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COVID-19 and Periodontitis: Associations and Clinical Implications

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Abstract

The COVID-19 pandemic has brought marked changes worldwide to the management of airborne infectious diseases. This sparked the development of the SARS-CoV-2 vaccine and pharmacotherapeutics to increase the survival rate during the acute viral phase and reduce the comorbidities associated with COVID-19. This review aims to evaluate the potential associations between periodontitis and COVID-19. Periodontal disease may increase the morbidity and perhaps the mortality of a COVID-19 infection. Gingival ulcerations induced by periodontal disease may weaken the protective oral epithelium and increase the risk of SARS-CoV-2 invasion. The potential of herpesviruses, especially as it is related to aggressive periodontitis may also be a comorbidity for COVID-19. Periodontitis patients infected with COVID-19 have increased gingival inflammation and abnormal bleeding. Periodontitis may increase COVID-19 biomarkers linked with COVID-19 severity. And COVID-19 may increase periodontitis biomarkers linked with increased probings and attachment loss. Thus, periodontal therapy and oral health maintenance may reduce COVID-19 complications, morbidity, and mortality.

Keywords: COVID-19; SARS-CoV-2; Periodontitis; Herpesviruses; Periodontal; Biomarkers

Inroduction

On March 11, 2020, the World Health Organization declared a global coronavirus disease of 2019 (COVID-19) pandemic [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) initiated the COVID-19 pandemic. When infected individuals speak, sneeze, cough, sing, or breathe, SARS-CoV-2 can spread from their mouth or nose via microscopic droplet particles. COVID-19 complications are more likely in older individuals and those with underlying medical disorders like cancers, diabetes, cardiovascular diseases, or chronic respiratory diseases [2-4]. These comorbidities are also associated with periodontitis [5-9]. Periodontitis is an inflammatory and immune-mediated disease related to bacterial dysbiosis resulting in the loss of periodontal tissue attachment and alveolar bone [10]. It is among the most widespread conditions affecting the oral cavity and continues to be a worldwide health concern. Periodontal disease must be treated quickly since it may impact the patient's general health [10].

The potential pathway for the relationship between periodontal health and systemic health includes periodontitis-associated putative pathogenic oral microbiota, and overexpression of local and systemic pro-inflammatory destructive cytokines [11, 12]. The reactivation of latent systemic herpesviruses may precipitate the onset of aggressive periodontitis [13]. Active human cytomegalovirus has been detected in the deep periodontal

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pockets in localized aggressive periodontitis patients [14]. Several viruses have recently been implicated in potentiating periodontal infections. It is plausible that this herpetic viral coinfection associated with aggressive periodontitis may have an additive effect on COVID-19 severity. The angiotensin-converting enzyme-2 (ACE-2) receptors on the host cell surface promote SARS-CoV-2 entry into the body. Systemic conditions can affect ACE-2 receptor expression. Systemic conditions like hypertension, diabetes, chronic obstructive pulmonary disease (COPD), renal dysfunctions, or hepatic disorders can facilitate viral entrance into host cells.[15] ACE activates the molecular signaling pathways for tissue damage and inflammation [16]. Periodontopathic bacteria can upregulate ACE-2 receptors in human pulmonary epithelial cells.[17] The ACE-2 receptors present in periodontal tissue allow viral entry and circulation to other parts of the body. The oral cavity expresses more ACE-2 receptors compared with the lungs and other parts of the body.[18-20] SARS-CoV-2 found in periodontal tissues and oral biofilm indicated that oral and periodontal environments have a role in COVID-19 infectivity.[21] Additionally, SARS-CoV-2 invasion can be blocked via blocking the ACE-2 receptors and decreasing transmembrane serine protease 2 (TMPRSS2). This may also prevent SARS-CoV-2 infection of the periodontal epithelium. [22]

