[50] In addition, increased IL-6 mRNA and protein expression have been observed in periodontitis patients when compared to periodontally healthy patients.[51] A recent study on periodontitis patients reported gingival IL-6 levels ranging from 3 to 13 pg/ml, with one patient presenting levels as high as 53.1 pg/ml.[52]

Serum levels of IL-6 In patients with periodontitis have been reported to be significantly higher than those for patients with a healthy periodontium, with values ranging from 0.25 pg/ml to 41.2 pg/ml in periodontitis.[53] Similar results have been confirmed by other investigations on chronic and aggressive periodontitis.[54,55] Interestingly, in a clinical study from Almaghlouth and co-workers,[56] the maximum serum IL-6 levels found in the periodontitis group was 216.3 pg/ml.

Impact of Periodontal Treatment on IL-6 Levels

D'Aiuto and co-workers (2004) investigated the effect of nonsurgical periodontal treatment in serum inflammatory markers in 94 systemically health participants presenting severe generalized periodontitis. A significant decrease in serum IL-6 (median decrease 0.2 ng/L) and CRP (median decrease 0.5 mg/L) was observed six months after treatment.[57] These findings were confirmed by other investigations, where serum levels of IL-6 were significantly reduced after conventional nonsurgical periodontal treatment in chronic periodontitis patients.[53,58,59] Interestingly, Lobao et al. (2019) noted an average IL-6 reduction of 12 ng/ml three months after

conventional periodontal treatment. In this study, even participants subjected to supragingival

conventional periodontal treatment. In this study, even participants subjected to supragingival scaling and polishing (control group) presented significant serum IL-6 comparable to the test group, which received supra and subgingival scaling and root planing.[60]

In another study from D'Aiuto et al. (2006), conventional nonsurgical periodontal treatment was compared to intensive periodontal treatment in 40 systemically healthy participants. Intensive therapy, which included local antimicrobial agents, resulted in greater reductions of serum IL-6 and CRP after two and six months.[61]

A recent systematic review and meta-analysis evaluated the effect of periodontal therapy on IL-6 levels in patients with diabetes. When obese participants were excluded, the majority of studies reported a significant decrease in serum IL-6 levels in diabetics after periodontal treatment.[62] Conventional periodontal therapy has also been shown to decrease IL-6 levels in patients with other systemic conditions, such as hypertension, metabolic syndrome, atherosclerosis and coronary heart disease.[9,63,64]

Altogether, these findings support a beneficial effect of periodontal therapy in serum IL-6 levels and in systemic inflammatory activity. The improvement in circulating IL-6 levels has been reported for systemically healthy patients and for patients with systemic conditions.

Summary: IL-6 Significance for Oral Diseases and Periodontitis

There is strong evidence on the key role played by IL-6 in the immune and inflammatory response and bone resorption in periodontitis based on the following findings:

- Genetic studies confirm that IL-6 polymorphisms can increase susceptibility to periodontitis.
- In vitro studies confirm that IL-6 can be produced by a variety of cells in the

periodontium, being a mediator for inflammation, host response and bone destruction.

- IL-6 levels are upregulated locally in periodontal tissues, GCF and potentially in saliva in periodontitis patients with the potential to spread to the systemic circulation as confirmed by elevated serum levels of IL-6 in periodontitis patients.
- Periodontal treatment can contribute to a decrease in local and circulating IL-6 levels in healthy individuals and in those who present systemic conditions.
- Pulpitis and periapical lesions can be linked to increased expression of IL-6 as well as oral squamous cell carcinoma; however, these associations have been investigated to a lesser degree compared to periodontitis.

Respiratory Diseases, Pulmonary Function and Periodontitis

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a highly prevalent inflammatory condition affecting nearly 24 million Americans. It is among the leading causes of the death in the U.S., being characterized by compromised pulmonary function, limited airflow and breathing problems.[65] Observational studies have linked COPD to periodontitis and the association was supported by results from a meta-analysis by Zeng et al. (2012). In total, 14 studies and nearly 4,000 COPD patients were included, and the results showed a robust association between COPD and periodontitis with OR = 2.08 (1.48–2.91). The authors concluded that periodontitis is an independent risk factor for COPD.[66]

