Relationship of COVID-19 pathogenesis for periodontal medicine research. Part II: Periodontal Medicine

Relação da patogênese de COVID-19 para pesquisa de medicina periodontal. Parte II: Medicina Periodontal

Relación de la patogénesis de COVID-19 para la investigación en medicina periodontal. Parte II: Medicina Periodontal

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Abstract
The dysfunctional immunoinflammatory response to SARS-CoV-2 infection leads to excessive infiltration of monocytes, macrophages and T cells, non-neutralizing antibody, systemic cytokine storm, microthrombi mediated by tissue factor and oxidative stress, lower platelet counts, increased D-dimer, C-reactive protein and coagulation abnormalities, increased vascular permeability, pulmonary edema and pneumonia, and widespread inflammation and multi-organ damage. Periodontal diseases have a chronic and multifactorial inflammatory profile, of infectious origin, with bidirectional systemic interactions linked to over 50 systemic conditions/diseases. Immunoinflammatory response of periodontal tissues to the microbial challenge, protective/repair response and the local destruction of periodontium influence and are influenced by systemic conditions/diseases. Renin-angiotensin system/ACE inhibitors are also related to pathogenesis of COVID-19 by SARS-CoV-2-ACE2 and to pathogenesis of periodontitis, through bone resorption regulated by the ACE2/Ang-(1-7)/MasR axis and IL1-β, positive regulation of the kinin/receptor pathway B2 due to Toll-like receptor 2 inflammation and Th1/Th17 responses, the expression of the type 1 angiotensin II receptor in the inflamed gingival tissue, and modulating IL-1β-induced IL-6 production in human gingival fibroblasts. It is possible that SARS-CoV-2 infection increases local inflammatory events in periodontal tissue leading to destruction of periodontal tissues, probably enhanced by the systemic effects of periodontitis. Despite limited or non-existent scientific evidence on the effects of COVID-19 on periodontal diseases and their systemic interactions to date, it is possible to expect its impact on periodontal medicine research from the natural history of periodontal diseases to their pathogenesis and relationship with systemic conditions and response to treatment, as an environmental and acquired risk factor.
Keywords: Coronavirus infections; Pathogenesis; Periodontics.

Resumo
A resposta imunoinflamatória à infecção por SARS-CoV-2 leva à infiltração excessiva de monócitos, macrófagos e células T, anticorpo não neutralizante, tempestade de citocinas sistêmica, microtrombos mediados por fator de tecido e

estresse oxidativo, contagem de plaquetas mais baixa, dímero D, aumentado proteína C reativa e anormalidades de coagulação, aumento da permeabilidade vascular, edema pulmonar, pneumonia, inflamação generalizada e danos a múltiplos órgãos. As doenças periodontais apresentam um perfil inflamatório crônico e multifatorial, de origem infecciosa, com interações sistêmicas vinculadas a mais de 50 condições sistêmicas. A resposta imunoinflamatória dos tecidos periodontais ao desafio microbiano, a resposta de proteção e a destruição local do periodonto influenciam e são influenciadas por condições sistêmicas. O sistema renina-angiotensina/inibidores da ECA também estão relacionados à patogênese do COVID-19 pelo SARS-CoV-2-ACE2 e à patogênese da periodontite, por meio da reabsorção óssea regulada pelo eixo ACE2/Ang (1-7) / MasR e IL1 - β, regulação positiva da via do receptor de quinina/B2 devido à inflamação do receptor Toll-like 2 e respostas Th1/Th17, expressão do receptor de angiotensina II tipo 1 em tecido gengival inflamado e modulação induzida por IL-1β 6 produção em fibroblastos gengivais humanos. É possível que a infecção por SARS-CoV-2 aumente os eventos inflamatórios locais no tecido periodontal, levando à destruição dos tecidos periodontais, provavelmente potencializado pelos efeitos sistêmicos da periodontite. Apesar das evidências científicas limitadas ou inexistentes sobre os efeitos do COVID-19 nas doenças periodontais e suas interações sistêmicas até o momento, é possível esperar seu impacto na pesquisa da medicina periodontal.

Palavras-chave: Infecção por Coronavírus; Patogênese; Periodontia.

Resumen

La respuesta inmunoinflamatoria a la infección por SARS-CoV-2 conduce a una infiltración excesiva de monocitos, macrófagos y células T, anticuerpos no neutralizantes, tormenta de citocinas sistémicas, menor recuento de plaquetas, aumento del dímero D, Proteína C reactiva y anomalías en la coagulación, aumento de la permeabilidad vascular, edema pulmonar, inflamación generalizada y daño multiorgánico. Las enfermedades periodontales tienen un perfil inflamatorio crónico, de origen infeccioso, con interacciones sistémicas vinculadas a más de 50 afecciones sistémicas. La respuesta inmunoinflamatoria de los tejidos periodontales al desafío microbiano, la respuesta protectora y la destrucción local de la influencia del periodonto están influenciadas por condiciones sistémicas. Los inhibidores del sistema renina-angiotensina/ECA también están relacionados con la patogenia de COVID-19 por SARS-CoV-2-ACE2 y con la patogénesis de la periodontitis, a través de la resorción ósea regulada por el eje ACE2/Ang- (1-7)/MasR e IL1 - β, regulación positiva de la vía cinina / receptor B2 debido a la inflamación del receptor 2 tipo Toll y respuestas Th1/Th17, la expresión del receptor de angiotensina II tipo 1 en el tejido gingival inflamado y la modulación de IL-1β inducida por IL- 6 producción en fibroblastos gingivales humanos. Es posible que la infección por SARS-CoV-2 aumente los eventos inflamatorios locales en el tejido periodontal que conducen a la destrucción de los tejidos periodontales. Apesar de la evidencia científica limitada o inexistente sobre los efectos del COVID-19 en las enfermedades periodontales y sus interacciones sistémicas hasta la fecha, es posible esperar su impacto en la investigación de la medicina periodontal.