SARS-CoV-2 must enter the host cells for a person to be vulnerable to it. There are multiple pathways by which SARS-CoV-2 can enter human cells.[23] These pathways involve host cells with SARS-CoV-2 entry molecules. These molecules include ACE-2 receptors, TMPRSS2, and furin. These SARS-CoV-2 entry molecules promote virus entry into host cells and are determinants of COVID-19 infection. [24, 25] SARS-CoV-2 entry molecules are mostly present on the stratified squamous epithelium of the dorsal tongue and gingiva. ACE-2, TMPRSS2, and furin mRNA expression have also been detected in taste bud cells.[26] The ACE-2-positive cells present in the oral tissue are mostly epithelial cells.[26] TMPRSS2 is present in the stratified squamous epithelium of the gingival keratinized surface layer and is also detected in tongue coatings and saliva. Furin is localized mostly in the lower layers of the stratified squamous epithelium and in saliva but not in tongue scrapings.[24, 25] The periodontal sulcular epithelium expresses both ACE-2 receptors and TMPRSS2 and may be an entry point for SARS-CoV-2. The thin sulcular epithelium may also contain microulcerations; which may increase the ease of SARS-CoV-2 entry [27]. Salivary levels of ACE-2 can increase the severity of periodontitis and aggravate alveolar bone loss [28]. ACE-2 receptors are the entry receptor for SARS-CoV [29]. SARS-CoV-2 shares 79.5% genome sequence identity with SARS-CoV. Thus, SARS-CoV-2 and SARS-CoV can enter the host cell via the same receptors [29]. Organ dysfunction caused by SARS-CoV-2, such as acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury, and acute hepatic injury, is common in severe cases. Interestingly, the overall mortality rate associated with SARS-CoV-2 was lower than SARS and MERS [29].

Other coronavirus receptors like aminopeptidase N and dipeptidyl peptidase (DPP4) do not have the same effect as SARS-CoV-2 entry into cells via ACE-2 expressing cells [30]. The binding affinity of the SARS-CoV-2 spike glycoprotein to the ACE-2 receptor is 10–20 fold higher than that of SARS-CoV [30, 31]. The ACE-2 receptor in the cell membrane and the furin cleavage site allowed SARS-CoV-2 to invade the host cells [32-34]. ACE-2 receptor and TMPRSS2 are also expressed in other organs throughout the body, including the heart, lung, pancreas, bladder, kidney, small intestine, and skin [24, 25]. TMPRSS2 is another essential factor that facilitates SARS-COV-2 entry and infectivity. TMPRSS2 is a cofactor to ACE-2 for viral entry via cleavage of viral spike protein. It is a crucial serine protease for SARS-CoV-2 invasion [35]. In an experimentally induced periodontitis model, gene expression analysis study of TMPRSS2 showed increased TMPRSS2 expression in gingiva especially in the keratinocyte cell membrane of periodontitis gingiva [12]. When activated by specific cellular enzymes like furin, SARS-CoV-2 spike protein binds the cell membrane [27]. Furin cleavage of the glycoprotein viral envelop enhances SARS-CoV-2 fusion to the host cell membrane. The furin cleavage site is not present in SARS-CoV. The furin enzyme may only activate specific cleavage sites on the SARS-CoV-2 spike protein [26], and facilitate SARS-CoV-2 cell fusion [36]. Furin expression are present in potential target organs such as the nose, lung, heart, colon, intestine, ileum, and rectum [26]. Among the furin-expressing cells analyzed, epithelial cells make up more than 55% [26]. Sites with active periodontitis have increased furin expression and cathepsin L proteases. This may increase the risk of virus-binding and periodontal tissue infections [37].

Once infected with SARS-CoV-2, an overt inflammatory response ensues. This inflammatory response releases biomarkers, some of which are associated with COVID-19 disease severity. Some inflammatory biomarkers released in COVID-19 are also increased in periodontal disease. COVID-19 and periodontitis may increase common biomarkers that can potentiate the severity of each disease. Certain biomarkers released in periodontitis overlap with COVID-19 biomarkers linked with increased COVID-19 complications and may be involved in increasing COVID-19 morbidity. This review aims to evaluate the current evidence on the associations between periodontitis and COVID-19. This review will also elaborate on the COVID biomarkers associated with periodontal disease progression and the periodontitis biomarkers increased by COVID-19 infections. PubMed, Embase, Web of Science, and Scopus were searched for relevant articles using the keywords “Periodontitis or Periodontal” and “COVID”. Clinical studies, case series and

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case reports on patients diagnosed with COVID-19 were included. Studies comparing patients with periodontitis with patients without periodontitis were included. Conference abstracts, posters, and non-English publications were excluded.

Clinical studies associating periodontitis and COVID-19

Periodontitis can increase COVID-19 complications and the risk of mortality (Table 1). COVID-19 infection can aggravate periodontal disease (Table 2). Research studies (Tables 1 and 2) in the form of prospective studies, retrospective studies, cross-sectional studies, longitudinal studies, case-control studies, case series, and case reports suggests a potential bidirectional relationship. The statistical significance and the risk of morbidity and mortality were reported in these studies.