More recent data show increased prevalence of periodontitis in COPD patients who require hospitalization.[67] Fewer remaining teeth, higher loss of attachment and higher levels of inflammatory mediators in the GCF were reported in COPD patients.[68]

Pneumonia

Pneumonia is the infection of the pulmonary parenchyma, which can be caused by bacteria and viruses. It presents high mortality rates worldwide and often affects individuals with impaired immune systems, being usually classified as community-acquired or hospital-acquired (nosocomial).[69] In a systematic review from Scannapieco et al. (2003) including nine randomized controlled trial (RCT) and 11 case-control studies, there was a significant association between nosocomial pneumonia and poor oral hygiene.[70]

In another systematic review, Azarpazhooh and Leake (2006) investigated the association between oral health and respiratory diseases. Based on findings from 19 studies, the authors found good evidence to support a link between antimicrobial oral hygiene interventions and decreased incidence of pneumonia in nursing home patients.[71]

Data from several RCT published since 2010 provide further evidence on the impact of poor oral hygiene and periodontitis in the incidence of nosocomial pneumonia in adults.[72] In intensive care patients, oral swabbing with 0.2% chlorhexidine (CHX) decreased the rate of nosocomial infection.[73] In patients scheduled for surgery for esophageal cancer, pre-operative toothbrushing alone reduced the rate of postoperative pneumonia.[74] In contrast, a study on nursing home patients failed to find reduction in pneumonia rates as a result of oral hygiene care interventions.[75]

Very interesting results were reported in one RCT, where comprehensive professional dental care provided by a dental surgeon in the intensive care unit was compared to routine oral hygiene offered by nurses. Dental treatment to intensive care patients (toothbrushing, tongue scraping, atraumatic caries treatment, removal of calculus and extractions) resulted in a

dramatic reduction in the incidence of respiratory infections and ventilator-associated pneumonia. These results suggest that in hospitalized patients, intense dental therapy can help prevent respiratory infections.[76]

Pulmonary Function

In a case-control study from Peter et al. (2013), worse periodontal status was observed in COPD patients and associated with increased lung obstruction measured as forced expiratory volume in one second (FEV1).[77] Another study investigated lung function in systemically healthy patients as part of the Study of Health in Pomerania, which included 1,463 subjects. Periodontal disease and number of missing teeth were positively associated with airflow limitation and reduced lung volume.[78] Similar findings were reported in a recent large study based on the NHANES III data, where poorer pulmonary function was associated with increased severity of periodontitis in systemically healthy participants.[79]

In one interventional study on the effect of periodontal therapy on lung function, the authors compared three treatment groups (scaling and root planing, supragingival scaling and oral hygiene instructions alone) and concluded that the two therapy groups resulted in improved lung function, measured as FEV.[80] A lack of correlation between pulmonary function and periodontitis has also been reported in one study.[81]

Asthma

Asthma is a prevalent chronic condition that can affect adults and children, characterized by alterations in the airways, bronchoconstriction and inflammation. Currently there are contradictory results regarding a potential association of periodontitis and asthma.[82] Two recent systematic reviews have addressed this association. The systematic review from Moraschini et

al. (2017) included 21 studies on adults and children and the results showed increased gingival inflammation in asthmatic subjects in relation to systemically healthy individuals, which can be related to the use of inhalers, mouth breathing and decreased salivary production.[82] The other systematic review focused on adults with asthma (Ferreira et al. 2019) and, based on results from 11 studies, the authors concluded that there was increased prevalence of periodontal disease, particularly gingivitis, in adults with asthma.[83]

In a case-control study by Soledade-Marques and co-workers (2017), severe asthma was associated with periodontitis with adjusted OR = 3.01-3.25. Prevalence of periodontitis was higher in patients with severe asthma (46.6%) in comparison to systemically healthy controls (22.3%) and periodontitis patients had a threefold increased risk of having severe asthma.[84]

Altogether, findings from most published studies on respiratory conditions and oral health suggest an association between periodontitis and COPD, pneumonia, worse lung function and potentially asthma. Oral hygiene interventions, dental and periodontal treatment are crucial to decrease the risk for nosocomial pneumonia and other respiratory conditions.