Palabras clave: Infecciones por Coronavirus; Pathogenesis; Periodoncia.

1. Introduction

SARS-CoV-2 infection appears to directly affect tissues and organs by exposure and presence of the angiotensin-converting enzyme 2 (ACE2) ectoenzyme and cellular proteases (Bertram et al., 2011, Glowacka et al., 2011, Raj et al., 2013, Wang et al., 2013, Gheblawi et al., 2020, Gralinski & Menachery, 2020, Hoffmann et al., 2020, Wan, Shang, Graham, Baric & Li, 2020, Zhou et al., 2020). The lungs are the most affected organs and the clinical evolution of severe forms of COVID-19 leads to abnormalities in the blood hematological and biochemical index, and systemic conditions/diseases on kidney, liver and coagulation biomarkers (Tay, Poh, Rénia, MacAry & Ng, 2020, Pedersen & Ho, 2020, Schett, Sticherling & Neurath, 2020, Zhang et al., 2020). The pathogenesis of COVID-19 and its systemic impacts are associated with intense pro-inflammatory events and loss of homeostasis, associated with a hyperinflammatory state, secondary bacterial infections, bacteremia, endotoxemia, loss of function and multiple organ failure (Cao & Li, 2020, Chen et al., 2020, Hadjadj et al., 2020, Henry, de Oliveira, Benoit, Plebani & Lippi, 2020, Huang et al., 2020, Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020, Merad & Martin, 2020, Qin et al., 2020, Wang, Jiang, Chen & Montaner, 2020, Wu et al., 2020, Ye, Wang & Mao, 2020, Zhou et al., 2020, García-Sastre, 2017, Schulert & Grom, 2015, Mayer-Barber et al., 2014). The systemic impacts of the COVID-19 have the potential to influence the relationships and interactions between periodontal diseases and systemic conditions/diseases, previously reported in the literature. In addition, the periodontal medicine research, the natural history of periodontal disease and the response to periodontal therapy during and after the COVID-19 pandemic may be affected by the disease.

This paper is a continuation of Part 1, in which the authors summarize and describe the immunoinflammatory and

clinical impacts of SARS-CoV-2 infection shared or correlated with systemic interactions of periodontal diseases. Two illustrations describe the immunoinflammatory response in COVID-19 disease and the COVID-19 multifactorial pathogenesis potentially associated with the pathogenesis of periodontal diseases and their bidirectional systemic interactions. Therefore, the aim of this study was to review the literature and propose a conceptual hypothesis on the subject, based on the interception between the pathogenesis of COVID-19 and its main systemic repercussions, and periodontal medicine.

2. Methodology

Theoretical essay based on studies on the pathogenesis of COVID-19, potentially related to systemic interactions of periodontal diseases. Searches were performed in the MEDLINE|PubMed, Scopus, Embase, Web of Science, Cochrane Library, and BIREME|bvs databases for articles published up to 2020 December 20, using MeSH terms, Emtree terms and DeCS/MeSH terms related to 'COVID-19', 'SARS-CoV-2', and 'pathogenesis', combined by the Boolean operators "OR" and "AND". The studies, mostly experimental and review, published in the main journals, were qualitatively summarized. The comparison of these findings with the main systemic interactions of periodontal diseases previously described resulted in conceptual hypotheses based on the literature about the potential impacts of the COVID-19 pandemic on the scientific investigation of these interactions.

3. Results and Discussion

Hyperinflammatory state in COVID-19

Increased C-reactive protein, ferritin and D-dimer (inflammatory markers) in the blood, the proportion of neutrophils/lymphocytes (Cao & Li, 2020, Henry, de Oliveira, Benoit, Plebani & Lippi, 2020, Wu et al., 2020, Zhou et al., 2020) and serum levels of inflammatory cytokines and chemokines (Chen et al., 2020, Ye, Wang & Mao, 2020, Huang et al., 2020, Qin et al., 2020, Wang, Jiang, Chen & Montaner, 2020) are associated with greater severity and death from COVID-19. There are similarities between the increased profile of cytokines in the macrophage activation syndrome and that observed in COVID-19: increase in IL-6, IL-7, the soluble form of the α-chain of the IL-2 receptor, TNF, inflammatory chemokines such as CC-chemokine 2 (CCL2), CCL3 and CXC-chemokine 10 ligand (CXCL10) (Merad & Martin, 2020).

Some studies suggest that unregulated activation of mononuclear phagocytes contributes to the hyperinflammatory state of patients with COVID-19 (Schulert & Grom, 2015, Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020). Patients who died with COVID-19 showed high levels of lymphocytic apoptosis in the spleen and lymph nodes related to increased expression of the death receptor FAS (cell death induced by activation). The recognition of antigens and high levels of IL-6, mediated by macrophages, may be associated with lymphopenia (Merad & Martin, 2020, Haigh et al., 2020).