Table 1: Periodontitis associated with COVID-19 severity.

Study	Type	Study period	Location	Aim	COVID-19 patients	Comorbidities	Blood parameters	No. of patients	Periodontal diagnosis	Statistical significance	Conclusion
Alnomay et al. 2022 [38]	Retrospective cohort study	Jan 2020-Jul 2021	Saudi Arabia	To investigate the association between periodontitis and COVID-19 severity in the central region of Saudi Arabia	COVID-19 with periodontitis COVID-19 without periodontitis	Diabetes, hypertension, obesity and other comorbidities including respiratory disorders, endocrine disorders, cardiovascular disorders, cancer, kidney dialysis or organ transplant	C- reactive protein (CRP)	COVID patients: 188 Periodontitis: 99 No periodontitis: 89	Periodontitis	Periodontitis associated with covid-19 complications: Statistically significant	Periodontitis is significantly associated with a higher risk of developing COVID-19 complications, including the need for assisted ventilation, ICU admission, and death
Cobas et al. 2022 [44]	Descriptive cross-sectional study	Mar 11, 2020- Mar 11, 2021	Cuba	To determine the relationship between self-reported periodontal disease, dental loss and COVID-19 activity	Patients infected with COVID-19 and survived	Hypertension, diabetes mellitus, heart disease, chronic respiratory disease, and morbid obesity	-	COVID infected and survived patients: 238	Periodontal disease and advanced periodontal disease (self-reported)	Periodontal disease and advanced periodontal disease associated with the severity of COVID-19: Not statistically significant	Periodontal disease and the severity of COVID-19 cannot be established
Costa et al. 2022 [40]	Short-term prospective study	Aug 2020-Mar 2021	Brazil	To assess the oral health conditions in COVID-19 patients and determine the association between oral health and disease outcomes, including the incidence of severe/critical symptoms, ICU admission	Hospitalized, infected COVID-19 patients with at least one typical COVID-19 symptoms	Hypertension, obesity, diabetes, Chronic obstructive pulmonary disease (COPD), asthma, cardiovascular diseases (CVD), liver diseases, cancer, osteoporosis, thyroid disease, arthritis, human immunodeficiency virus (HIV) or other sexually transmitted disease (STD)	-	128 patients	Periodontitis	Periodontitis and ICU admission, severe critical symptoms and invasive ventilation: Statistically significant	Periodontitis was associated with a higher occurrence of critical COVID-19 symptoms and the need for intensive medical care and death, even when adjusted for age and presence of comorbidities

Gupta et al. 2021 [41]	Cross-sectional analytical study	15 Jan 2021- 20 Feb 2021	India	To assess the association of periodontal health on the complications of COVID-19	COVID-19 patients	Diabetes, hypertension, pulmonary disease, chronic kidney disease, cancer, coronary artery disease, obesity and any other comorbidities	CRP, D-dimer, platelet count, ferritin, glycosylated hemoglobin (HbA1c), haemoglobin (Hb), vitamin D3, neutrophil/ lymphocyte ratio (N/L), troponin, procalcitonin and N-terminal-pro-brain natriuretic peptide (NT-proBNP)	82 patients	Stages of periodontitis I- IV	Stages of periodontitis and eventual survival, hospital admission, oxygen requirement, COVID-19 pneumonia, D-dimer, troponin and pro-BNP: Statistically significant	There is a direct association between periodontal disease and COVID-19-related outcomes
Larvin et al. 2020 [47]	National, longitudinal cohort study	Study recruitment: 2006- 2010 Data extraction: till August 2020	UK	To quantify the impact of periodontal disease on COVID-19 infection and related outcomes utilizing the UK Biobank data	COVID-19 tested participants with self-reported history of periodontal disease COVID-19 tested participants with no self-reported history of periodontal disease	Cancer, hypertension, angina, cardiac arrest, diabetes, myocardial infarction, stroke, peripheral artery disease, atrial fibrillation, respiratory disease	Systolic and diastolic blood pressure and resting heart rate, biomarkers	13,253 patients	Painful/ bleeding gums and loose teeth	Painful/ bleeding gums and mortality for participants with COVID-19 infection: Suggestive of risk (OR= 1.71)	There was a suggestive risk of mortality for COVID-19 positive participants with periodontal disease
Larvin et al. 2021 [46]	National, longitudinal cohort study	Study recruitment: 2006- 2010 Data extraction: till August 2020	UK	To examine the impact of periodontal disease in obesity on COVID-19 infection and associated outcomes	Participants with records of COVID-19 test result and oral health status and body mass index (BMI) ≥18.5 kg/m^2	Cancer, CVD, diabetes, hypertension, inflammatory disease and respiratory disease	Systolic and diastolic blood pressure and CRP	58,897 patients	Periodontal disease	The COVID-19 infection in individuals with periodontal disease in participants who were overweight: Suggestive of risk (OR= 1.21) The COVID-19 infection in individuals with periodontal disease in participants who were obese: Suggestive of risk (OR= 1.37)	Periodontal disease may exacerbate the effect of obesity on hospitalization and mortality following COVID-19 infection
Guardado-Luevanos I et al. 2022 [100]	Blinded case-control study	Dec 2020- Jan 2021	Mexico	To measure periodontal status through a previously validated test in individuals who were tested for SARS-CoV-2 infection	COVID-19 positive COVID-19 negative patients	-	-	COVID positive: 117 COVID negative: 117	Periodontal disease	Periodontal disease and SARS-CoV-2 positive individuals: Medium risk (OR= 3.3)	Self-reported periodontal disease can be an adjuvant marker to assume the risk of SARS-CoV-2 infection These individuals present more symptoms at the onset of the disease