IL-6, Viral Infections and COVID-19

The coronavirus disease is caused by a new coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and due to high transmission rates, it has spread catastrophically in most countries, including the U.S. The pandemic caused by the virus is unprecedented according to the WHO and has put strain on primary health care systems around the world.[85]

Although most cases have been described as mild to moderate with self-limiting cold-like

symptoms or no symptoms, around 20% of patients can develop more severe complications that require hospitalization, from which approximately 5% need intensive care and mechanical ventilation. Mortality rates range from 0.25% to 3.0% on average, being higher for vulnerable subjects presenting certain risk factors such as age over 70, respiratory disease, diabetes, cardiovascular disease and cancer. The most frequent cause of mortality is COVID-19-related pneumonia and acute respiratory distress syndrome (ARDS), with some patients also presenting severe cardiovascular damage. In severe cases, mortality rates can be as high as 60.5%.[8 6]

The virus infects host cells through the angiotensin converting enzyme 2 (ACE2) receptor, which is highly expressed in several organs, including salivary glands.[87] Studies on the coronavirus disease suggest that there is a massive activation of mononuclear macrophages and T lymphocytes and release of inflammatory mediators such as IL-6. In SARS-CoV-2, IL-6 seems to bind to target cells, inducing increased cytokine production that perpetuates inflammation in the pulmonary tissues and in other organs.[88]

Some studies have investigated the potential role of upregulated levels of IL-6 in the exacerbation of viral diseases before the pandemic, suggesting that IL-6 has the potential to promote worsening of clinical symptoms and facilitate virus survival.[3]Of interest, IL-6 has been suggested to contribute to viral persistence, with serum upregulation of IL-6 being linked to other viral infections in humans, including influenza virus and human immunodeficiency virus.[89]

During infection, together with IL-1β and TNF-α, IL-6 is a crucial mediator.[90] The potential biological mechanisms for increased IL-6 production during viral infection include the potential

ability of some viruses to evade the immune response and increase IL-6 levels as viral loads increase, and the presence of genetic IL-6 polymorphisms leading to overproduction of IL-6 during the infection.[91] Furthermore, studies on COVID19 suggest that higher IL-6 levels can worsen alveolar capillary blood gas exchange in the lungs and oxygen diffusion, potentially contributing to fibrosis and pulmonary failure.[88]

Recently, a study on IL-6 levels in hospitalized COVID19 patients suggested an important role of this cytokine in predicting the need for mechanical ventilation.[4] Forty hospitalized COVID-19 patients were included, from which 32.5% deteriorated and required mechanical ventilation. There was a strong association between the need for ventilation and IL-6 serum levels above 80 pg/ml. High IL-6 levels accurately predicted respiratory failure, with 22 times higher risk for respiratory complications. The authors highlighted that the accuracy of the cutoff value needs to be further assessed due to the small sample size.[4] In a recent meta-analysis, severe COVID19 cases presented a 2.9 fold increase in IL-6 levels when compared to mild to moderate cases without complications.[92] With the current shortage of health care resources due to the high number of infections, identification of patients who have increased risk for respiratory complications can be crucial for resource allocation.[11]

The importance of IL-6 for COVID19-related pulmonary complications has been confirmed by a small study in China, where tocilizumab was given to 20 hospitalized patients who had severe coronavirus disease. The drug had excellent results, with 90.5% of patients recovering after an average of 13.5 days.[93] Tocilizumab is a humanized IL-6 receptor monoclonal antibody, which has high affinity for IL-6 receptors. It binds to these receptors, preventing IL-6 from altering cellular behavior and ultimately improving inflammation. Currently, two RCTs are underway to further investigate the effect of IL-6 receptor antagonists in severe COVID19 cases (NCT04310228 and NCT04315298).[93]

Further confirmation on the importance of an intense inflammatory reaction in critically ill COVID-19 patients comes from a recent report from the RECOVERY Trial. This RCT from the U.K. included 2,100 participants in the dexamethasone arm (6mg/day for 10 days) and 4,300 participants in the standard care arm. Preliminary results show that in COVID-19 patients who were on ventilators, dexamethasone decreased mortality by one-third. Previous studies show that dexamethasone inhibit T-cell activation and downregulates IL-6 and other proinflammatory cytokines, promoting a shift towards an anti-inflammatory direction.[94]

Another line of treatment currently being investigated is the use of inhaled steroids, with ongoing studies taking place in the U.S., France and England. Inhaled steroids are thought to reduce virus replication and inflammation in the airways, leading to less immunosuppression than systemic steroids.[95]

Findings from COVID-19 studies and the current treatment options under investigation suggest a pivotal role of cytokine storms in the mortality associated with COVID-19 complications, hence mitigating sources of inflammation is prudent.