Monocytes represent 80 % of the total cells present in the bronchoalveolar fluid of patients with COVID-19, enriched in CCL2 and CCL7 [chemokines for recruiting CC-chemokine receptor 2-positive (CCR2^{+}) monocytes]. Monocyte chemotaxis and cell count increase with disease severity; tissue-resident macrophages are depleted and there is a significant increase in monocyte-derived macrophages (Azkur et al., 2020). The bronchoalveolar fluid of patients with mild COVID-19 has clonal expansion of subsets of CD8^{+} T cells (signature of the T cell gene with memory residing in the tissue) and minimal inflammatory monocyte infiltration. These characteristics seem to be associated with better control of viral load, less tissue damage and systemic complications mediated by inflammation. Severe cases of COVID-19 in ICUs show a significant increase in CD14^{+}CD16^{+} monocytes producing IL-6 in the peripheral blood (Chu et al., 2020, Alzaid et al., 2020, Bouadma et al., 2020). COVID-19 leads to populations of subcapsular and splenic macrophages in the marginal zone of the CD169^{+} lymph node (tissue post-mortem immunostaining), by the expression of the ACE2 or CD147 receptor (Haigh et al., 2020, Helal et al., 2020). IL6^{+} macrophages with endocytosed viral particles were associated with depletion of spleen and lymph node lymphocytes (Hadjadj

et al., 2020). CD68^{+}NP^{+} macrophages and monocytes have been associated with acute renal tubular injury in patients with COVID-19 (Mehta, McAuley, Brown, Sanchez, Tattersall & Manson, 2020). Lung damage (focal necrosis and lymphocytic and monocytic infiltration), spleen (necrosis), heart, liver and muscles, caused by COVID-19, were also observed. SARS-CoV-2 infection leads to high levels of IFN-γ, IL-1β, IL-6, IL-10, IL-12, TGFβ, CCL2, CXCL10, CXCL9 and IL-8, in addition to hyperinflammatory macrophages in the lungs of those killed by COVID-19. In view of the blocking of the production of type I interferon in coronavirus-infected cells (García-Sastre, 2017), the hyperinflammatory responses of COVID-19 (Hadjadj et al., 2020) may be associated with the activation of the inflammasome (Merad & Martin, 2020, Mayer-Barber et al., 2014).

Pulmonary epithelial cells secrete IL6, MCP1, IP-10, MIP1β and MIP1α that stimulate T cells, monocytes and macrophages, which in turn increase IFN-γ levels, establishing positive feedback that sustains the hyperinflammatory state. If the cellular response mediated by CD4^{+} and CD8^{+} T cells is efficient, the alveolar macrophages recognize and phagocytize the apoptotic cell (no virus release), and the alveolar macrophages eliminate the virus neutralized by the antibodies. However, the evolution of the infection results in cytokine storms (IL-6, IP-10, IFN-γ, IL-2, IL-10, G-CSF, MIP1α and TNF) and leakage caused by vascular permeability, with non-neutralizing antibody. The dysfunctional immune response leads to excessive infiltration of monocytes, macrophages and T cells, systemic cytokine storm, pulmonary edema and pneumonia, and widespread inflammation and multi-organ damage (Tay, Poh, Rénia, MacAry & Ng, 2020). Li et al. (2020) observed typical clinical manifestations of shock in critically ill COVID-19 patients and described it as a viral sepsis.

Lower platelet counts, increased D-dimer (fibrin degradation product) and coagulation abnormalities are associated with organ failure and death in patients with severe COVID-19 (Xiang-Hua et al., 2010, Helms et al., 2020, Tang, Bai, Chen, Gong, Li & Sun, 2020). Many of these patients have microthrombi in the lungs, lower limbs, hands, brain, heart, liver and kidneys (Liu, Blet, Smyth & Li, 2020, Zhang et al., 2020). The cytokine storm can activate intravascular coagulation and lead to organ damage and sepsis, (Levi & van der Poll, 2010) mediated by the expression of the TF pathway (or CD142 or coagulation factor III) (Simmons & Pittet, 2015, Iba, Levy, Raj & Warkentin, 2019). Mononuclear cells and vascular endothelial cells express TF in response to pro-inflammatory cytokines (especially IL-6), capable of transforming prothrombin into thrombin, which in turn converts circulating fibrinogen into fibrin (van der Poll, van de Veerdonk, Scicluna & Netea, 2017). Antithrombin and the TF pathway inhibitor (natural anticoagulants) can be impaired during inflammation. Coagulation can start with vascular injury or with the recruitment of TF-expressing inflammatory monocytes by activated endothelial cells (von Brühl et al., 2012). In SARS-CoV infection, oxidized phospholipids present in the lungs as a result of oxidative stress increase TF expression, monocyte recruitment and activation of endothelial cells and macrophages via the TLR4–TRIF–TRAF6–NF-κB pathway (Merad & Martin, 2020, Berliner, Leitinger & Tsimikas, 2009, Imai et al., 2008, Owens et al., 2012).