Marouf et al. 2021[45]	Case-control study	27 Feb 2020- 31 Jul 2020	Qatar	To estimate the extent to which periodontitis is associated with COVID-19 complications	COVID-19 positive patients with and without complications	Diabetes and comorbidities	HbA1C, Vit-D, lymphocyte, D-dimer, CRP, white blood cells (WBC)	COVID-19 patients with complications: 40 (cases) COVID-19 patients without complications: 528 (controls)	Periodontitis	Periodontitis and risk of having COVID-19 complications: Medium risk (OR= 6.34) Periodontitis and risk of having eventual death: High risk (OR=17.5) Periodontitis and risk of having ICU admission: Medium risk (OR= 5.57) Periodontitis and risk of needing assisted ventilation: Medium risk (OR=7.31)	Periodontitis was significantly associated with a higher risk of complications from COVID-19, including ICU admission, need for assisted ventilation and death Increased blood levels of markers linked with worse COVID-19 outcome were D-dimer, WBC and CRP
Mishra et al. 2022 [43]	Cross-sectional study	Apr 2021- Aug 2021	India	To determine whether an association exists between periodontitis and COVID-19	COVID-19 positive patients	Diabetes and Hypertension	-	294 patients	Stage I-IV periodontitis	Periodontitis and COVID-19 pneumonia: Statistically significant	Periodontitis is associated with severe COVID-19
Said et al. 2022 [39]	Case control study	Mar 1, 2020- Dec 31, 2020	Qatar	To test the hypothesis that a history of periodontal therapy could be associated with lower risk of COVID-19 complications	Patients that experienced COVID-19-related complications such as ICU admission, mechanical ventilation and/or death and COVID-19 patients that recovered without major complications	Asthma, chronic respiratory diseases, chronic heart disease, diabetes, dermatitis, chronic liver disease, autoimmune diseases, solid organ transplant, peptic ulcer, immunosuppressive conditions, cancer, chronic kidney disease, hypertension, cerebrovascular accidents and deep vein thrombosis	D-dimer, CRP, urea, creatinine, ferritin, interleukin-6 (IL-6), HbA1c, vitamin D, WBC and lymphocytes	1325 patients (71 suffered severe COVID-19 complications)	Periodontitis (non-treated and treated)	Non-treated periodontitis and assisted ventilation: Statistically significant Non-treated periodontitis and D-dimer and ferritin: Statistically significant	COVID-19 patients with non-treated periodontitis (stages 2–4) were significantly more likely to need mechanical ventilation Increased blood levels of D-dimer and ferritin in patients with non-treated periodontitis compared to periodontally healthy and treated periodontitis patients could imply that periodontitis increases the risk of COVID-19 complications

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Table 2. Effects of COVID-19 on periodontitis.