Biological Mechanisms Behind the Connection Between Periodontal Disease and Pulmonary Conditions, Including COVID-19-Related Respiratory Complications

Systemic Inflammation

In the presence of inflammation in the periodontium, several host cells can increase production of IL-6, which can diffuse into the systemic circulation together with other cytokines. Elevated

IL-6 levels have been reported in periodontal tissues, saliva, GCF and serum in periodontitis patients, as discussed previously in this review. Once in the blood, IL-6 and other mediators have the potential to affect distant organs and tissues, such as the lungs, through the activation of circulating immune cells and endothelial cells, which induces further release of inflammatory mediators and potentially contributes to inflammation in the respiratory tissues.[10]

Entrance of oral pathogens into the systemic circulation is another potential mechanism that can result in upregulated production of inflammatory mediators in the body. Endothelial cells and leukocytes respond to circulating bacterial antigens with secretion of proinflammatory mediators. Continuous systemic exposure to bacterial antigens cause formation of immune complexes that further promote production of TNF-α, IL-6 and IL-1β. Moreover, in periodontitis patients, peripheral blood neutrophils present a hyperactive profile characterized by increased production of proinflammatory cytokines and reactive oxygen species.[96]

Bacterial Load

Approximately 100 million bacteria are present in every cubic millimeter of oral biofilm, which can function as a reservoir for periodontal and respiratory pathogens.[97] According to Scannapieco et al., there are four possible ways through which oral pathogens can contribute to respiratory diseases.[98] The first is the aspiration of secretions from the oropharynx into the upper and lower airways. They can adhere to the respiratory epithelium and initiate/exacerbate infection indirectly through the release of LPS or directly through signal transduction via adhesion receptors. Second, enzymes produced in periodontal disease can alter the surface of the respiratory epithelium and facilitate adherence of respiratory pathogens. Third, hydrolytic enzymes produced in periodontal disease can deteriorate salivary proteins on bacterial surfaces, facilitating their adherence to mucosa. Lastly, cytokines can modulate bacterial adhesion of

pathogens to the pulmonary epithelium

pathogens to the pulmonary epithelium.

Elimination of aspirated bacteria by the immune system is impaired in patients with impaired saliva production, swallowing disorders and poor cough reflex, putting these patients at higher risk for lung infections. For intensive care patients, intubation and mechanical ventilation decreases clearance of oral secretions leading to increased oral bacterial load and risk for pneumonia.[99] In support of these findings, studies have reported cultures of oral facultative and anaerobe species from infected lung fluids, such as Porphyromonas gingivalis, Eikenella corrodens, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans and Peptostreptococci.[100]

Studies have suggested that bacteria and/or bacterial products of oral origin are able to induce secretion of cytokines from pulmonary epithelial cells, leading to recruitment of inflammatory cells. The inflamed respiratory epithelium can in turn become more susceptible to infection due to epithelial inflammation.[98] Some oral pathogens are able to stimulate epithelial cells to produce proinflammatory cytokines to a similar degree to that observed for respiratory pathogens.[101]

Gut Dysbiosis

Gut dysbiosis has been suggested as a potential novel pathogenic mechanism linked to changes in immunity, systemic inflammation and development of respiratory disease.[102]New research suggests that periodontal pathogens can contribute to gut dysbiosis, given that oral bacteria are frequently swallowed through saliva. Thus, periodontal pathogens can reach the intestines, alter the local microbiota, increase gut permeability and the risk for endotoxemia, which is defined as the entrance of LPS in the blood circulation and promotes systemic inflammation.[103] In vitro experiments have shown that Porphyromonas gingivalis was able to successfully withstand stomach acids and colonize the colon, leading to functional changes.[104] In health, oral

microorganisms are poor colonizers of the gastrointestinal tract; however, when systemic conditions such as viral infections are present, higher numbers of oral bacteria have been identified in the intestines.[105]

Despite the early stages of research on gut dysbiosis in periodontitis patients, this can become an additional biological mechanism to explain the proinflammatory effect of periodontitis in the systemic environment and the lungs.