During neutrophil and monocyte/macrophage response in severe stage of COVID-19, T cells activated by SARS-CoV-2^{+} antigen presenting cells lead to an increase in IL-6 and GM-CSF and the accumulation of hyaline membrane in the bronchi. IL-1 and TNF are also elevated in the lung during acute respiratory distress syndrome and both induce HA-synthase-2 in CD31^{+} endothelial cells, responsible for the production of hyaluranonan. In addition to local tissue damage by the hyperinflammatory response, the accumulation of hyaluronan contributes to the reduction of oxygen saturation, as it absorbs water up to 1,000 times its molecular weight (Shi et al., 2020).

Rao et al. (2020) described the role of mesenchymal stem cells as bridge catalysts between innate and adaptive immunity in COVID-19. The reduction of the immune response in the early infectious phase of COVID-19, marked by IL-10 and TNF-β, exerts positive feedback on mesenchymal stem cells, resulting in: i) increased mobilization, proliferation and activation of T cells; ii) increased activity of cytotoxic T cells; iii) IFN-γ and negative regulation of nitric oxide and enzyme indoleamine 2, 3-dioxygenase, resulting in the activation of M1 macrophages, regulation of NK cell activity and production of IFN-γ based on the

type of stimulus, and; iv) upregulation of T regulatory cells and TGF-β production. This positive feedback results in the up regulation of immune system with increase in production of proinflammatory cytokines. The increase in pro-inflammatory cytokines, such as IL-6, TGF-α and IFN-γ, leads to negative feedback from mesenchymal stem cells. In this case, the following occurs: i) decrease the activity of regulatory T cells and reduce TGF-β; ii) secretion of soluble factors such as nitric oxide, enzyme indoleamine 2, 3-dioxigenase, TGF-β, prostaglandin E2 (PGE_2), human leukocyte antigens (HLA) and soluble IL-6, resulting in regulation of NK cell activity and production of IFN-γ based in the type of stimulus, inhibition of the dendritic cell, leading to decreased TNF-α and decreased presentation of antigens, and decreased chemotaxis and increased neutrophil mobilization; iii) decreased TH1 cell lines and decreased T cell activation; iv) decreased activity of cytotoxic T cells. This negative feedback results in the downregulation of excessive immune response, decrease in pro-inflammatory cytokines, increased tissue regeneration and repair.

The immunological profile of patients with moderate and severe COVID-19 shows an overall increase in innate cell lines and a concomitant reduction in T cell counts, early and elevated pro-inflammatory cytokines and an increase in chemokines and growth factors; the latter was correlated with a better course of the disease. In the most severe cases, type 1 (antiviral) and type 3 (antifungal) responses remain elevated throughout the disease. In addition to multiple type 2 effectors (anthelmintics), such as IL-5, IL-13, IgE and eosinophils. Early immune signatures and abnormal immune responses influence the trajectory of COVID-19 (Lucas et al., 2020).

The immunoinflammatory events involved with the pathogenesis of COVID-19 are compiled in Figure 1:

Figure 1: Immunoinflammatory response in COVID-19 disease.
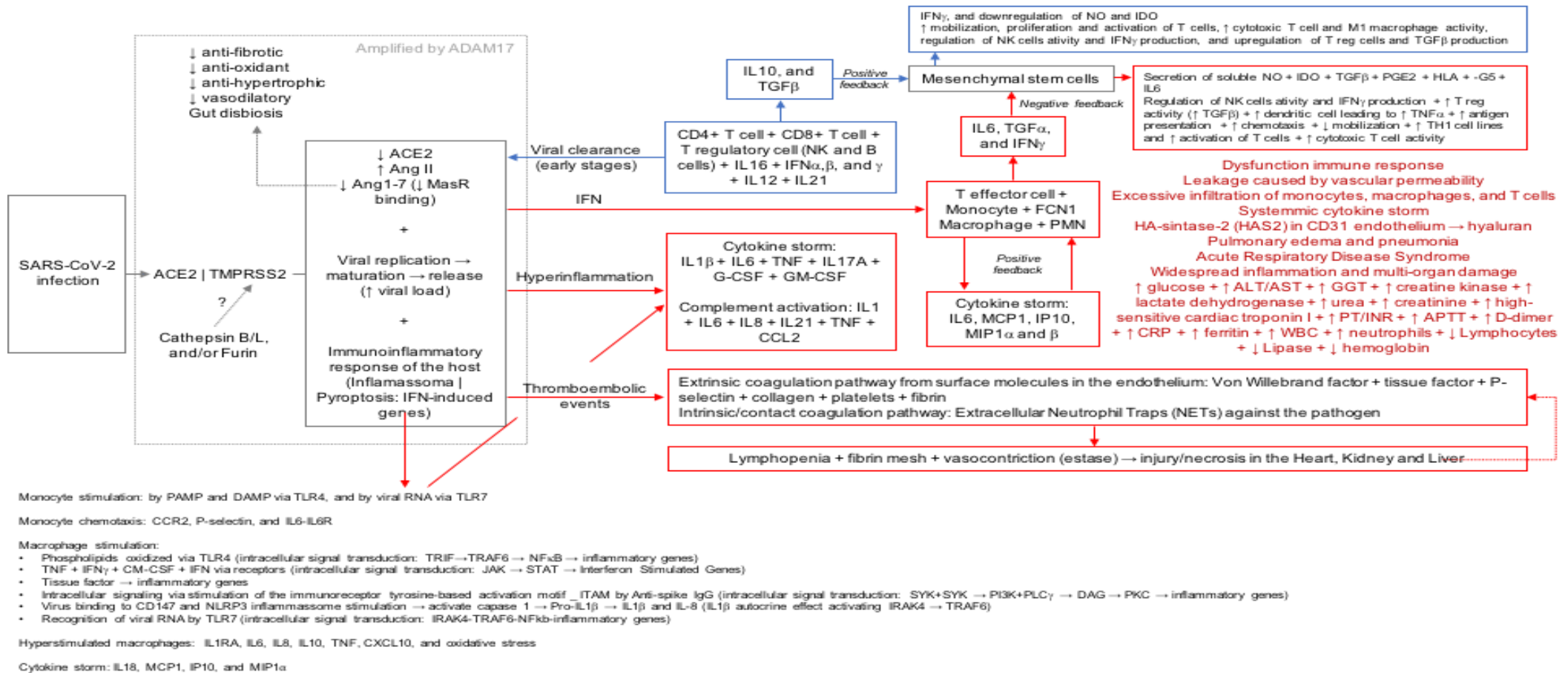
Source: Authors.