Study	Type	Study period	Location	Aim	COVID-19 patients	Comorbidities	No. of patients	Periodontal diagnosis	Results	Conclusion
Anand et al. 2021 [48]	Case control study	Aug 2020-Feb 2021	India	To determine whether periodontitis and poor oral hygiene are associated with COVID-19	COVID-19 patients	Diabetes, hypertension, neoplasia	COVID-19 positive patients: 79 COVID-19 negative patients: 71	Periodontitis	COVID-19 associated with periodontitis severity: Statistically significant COVID-19 and increased gingival inflammation: Statistically significant	SARS-CoV-2 infection may increase the prevalence and severity of periodontitis, as well as increase gingival inflammation, and is associated with poor oral hygiene
Kaur et al. 2022 [42]	Comparative study	Mar-21	India	To assess the correlation of COVID-19 infection and severity of periodontitis in subjects who had a mild form of the disease as compared to subjects having a moderate form of the disease and requiring hospitalization	Moderate COVID-19 patients recovering in COVID ward of the hospital Mild COVID-19 patients recovering at home	Diabetes	COVID-19 (moderate form of COVID) patients in the COVID ward of the hospital: 58 COVID-19 (mild form of COVID) patients at home: 58	Stages 0- 4 periodontal condition	The odds of getting severe periodontal disease were 6.32 times more in subjects with moderate COVID-19 compared to mild COVID-19 Moderate form of COVID-19 and periodontal disease severity: Statistically significant Stages 0-1 periodontal condition: The increase in HbA1C, lymphocyte and CRP of moderate compared to mild COVID-19: Statistically significant Stages 2-4 periodontal condition: The increased in HbA1C, lymphocyte, WBC and CRP of moderate compared to mild COVID-19: Statistically significant	Subjects with moderate form of COVID had more severe periodontitis

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Loukas et al. 2022 [49]	Case report	Jul-20	Netherlands	To present a 38-year-old woman with generalized stage III, grade C periodontitis with a distorted post-operative blood clot formation who tested positive for COVID-19 after periodontal surgery	-	No known prior comorbidities	1	Generalized stage III, grade C periodontitis with an abnormal post-operative blood clot formation	Initial phase: Uneventful 6 months follow-up: periodontal tissues responded favorably Surgical phase (1-4): 1.Upper right sextant: Healing uneventful 2. Lower right sextant: Healing uneventful 3.Upper anterior sextant: Day 1: No complaints (COVID-19 diagnosis) Day 2: Patient reported intraoral bleeding, fever, loss of taste, and abnormal blood clots Day 3: Bleeding noted, further suturing done Day 4: Patient reported no further bleeding 4.Lower left posterior: Healing uneventful 6 months follow-up: Healing uneventful	Abnormal postoperative bleeding tendency was associated with an active phase of COVID-19
Manzalawi et al. 2020 [50]	Case series	Apr 2020-May 2020	Saudi Arabia	Three patients from three different Saudi cities who reported extensive gingival bleeding and pain preceding or coincidental with the confirmation of their COVID-19 infection	COVID-19 patients in hospital quarantine	No medical history	3	Gingival bleeding	The cases reported unprecedented profuse gingival bleeding that was not present before active signs of COVID-19 After COVID-19 infection subsided, gingival bleeding markedly declined	COVID-19 infection is associated with a heightened inflammatory reaction and clinical signs of profuse gingival bleeding

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Periodontitis associated with COVID-19 Severity

Studies (Table 1) reported that periodontitis is significantly associated with COVID-19 complications, the severity of COVID-19 symptoms, the need for assisted ventilation, ICU admissions, and death [38-43]. Furthermore, COVID-19 patients with untreated periodontitis have significantly increased levels of inflammatory biomarkers associated with COVID-19, such as ferritin and D-dimer [39]. Subjects with the moderate form of COVID-19 had more severe periodontitis when compared to those with the mild form of COVID-19 [42]. These collective studies appear to demonstrate a biologic gradient for periodontitis severity and risk for progressive COVID-19. On the contrary, one study reported no statistical significance associated with COVID-19 and periodontitis; this could be attributed to the limitations of self-reported data on periodontal disease [44]. Of significance, COVID-19 patients with periodontitis have a high risk of mortality from COVID-19 and a medium risk of COVID-19 complications, ICU admission, and assisted ventilation [45]. Obese patients with periodontal disease and COVID-19 have a suggestive risk of a higher incidence of hospitalization and mortality [46]. Similarly, COVID-19 patients with loose teeth and bleeding gums also have a suggestive risk of hospitalization and mortality [47].