Endothelial Dysfunction

Endothelial dysfunction encompasses changes in endothelial physiology, representing an early step in atherosclerosis. It is mainly characterized by reduced production of nitric oxide and impaired endothelium-dependent vasodilatation. Periodontitis has been linked to endothelial dysfunction in healthy patients and in patients with hypertension.[106] Accordingly, periodontal treatment was able to improve acetylcholine-induced vasodilation in hypertensive and normal patients, suggesting a positive effect on endothelial dysfunction irrespective of the patient's general condition.[107,108]

To conclude, there are several biological pathways for the link between periodontitis and COVID-19. The oral bacterial load and systemic inflammation resulting from periodontal disease can affect the lung endothelium and the gut microbiome. Aspiration of oral bacteria is another potential mechanism through which oral pathogens can reach the respiratory tract and potentially interact with the SARS-CoV-2 virus to increase severity and mortality. In the lungs,

circulating bacteria and cytokines such as IL-6 can alter the respiratory tissues, leading to decreased lung function, increased risk for infection and other complications, particularly in patients with COVID-19 (FIGURE). Changes in the lungs have been reported even in systemically healthy patients as a consequence of periodontitis, suggesting that periodontal and dental treatment are essential for both healthy subjects and for those who have lung diseases or other chronic diseases, such as hypertension, diabetes and atherosclerosis. Directly, through high IL-6 levels or indirectly, through alterations in the lung endothelium and gut microbiome, periodontitis can increase the risk for COVID-19 severity and complications, potentially affecting the course of the disease. Of note, chronic psychological stress has also been linked to elevated circulating IL-6 levels.[109] Considering the widespread psychological and financial stress brought by the pandemic, it can be a significant contributor to periodontal and systemic inflammation, further increasing IL-6 levels and the risk for COVID-19 related complications.

Periodontal Screening and Treatment as Preventive Tool Against COVID-19

Considering the potential impact of poor oral hygiene and periodontitis on respiratory infections and COVID-19, periodontal interventions are important to reduce the burden of oral bacteria and potentially decrease systemic inflammation.[57,60,61] As dental offices remained closed for elective procedures during lockdown, millions of dental cleaning appointments were postponed, suggesting a possible increase in the rates of gingivitis and periodontitis, with consequent elevation of systemic inflammation. Given the high transmission rate of the virus and the 22 times higher risk for COVID-19 respiratory issues linked to high IL-6 levels,[4] every attempt to decrease this inflammatory mediator should be prioritized. Furthermore, periodontitis is considered as a risk factor for cardiovascular disease, hypertension and diabetes, which are comorbidities associated with increased mortality rate for COVID-19.[110]

In nursing homes and ICUs, oral hygiene and professional oral health have been shown to reduce the rate of pneumonia and mortality.[111] In Brazil, hospitals that have a dentist presented a reduction in aspiration pneumonia and hospital infections, decreased need for antibiotics, shorter hospitalization time, lower costs, reduced mortality and improved general well-being.[112] Based on these findings, a national law was approved in 2016 requiring the presence of a dentist in private and public hospitals that have an ICU in Brazil.[112]

The Centers for Disease Control and Prevention (CDC) has estimated that up to 30% of COVID-19 cases in the U.S. require hospitalization. With the evidence that dental care, including topical application of CHX, can be effective in the prevention of respiratory infections, it is tempting to wonder if hospital dentistry or dental care delivered by hospital nurses could make a difference in the disease course of thousands of hospitalized COVID-19 patients.

Because the throat seems to be crucial for virus replication early after infection with COVID-19, oral rinses can potentially alter the viral lipid envelope, reducing the viral load and the risk of transmission.[113] Despite the lack of human studies on the effect of mouthwashes on SARS-CoV-2, the American Dental Association (ADA) recommends the following agents to help reduce transmission of the virus: 1% hydrogen peroxide and 0.2–0.5% povidone.