SARS-CoV-2 infection and periodontal medicine research

Considering all that has been exposed the pathogenesis of COVID-19 may directly influence the natural history of periodontal diseases, response to periodontal therapy, and the investigation of the causal and bidirectional relationships between periodontitis and systemic diseases. Even the diagnosis and classification of periodontal and peri-implant diseases and conditions can be influenced by SARS-CoV-2 infection and the development of COVID-19. Given the complexity of the pathogenesis of COVID-19 and the uncertainties of its effects on patients, perhaps SARS-CoV-2 infection in its different clinical manifestations (e.g. asymptomatic, mild and severe cases) should represent an exclusion criterion in certain studies of periodontal medicine.

For Page and Kornman (1997), "Antigens and various other virulence factors, and in some cases invading bacteria, comprise the microbial challenge, and the host responds with an immediate inflammatory and immune response that can influence the challenge. The host response results in production of cytokines, eicosanoids, other inflammatory mediators such as the kinins, complement activation products and matrix metalloproteinases, which perpetuate the response and mediate connective tissue and bone destruction. All of these events are influenced by disease modifiers, both genetic and environmental or acquired." Through a microbial challenge, antigens, lipopolysaccharides and other virulence factors stimulate the host's immune-inflammatory response, and then polymorphonuclear cells and antibodies fight microorganisms while cytokines and prostanoids and matrix metalloproteinases act on connective tissue and metabolism bone, resulting in clinical signs of disease initiation and progression. Genetic risk factors and environmental and acquired risk factors influence this process. Considering this non-linear or multifactorial model of the pathogenesis of periodontal diseases, the SARS-CoV-2 infection and social isolation may represent acquired risk factors for periodontal diseases and/or its association with systemic diseases (Kornman, 2008).

Social isolation must compromise the treatment and supportive periodontal therapy of patients with periodontitis. Likewise, patients with chronic non-communicable diseases, for example, should also stop treatment and follow-up. In this context, the bidirectional relationship between periodontitis and systemic diseases, such as diabetes mellitus and cardiovascular diseases, suggests a critical situation during the COVID-19 pandemic (Grasselli et al., 2020). The immunoinflammatory and infectious component, as well as the impairment of homeostasis between the systems, observed in these diseases, offer an even greater risk for these patients to develop severe forms of COVID-19. In addition, the pathogenic profile of oral bacteria associated with periodontitis also poses a risk of systemic infectious complications, both due to aspiration and bacteremia.

Given the intensity of the effects of COVID-19 in different host systems, it is possible that the relationships between periodontal diseases and systemic diseases, investigated in periodontal medicine, are modified or amplified (Figure 2). Despite scientific evidence about the infectious nature of periodontitis, bacteria can be considered essential, but not sufficient, for the clinical evolution of the disease (Page, Offenbacher, Schroeder, Seymour & Kornman, 1997).

Although there are still no studies on the interaction between SARS-CoV-2 infection and periodontal tissues, the pathogenesis of COVID-19 has numerous factors directly related to the biological plausibility of the bi-directional relationships investigated in periodontal medicine. The interpretation of serum levels of pro-inflammatory cytokines and C-reactive protein in patients with periodontitis and systemic diseases should be changed by COVID-19. Likewise, the loss of homeostasis and the impairment of tissues and organs diagnosed also by specific biomarkers in the blood may compromise the causality studies between periodontitis and systemic diseases.

In addition, the treatment of COVID-19 should be considered an important modifying factor in the systemic immunoinflammatory profile of these patients. Different protocols and therapeutic drugs have been used worldwide in the treatment of COVID-19 and may also vary according to the severity of each case. Antibiotics, antivirals, chloroquine/hydroxychloroquine, ivermectin, anti-inflammatories, glucocorticoids, anticoagulants, immunomodulatory drugs and convalescent plasma transfusion have been widely used. Patients recovering from COVID-19 may have systemic

abnormalities or sequelae caused by the disease or related to treatment, for a period not yet known. Gut dysbiosis was also observed in patients with COVID-19, and associated with ACE2 imbalance (Viana, Nunes & Reis, 2020). The relationship between the renin-angiotensin system/ACE inhibitors and periodontitis can occur through bone resorption regulated by the ACE2/Ang-(1-7)/MasR axis and IL1-β, positive regulation of the kinin/receptor pathway B2 (B2R) due to TLR2 inflammation and Th1/Th17 responses, (Hollá et al., 2001, Gürkan et al., 2009, Santos et al., 2009, Santos et al., 2015, Rodrigues et al., 2016) but also by the expression of the type 1 angiotensin II receptor (AT1R) in the inflamed gingival tissue, modulating IL-1β-induced IL-6 production in human gingival fibroblasts (Nakamura et al., 2011).