Effects of COVID-19 on periodontal disease

COVID-19 can aggravate periodontal disease, delay periodontal healing, and hinder response to treatment (Table 2). In a case-control study, COVID-19 infection is significantly associated with more severe periodontitis and gingival inflammation [48]. Furthermore, patients with moderate COVID-19 infection had more severe periodontal disease than those with mild COVID-19 infection [42]. In a case report, a 38 year old woman with generalized periodontitis suffered abnormal postoperative bleeding after contracting COVID-19 after periodontal surgery. This contrasts with her uneventful postoperative visits from previous periodontal surgeries. Therefore, abnormal postoperative bleeding was reported to be associated with an active degree of COVID-19 [49]. In a case series of three systemically healthy patients who contracted COVID-19, these patients experienced gingival bleeding, which was not present before active signs of COVID-19. After the COVID-19 infection subsided, gingival bleeding markedly declined in these patients. This report suggested that gingival bleeding may be attributed to COVID-19 [50].

In a systematic review, SARS-CoV-2 positive patients were found to have desquamative gingivitis (0.9%), necrotizing periodontal disease (1.64%), and oral candidiasis (10.74%) [51]. Necrotizing periodontal disease may be linked to bacterial coinfection in COVID-19 patients. Unusually high bacterial counts of *Prevotella intermedia*, *Streptococci*, *Treponema*, *Fusobacterium*, and *Veillonella* were detected in these COVID-19 patients [52]. COVID-19 patients are prone to *Candida albicans* and *Candida tropicalis* overgrowth [53]. Oral candidiasis may be aggravated by the immunological dysregulation caused by SARS-CoV-2 infection [54]. Oral candidiasis symptoms appear within 30 days after the onset of COVID-19 symptoms [55-57].

Inflammatory biomarkers involved in COVID-19

Inflammatory markers identified in COVID-19 included C-reactive protein (CRP), procalcitonin (PCT), Interleukin-6 (IL-6), cytokines, albumin, serum ferritin, serum amyloid A, cardiac troponin, D-dimer, and renal biomarkers such as creatinine and urea [58-60]. The following are elevated in COVID-19 inflammation and infection: lactose dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), platelet count and leukocyte.

CRP [61], PCT, IL-6 [62], and ESR are inflammatory markers associated with the severity of COVID-19. Biomarkers in COVID-19 can be useful for: (1) early detection of disease; (2) classifying disease severity; (3) hospital admission criteria; (4) identifing high-risk cohort; (5) ICU admission criteria; (6) determination of therapies; (7) assessment of therapies; (8) outcome prediction; and (9) criteria for discharge from the hospital [61]. Interestingly, studies on systemically healthy patients with periodontitis progression also reported the following COVID-19 biomarkers: CRP, D-dimer, ferritin, PCT[62], N-terminal-pro-brain natriuretic peptide (NT-proBNP) [63, 64], and IL-6.

Inflammatory biomarkers linked with periodontitis

Periodontitis induced inflammatory markers consist of serum and salivary biomarkers [65, 66]. Periodontal serum biomarkers include IL-1 [67-69], IL-6, TNF-α, CRP, surfactant protein-D, osteocalcin, oncostatin M, cortisol, albumin matrix metalloproteinases-3 (MMP-3), MMP-8, MMP-9 [70]. Periodontal salivary biomarkers include IL1-beta, IL-6, TNF- α, MMP-8, macrophage inflammatory protein-1 α, tissue inhibitor of metalloproteinases-1 (TIMP-1), lactate dehydrogenase (LDH), receptor activator of nuclear factor kappa-B ligand (RANKL), alanine transaminase (ALT) and aspartate aminotransferase (AST) [71]. These periodontal biomarkers present in COVID-19 infections are also associated with systemic comorbidities [72, 73].

Inflammatory biomarkers associating periodontitis and COVID-19

Periodontitis inflammatory biomarkers (Table 3) found in COVID-19 patients include C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer, and pro-brain natriuretic peptide (Pro-BNP) [62, 63]. Elevation of these

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inflammatory COVID biomarkers may reduce survival and prognosis. It can increase the risk of stroke, acute respiratory disease syndrome (ARDS) and acute kidney injury [65]. Periodontitis patients with moderate forms of COVID-19 compared to mild forms have significantly increased HbA1C, lymphocyte, and CRP [42].