The current recommendations for use of oral rinses include preoperative for all patients during the pandemic (ADA). Challacombe et al. (2020) suggest the use of povidone 0.5% every two to three hours (up to four times daily) for dentists and dental assistants to reduce their risk of infection.[114]

Despite the fact that CHX can reduce risk of pneumonia in hospitalized patients undergoing mechanical ventilation, few in vitro studies suggest less effectiveness against viruses when

compared to povidone and hydrogen peroxide. A study from England suggests mouthwashes containing 21%–27% ethanol combined with essential oils can be effective against viruses; however, they require further clinical studies.[113]

IL-6 Genetic Testing

Findings from studies on the -174 IL-6 genetic polymorphism suggest that the G/G genotype increases the risk for severe periodontitis due to exacerbated inflammatory response characterized by elevated IL-6 levels.[19,24] According to data from 12,000 salivary tests performed by OralDNA Labs (Eden Prairie, Minn.) for the -174 IL-6 polymorphism, 45.2% of periodontitis patients have the high risk genotype (G/G), 41.0% have intermediate risk (C/G) and 13.8% have low risk (C/C) (unpublished data). In the study from Trevilatto et al. (2003), 71% of severe periodontitis and 50% of moderate periodontitis patients presented the G/G genotype.[17] Despite the fact that periodontitis is multifactorial and associated with multiple cytokines,[103] recent findings on the pivotal role of IL-6 in cytokine storms in hospitalized COVID-19 patients make it a promising choice for genetic testing.

Currently, there are no studies on the role of -174 IL-6 polymorphism in coronavirus disease. In the near future, IL-6 genetic testing for COVID-19 patients could help identify those at risk for cytokine storms and guide treatment to decrease complications and mortality. It will be interesting to investigate if the high-risk G/G genotype that predisposes to severe periodontitis is also linked to the severity of coronavirus disease.

Solutions Section

Based on the scientific evidence provided in this review and on guidelines from the ADA, the following solutions are recommended for the oral team during these unprecedented times.

Promotion of Oral Hygiene To Decrease the Burden of Bacteria and Screening for Untreated Periodontitis

Good personal hygiene has never been so crucial, including optimal daily oral hygiene. Bacterial plaque can harbor respiratory and periodontal pathogens, which can reach the systemic circulation and invade host cells. Keeping the burden of oral bacteria as low as possible can reduce the risk of aspiration to the respiratory tract. Patients should be encouraged to brush their teeth twice per day for a minimum of two minutes with fluoridated toothpaste and perform interproximal cleaning. In a recent meta-analysis, interdental brushes and water-jets showed the highest reduction in gingival bleeding, while unsupervised flossing was not effective.[115] For management of gingivitis, the consensus from the 11th European Workshop in Periodontology suggests that flossing should only take place when there is no space for an interdental brush. For periodontitis patients, two minutes of toothbrushing might not be enough, hence instructions for periodontitis patients need to be customized. Early identification of patients with periodontitis is very important for timely treatment and reduction of the inflammatory response.

Professional Teeth Cleaning and Periodontal Treatment To Decrease the Burden of Inflammation

Not all patients have motivation and/or fine motor skills to maintain optimal plaque control. The consensus from the 11th European Workshop is in support of professional plaque control as a way to improve gingival inflammation, decrease plaque and reinforce oral hygiene habits.[116]

As discussed previously, it is imperative for periodontitis patients to undergo comprehensive treatment to control alveolar bone loss and decrease systemic inflammation and IL-6 levels. For

advanced cases, systemic antibiotics can be considered as an adjunct to periodontal treatment for better clinical and microbiological effects, taking into consideration both local and systemic health. Successful control of periodontal inflammation can be beneficial to the lungs, possibly decreasing severity and risk of COVID-19 respiratory problems.

Genetic IL-6 Testing To Provide Risk Assessment for Periodontitis

The G alleles in the IL-6 polymorphism in the -174 promoter region have been linked to increased risk for severe periodontitis.[17–19] IL-6 genetic testing can be a useful tool to provide information on the risk for severe periodontitis and guide treatment, as more aggressive approaches may be required in patients that carry the G allele in order to diminish the inflammatory response. Currently there are no studies evaluating genetic variations in this position of the IL-6 gene in COVID-19 patients.

Infection Control Measures To Decrease the Spread of SARS-CoV-2

The ADA (ADA COVID-19 Center) and the CDC have provided comprehensive recommendations to mitigate the spread of SARS-CoV-2 in dental practices regarding patient management, personnel, facility and equipment considerations, administrative and engineering controls, infection control, personal protective equipment (PPE) and hygiene.[117]

As mentioned previously, hydrogen peroxide has been recommended as a preprocedural rinse with the potential to decrease the transmission of SARS-CoV-2 because it is vulnerable to oxidation. Although it has not been tested in clinical trials, in vitro studies report that it can inhibit virus replication in epithelial cells.