Figure 2: COVID-19 multifactorial pathogenesis potentially associated with the pathogenesis of periodontal diseases and their bidirectional systemic interactions.
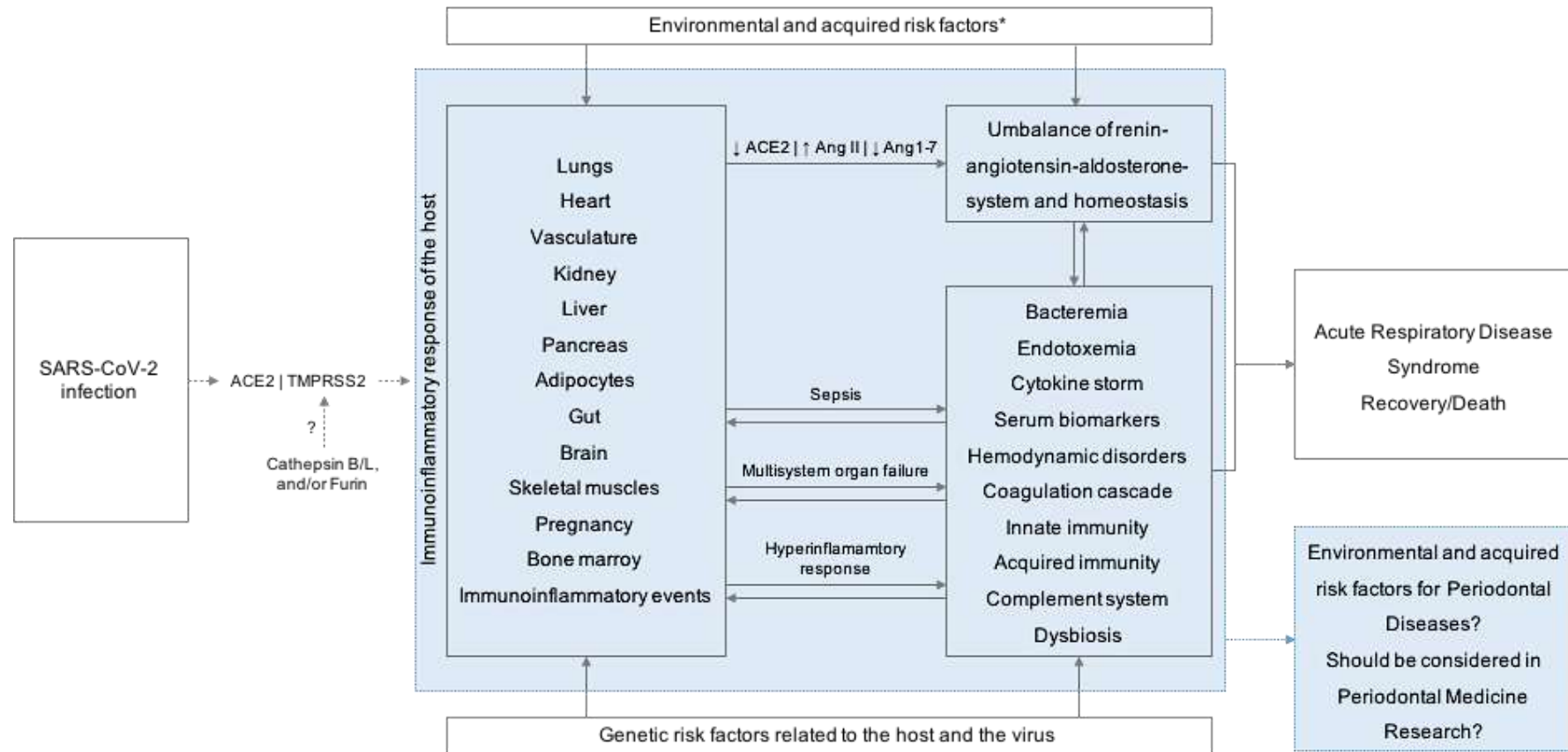
Environment risk factors (e.g., environmental exposure, wild animals, climate, social and physical contact, etc.), and acquired (e.g.,age, smoking, commorbidities, glucocosticoids, etc.).

Source: Authors.