Periodontitis biomarkers can be increased by COVID-19 infections [65, 67]. Periodontitis biomarkers in COVID-19 patients can aggravate periodontitis disease progression [68, 74]. Periodontitis biomarkers include IL-1β [67, 68], aspartate aminotransferase (AST), and TNF-α [69-71, 75-77]. The elevation of periodontitis biomarkers may increase probing depth, clinical attachment loss, acute ischemic events, insulin resistance, osteoarthritis, autoimmune disorders, rheumatoid arthritis, noninfectious uveitis, inflammatory bowel disease, vascular dysfunction, atherosclerotic lesions, and hypertension [74].

C-reactive protein

CRP produced by hepatocytes, is increased in acute infections and inflammation. CRP is an inflammatory biomarker present in the plasma released in response to inflammation [78]. CRP is increased in COVID-19 pneumonia [79]. Poor periodontal outcomes are associated with increased CRP levels in patients with COVID-19. CRP secretion commences 4–10 hours after an inflammatory stimulus, peaking at 48 hours, and has a half-life of 19 hours. Increased CRP associated with worse outcomes may be correlated to a COVID-19-related "cytokine storm." When evaluating a range of hematological and immunological markers, it was found that CRP was one of the markers predictive of death from COVID-19 [80]. Patients with periodontitis are at a higher risk of COVID-19 complications and have higher CRP levels [45]. CRP levels is significantly link to different stages of periodontitis [42].

Table 3. Biomarkers found in COVID-19 and periodontal disease.

Biomarkers	Area affected	Clinical significance
COVID biomarkers associated with periodontal disease progression		
CRP	Pulmonary function	Reduced extubation survival
	Neurological manifestation	Ischemic stroke occurrence
D-dimer	Pulmonary function	Reduced extubation survival
	Cardiovascular function	Poorer prognosis
	Coagulation and hemostasis	Risk of mortality
	Neurological manifestation	Ischemic stroke occurrence
Ferritin	Pulmonary function	ARDS development
PCT	Inflammation and infection	Severity and risk of mortality
	Neurological manifestation	Ischemic stroke occurrence
	Kidney and liver function	Acute kidney injury
Pro-BNP	Cardiovascular function	Poorer prognosis
Periodontitis biomarkers increased by COVID-19 infections		
AST [101]	Periodontium	Increased probing depths
		Clinical attachment loss
IL-1β [67, 68]	Periodontium	Increased probing depths
		Clinical attachment loss
	Immune system	Autoimmune disorder
		Osteoarthritis
	Glucose metabolism	Insulin resistance
	Cardiovascular function	Acute ischemic events
TNF-α [75-77]	Periodontium	Increased probing depths
		Clinical attachment loss
	Immune system	Autoimmune disorder
		Rheumatoid arthritis
		Inflammatory bowel disease
		Noninfectious uveitis
	Cardiovascular function	Atherosclerotic lesions
		Vascular dysfunction
		Hypertension
	Glucose metabolism	Insulin resistance
	Lipid metabolism	Formation of atherogenic plaque

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D-dimer

D-dimer is a by-product of blood clotting. The clinical significance of D-dimer is related to pulmonary embolism, deep vein thrombosis, and disseminated intravascular coagulation [65]. D-dimer is a biomarker related to fibrin production; high D-dimer levels is associated with blood hypercoagulability [65]. In a case-control study, it was reported that D-dimer levels were elevated in patients with COVID-19 infection and became significantly higher with critical illness [81]. D-dimer levels are higher in chronic periodontitis [82]. Oral hygiene may have an effect on the d-dimer levels. COVID-19 patients with periodontal care had significantly lower D-dimer levels than those without [39]. The D-dimer levels in periodontitis have been significantly correlated with a higher risk of COVID-19 complications [39, 41, 45].

Ferritin

Human ferritin is composed of a ferritin heavy chain (FTH) and a ferritin light chain (FTL). The synthesis of ferritin is regulated by nitrous oxide, glutathione, and other "reactive oxygen species." An increased ferritin level indicates activation of the monocyte-macrophage system. The magnitude of inflammation reflected by high ferritin levels at the admission of COVID-19 patients is independently predictive of in-hospital mortality [83].