As discussed earlier, hospitalized patients are unable to maintain oral hygiene, resulting in

plaque build-up that can provide a niche for respiratory pathogens and a source for aspiration of oral pathogens. This increases the risk for pneumonia and respiratory problems and can have a negative impact in COVID-19 related respiratory complications, although there is currently no studies on this topic. Based on data from pneumonia studies, it can be speculated if use of hydrogen peroxide or chlorhexidine could have positive affect the course of the coronavirus disease in hospitalized patients.

Virtual Dental Consultations and Monitoring and Mobile Dentistry for Patients Who Want To Avoid Leaving Their Homes

With the high transmission rate of SARS-CoV-2, it is understandable that patients want to avoid potential exposure to the virus, particularly those with comorbidities. Teledentistry can be a solution, as several platforms have emerged to offer dentists complete solutions to provide virtual dental consultations. Even though professional cleaning and periodontal treatment require in-office visits, triaging for dental emergencies and oral hygiene reinforcement can be done virtually. In addition, mobile dentistry can become a necessary solution in the future to offer treatment in the comfort of the patient's home or workplace.[118]

Take-Home Message

- The coronavirus disease can dysregulate the host immune response and elevate IL-6 levels. High IL-6 levels increase the risk for mechanical ventilation in hospitalized patients by 22 times, being a predictor for COVID-19-related respiratory complications. IL-6 receptor antagonists and dexamethasone have the potential to improve disease severity in hospitalized patients through changes in the inflammatory response, however, results from robust trials need to confirm safety and effectiveness for this treatment.
- Oral diseases, particularly periodontitis, can contribute to a systemic inflammatory

response with high circulating IL-6 levels. Certain genetic variations of the IL-6 gene can increase the risk to severe periodontitis through an exacerbated IL-6 response. Genetic testing can be useful to identify patients at high risk and guide treatment. High IL-6 levels in periodontitis patients can contribute to COVID-19 respiratory complications.

- Oral bacteria can be aspirated and affect lung function, increasing the risk for pneumonia, COPD and potentially COVID-19-related pulmonary complications.
- Oral hygiene interventions, periodontal and dental treatment have the potential to decrease the oral bacterial burden and the systemic inflammatory response. Thus, is it essential to treat periodontitis and promote good plaque control for general health and decrease the risk to COVID-19 problems.

- Periodontal treatment is beneficial for systemically healthy patients and for those with pulmonary conditions, as it can decrease IL-6 levels and decreased inflammation. Periodontal health can help prevent severe COVID-19 respiratory complications.
- Prevention of COVID-19-related pulmonary complications can have a huge impact on health care systems with the potential to decrease the need to intensive care and mechanical ventilation and decrease mortality rates.

Conclusion

There are several biological reasons to consider periodontitis as a risk factor for respiratory diseases, and as such, it can contribute to the development of respiratory complications in COVID-19 patients. Several mechanisms are proposed as possible explanations for the link between the oral environment and the lungs, including systemic inflammation, bacterial load, gut dysbiosis and endothelial function. High serum IL-6 levels can predict COVID-19-related respiratory complications and the need for mechanical ventilation, hence dentists should focus on eliminating underlying conditions that promote systemic inflammation, such as

periodontitis and other oral conditions. Despite the current lack of studies on this topic, the potential of oral hygiene and periodontal interventions to decrease the burden of oral bacteria and inflammation, improve general health and protect against severe complications from coronavirus disease should not be underestimated.