If the effects of SARS-CoV-2 infection or the COVID-19 disease on periodontal tissues are confirmed, this condition may be classified as "Periodontal manifestations of systemic diseases and acquired and developmental conditions - Systemic disorders that have a major impact on the loss of periodontal tissues by influencing the periodontal inflammation" (Jepsen et al., 2018). The new classification for periodontal and peri-implant diseases and conditions considers C-reactive protein as an important biomarker in the diagnosis of periodontitis. However, COVID-19 increases serum levels of C-reactive protein, which can remain high in cases of liver damage or other pathologies. In addition, cytokines such as IL-1β, IL-2, IL-6, IL-7, IP-10, G-CSF, IFN-α, IFN-β, IFN-γ, MCP-1, MIP-1A and TNFα, as well as chemokines (IL-8 and CCL2) and the activation of endothelial adhesion molecules (intracellular adhesion molecule-1 (ICAM-1) and TF) increased in COVID-19 (Huang et al., 2020, Channappanavar & Perlman, 2017). Pyroptosis, lymphopenia, neutrophilic infiltration in tissues, increased neutrophil/lymphocyte ratio and recruitment of hyperactive monocytes/macrophages contribute to a hyperinflammatory response and local tissue damage.

Epidemiological and experimental studies have linked periodontitis to the development or exacerbation of other chronic inflammatory diseases. This relationship was attributed to the patient's systemic inflammatory state, with consequences distal to oral inflammation resulting from bacteremia and endotoxemia (bacterial lipopolysaccharides), increased pro-inflammatory mediators IL-1β e IL-6, IL-17, IFN-γ, TNF-α, GM-CSF, acute phase proteins, such as C-reactive protein, haptoglobin, fibrinogen, serum amyloid A, and serum amyloid P. A prolonged or excessive acute phase response is associated with sepsis and reperfusion injuries. Like COVID-19, activated monocytes, $CD4^+$ T, Th2/B and Th17 cells, aberrant immune responses, neutrophil-mediated hyperinflammation (NETs), complementary factors and inflammatory mediators (IL-1β, IL-6, IL-17, IFN-γ, TNF-α, GM-CSF, PGE_2, thymic stromal lymphopoietin (TSLP), short chain fatty acids and nitrite) increased in the blood by host factors and microbial factors in periodontitis can result in hematopoiesis alterations of the dysfunction endothelial by cytokines or neuronal stimulus, altered immune cell trafficking, reactive microglia, altered immune cell function, altered vascular tone, altered myelopoiesis and trained monocytes. Atherosclerosis, Alzheimer's disease, stroke, obesity, lung infections, rheumatoid arthritis, inflammatory bowel disease, colon cancer, pregnancy complications and diabetes are related to the distal effects of inflammatory mediators, bacteria or antigens that can enter the bloodstream in patients with periodontitis (Van Dyke, 2008, Van Dyke & Kornman, 2008, Cekici, Kantarci, Hasturk & Van Dyke, 2014, Hajishengallis, 2014, Hajishengallis & Sahingur, 2014, Hirschfeld et al., 2015, Meyle & Chapple, 2015, White et al., 2016, Magán-Fernández, O'Valle, Abadía-Molina, Muñoz, Puga-Guil & Mesa, 2019, Konkel , O'Boyle & Krishnan, 2019, Pan, Wang & Chen, 2019).

The alveolar bone loss in periodontitis is also mediated by the host's immunoinflammatory response to a local stimulus, but it can be increased by a systemic inflammatory condition. M-CSF, ligand RANK and osteoprotegerin are responsible for the cell differentiation of monocytes/macrophages in osteoclasts. These cells are activated by TNF-α, IL-1 and PGE_2, mainly in inflammatory osteolysis found in periodontitis. The regulation of the Th1-Th2-Th17 regulatory axis of the adaptive immune response promotes bone loss mediated by macrophages and neutrophils of Th1, B cells that release pro-inflammatory mediators and activate RANK-L expression pathways (Hienz, Paliwal & Ivanovski, 2015, Hajishengallis, Moutsopoulos, Hajishengallis & Chavakis, 2016). Thus, it is possible that the hyperinflammatory state related to the cytokine storm and the systemic complications of COVID-19 potentiate inflammatory events and periodontal tissue destruction, as well as the systemic effects of periodontitis.

Monsarrat et al. (2016) described 57 systemic conditions potentially related to periodontal diseases, in a systematic review of clinical trials from World Health Organization International Clinical Trials Registry Platform. In 2019, Beck et al. published an article entitled "Periodontal Medicine: 100 Years of Progress", based on the 'periodontal medicine' concept proposed by Dr. S. Offenbacher as "[…] a term used to describe how periodontal infection/inflammation may impact extraoral health." The authors reported that "Periodontitis has been linked to over 50 systemic diseases and conditions" with emphasis on

the timeline of cardiovascular disease, diabetes *mellitus*, adverse pregnancy outcomes and biologic mechanisms mediating the systemic effects of periodontitis (Beck, Papapanou, Philips & Offenbacher, 2019). Therefore, given the significant number of interrelationships between periodontal diseases and systemic conditions/diseases established or proposed in the literature, it is very likely that the systemic effects of COVID-19 or SARS-CoV-2 infection will directly or indirectly influence these diseases/conditions.