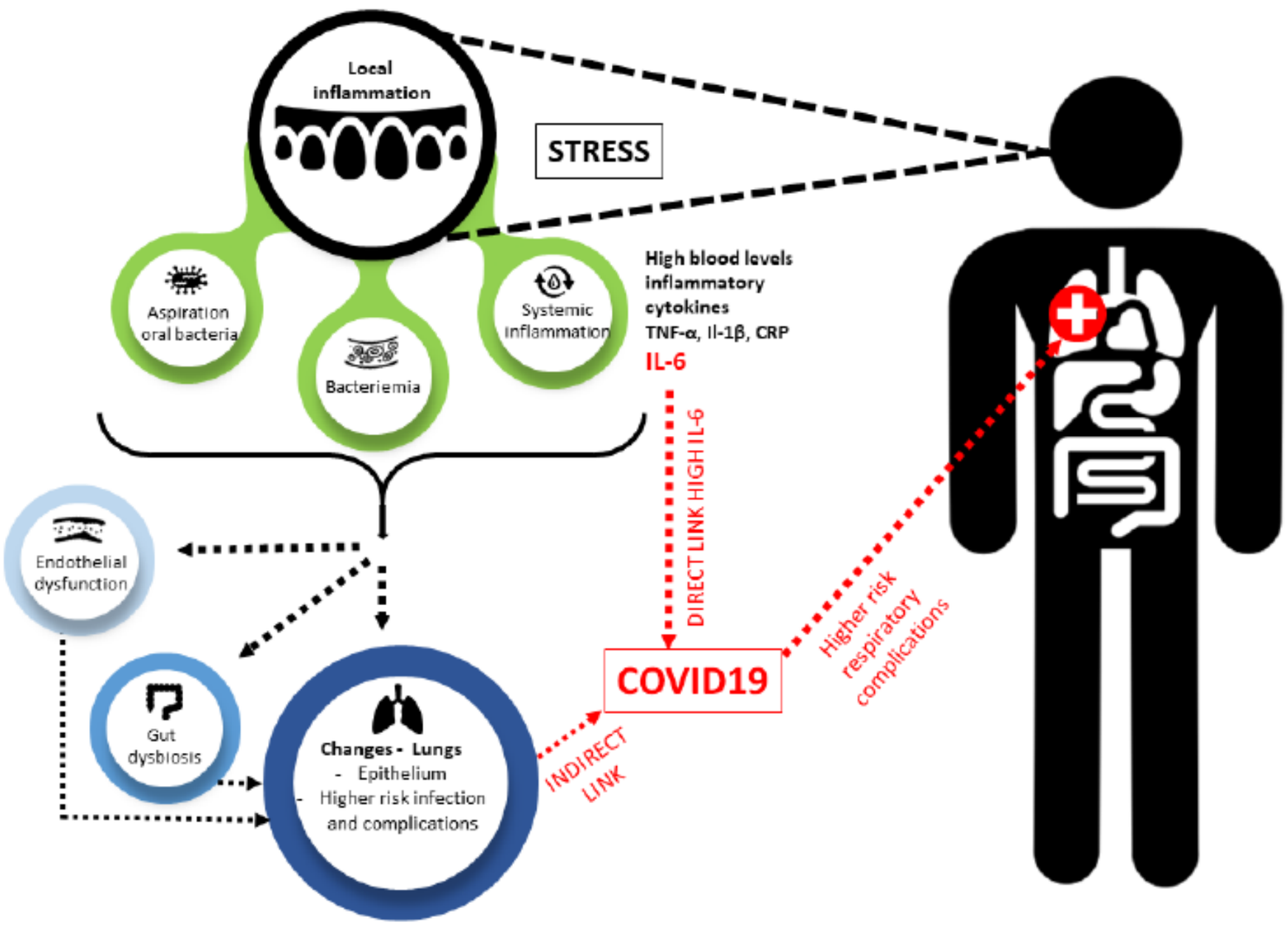

FIGURE 1. Proposed biological mechanisms behind the link between periodontitis and increased risk for COVID-19 complications. Local inflammation in the periodontium can affect the body through three main pathways: spill over of locally produced inflammatory mediators to the systemic circulation, leading to systemic inflammation; entrance of bacteria or bacterial

products to the systemic circulation through the gingival sulcus (bacteriemia); and aspiration of oral bacteria, which can reach the upper and lower respiratory tract. Stress can further contribute to local and systemic inflammation. Combined, these pathways can enhance endothelial dysfunction, gut dysbiosis, potentially predisposing to changes in the lungs. Gut dysbiosis and endothelial dysfunction can affect several organs and systems, including the lungs. Circulating cytokines and bacteria can alter the respiratory epithelium, predisposing to infection, inflammation and potential pulmonary complications. The elevated levels of cytokines in periodontitis patients, particularly IL-6, has the potential to directly increase the risk for COVID-19 pulmonary complications. Changes in the lung tissues can constitute an indirect pathway through which periodontitis can influence the course of the coronavirus disease.

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