Changes in the microbial profile,(Dhar & Mohanty, 2020, Gu et al., 2020, Zuo et al., 2020) social isolation, (Magán-Fernández, O'Valle, Abadía-Molina, Muñoz, Puga-Guil & Mesa, 2019, Wilder-Smith & Freedman, 2020) the use of different drugs during the treatment (Jean, Lee & Hsueh, 2020, McKee, Sternberg, Stange, Laufer & Naujokat, 2020, Zhang et al., 2020) and recovery of patients infected with SARS-CoV-2 may also influence the course of periodontal diseases, their responses to treatment and their systemic relationship as a cause or consequence of pathological conditions (Gu et al., 2020, Zuo et al., 2020, Tamburini, Shen, Wu & Clemente, 2016, Acharya, Sahingur & Bajaj, 2017, Blasco-Baque et al., 2017, Lamont, Koo & Hajishengallis, 2018, He et al., 2020, Wong, Lui & Sung, 2020). For the clinical immunologists, the anti-inflammatory treatment of severe COVID-19, including glucocorticoids, IL-6 antagonist, JAK inhibitors and choloroquine/hydrochloroquine can compromise the patient's immune system for other diseases (Zhang et al., 2020). Furthermore, the widespread use of antibiotics during the COVID-19 pandemic can contribute to microbial resistance to these drugs and changes in the microbial configuration in different areas/systems of the individuals (Rawson, Ming, Ahmad, Moore & Holmes, 2020).

4. Final Considerations

Based on the pathogenesis of COVID-19 and its systemic effects, the population infected by SARS-CoV-2, from asymptomatic disease to severe cases of a long period in-hospital patients, represents a challenge to investigate its relationship with periodontal diseases. Besides that, another point represents a new reality in studies in periodontal medicine: Patients previously infected with SARS-CoV-2 and/or who developed COVID-19 represent a bias in studies of the association between periodontal and systemic diseases? What variables directly or indirectly influence these relationships and to what extent? Which diagnostic protocols should be included in the eligibility criteria in periodontal research, mainly in longitudinal studies?

The late effects of COVID-19 and its treatment are not yet known. Perhaps the ideal sample for clinical studies in periodontal medicine research should be patients who have not been infected with asymptomatic SARS-CoV-2 or COVID-19, with no clinical signs and symptoms of the disease, its complications, or use of drugs for its treatment. Previous exposure to SARS-CoV-2 can be assessed by serological tests, regardless of whether or not there is efficient immunity against the virus. However, the diagnosis of COVID-19 and confirmation of infection by SARS-CoV-2 are made by RT-PCR test. Its sensitivity differs between biological samples: 93 % for bronchoalveolar lavage, 72 % for sputum, 63 % for nasal swab, 32 % for oropharyngeal swab, 29 % for feces, 1 % for blood and 0 % for urine (Wang et al., 2020). The time interval for peak viral load levels in COVID-19 is still unknown and the ideal time for diagnosing the infection by RT-PCR has not been established (an average interval of 5 to 7 days) (Xie et al., 2020). The period in which patients remain infectious is not yet fully understood (Zou et al., 2020). Multiple samples for RT-PCR at different times seems to be necessary for the diagnosis of COVID-19 and its monitoring over time, in the case of longitudinal studies in which the disease may represent a confounding variable. We must consider the possibility of assessing previous or current exposure to SARS-CoV-2, drugs used, complementary exams and medical records data in cases of hospitalization for COVID-19 in periodontal researches from now on. Until an effective vaccine is widely distributed to the entire population, RT-PCR tests will be required to screen participants for clinical research and throughout the follow-up period in longitudinal studies.

In the case of investigating the interceptions between the pathogenesis of COVID-19 and periodontal diseases, even during the pandemic, experimental tests can be performed and play a vital role in the discovery of pathogenic mechanisms and

can be applied to investigate the systemic interaction between SARS-CoV-2 infection and periodontal diseases. Due to the genomic similarity of SARS-CoV-2 with SARS-CoV, the experimental models used previously represent alternatives for new studies *in vivo* and *in vitro*: genetically modified hamsters mediated by TALEN or CRISPR, mice (F344), mice and clinical isolates (cell culture) (Shereen, Khan, Kazmi, Bashir & Siddique, 2020).

Recently, Marouf et al. (2021) published a paper on the association between periodontitis and severity of COVID-19 infection. In this case-control study, the authors evaluated 568 patients and reported an odds ratio of 8.81 (95% CI 1.00-77.7), 3.54 (95% CI 1.39-9.05) and 4.57 (95% CI 1.19-17.4) for death, admission to the intensive care unit and the need for assisted ventilation in patients with COVID-19 and periodontities, respectively. This result was significant and adjusted for potential confounders (Marouf et al., 2021).

We should also take into account that the oral cavity is colonized by a large number and variety of micro-organisms, including bacteria, fungi, and viruses (Sultan, Kong, Rizk & Jabra-Rizk, 2018). In addition to host–microbe interactions, we know from the literature that the interfaces of periodontal pathogens with other non-host pathogens, such as herpesviruses like Epstein–Barr virus and cytomegalovirus, can contribute to the pathogenesis of the periodontal disease, or can affect the outcome of viral infection and dissemination (Tonoyan, Vincent-Bugnas, Olivieri & Doglio, 2019).

This theoretical essay supports the conceptual hypothesis that high rate of SARS-CoV-2 contamination or herd immunity should change pre-COVID-19 health status of periodontal patients, due to the direct effects or indirect effects of the virus/disease. Despite limited or non-existent scientific evidence on the effects of COVID-19 on periodontal diseases and their systemic interactions, it is possible to expect its impact on periodontal medicine research from the natural history of periodontal diseases to their pathogenesis and relationship with systemic conditions and response to treatment.

Acknowledgments

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