Procalcitonin

PCT is a precursor of calcitonin and has been used as a biomarker for the diagnosis of bacterial infection. Elevated PCT serum levels is correlated to increased disease severity [84]. The mean serum PCT levels were over four times greater in severe COVID-19 patients than in moderate COVID-19 patients [85]. PCT levels increased over 8 times in critical COVID-19 patients compared to moderate COVID-19 patients. High PCT levels have been associated with high rates of severe COVID-19 infections in patients admitted to the emergency department [86].

Pro-BNP

Patients with elevated levels of NT-proBNP values have a significantly increased risk of death from COVID-19 compared to patients with lower values [63, 87]. The plasma NT-proBNP values were mainly related to the severity of pneumonia [87]. Similarly, the pro-BNP serum levels were also linked with periodontitis [88-91].

Herpesvirus reactivation linking periodontitis and COVID-19

Herpesvirus infection and reactivation have been reported in varying degrees of COVID-19 severity. Viral coinfection [13, 92], and active herpesviruses [14] have also been reported in aggressive periodontitis. Herpesvirus activation by periodontal disease results in release of proinflammatory cytokines and chemokines including IL1, IL-6, IL-10, TNF-α, MIP-l-a, and y-interferon [93]. Similar cytokines were also released by COVID-19 disease. These overlapping cytokines may have an additive effect on either periodontitis or COVID-19. Severely affected COVID-19 patients in the Intensive care unit (ICU) were reported to have reactivation of cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), and human herpesvirus 6 (HHV-6) [94-96]. Patients with severe Covid-19 infection have a higher rate of EBV DNA positivity compared to patients with mild COVID-19. The median EBV DNA levels were also significantly higher in the severe COVID-19 patients compared to the mild COVID-19 patients [97]. In a cross-sectional study of mild to severe COVID-19 patients, the patient group with EBV viremia reported more severe pneumonia than the EBV-negative group [91, 98]. On the other hand, non-geriatric patients with severe COVID-19 were presented with a high prevalence of CMV-seropositivity compared to patients with mild COVID-19. Interestingly, CMV-seropositivity was not significant in older patients with COVID-19. Thus, CMV-seropositivity may be a potential risk factor for severe COVID-19 in non-geriatric individuals [99].

Herpesvirus reactivation [14] and coinfections [13, 92] have been linked to aggressive forms of periodontal disease. Herpesvirus reactivation by COVID-19 infections may aggravate aggressive periodontitis and result in rapidly progressive bone and attachment loss. It may also have the potential to aggravate chronic or quiescent periodontitis towards more attachment and bone loss. It is well known in medicine that viral synergistic infections potentiate one or more of the indicated viral etiologic agents. Herpesviruses found in aggressive periodontitis can also be reactivated during a COVID-19 infection. Herpesvirus reactivation may have an effect on the severity of COVID-19 and may reinitiate quiescent periodontitis in the periodontium.

Limitations of existing studies

Periodontitis is a spectrum of diseases including forms of periodontitis ranging from chronic to aggressive periodontitis. This paper encompasses a wide variety of different forms of the disease and does not focus on any specific type of periodontitis. Periodontitis may show an impact on COVID -19 biomarkers. However, the biomarkers referred to in this study may not compass all the cytokines or all the proteolytic and hydrolytic enzymes involved in the pathogenesis. COVID -19 may also increase the possibilities of biomarkers linked with periodontitis. These additional biomarkers have not been reported or investigated for periodontitis and COVID -19 as risk factors presently.

Other limitations of this study involve the dependence on

clinical probings and radiographic attachment loss for data collection, and this data may not be standardized between clinicians during the data collection. Therefore, the viability of the study is contingent upon the accuracy of the probings and the clinician's ability to interpret radiographs that have not been standardized. Furthermore, more definitive studies are necessary to further define this relationship.

Conclusion

There is a potential association between periodontal disease and COVID-19. Studies (Table 1) on COVID-19 patients with periodontal disease reported worse COVID-19 symptoms and outcomes. Studies (Table 2) on periodontitis patients who detected COVID-19 infection reported abnormal bleeding in the periodontium and increased gingival inflammation. Biomarkers found in COVID-19 linked with increased morbidity (Table 3) are also found to be increased by periodontal disease. These biomarkers increase the risk of ischemic stroke, ARDS development, acute kidney injury, poorer prognosis and increase mortality. Periodontitis biomarkers are also found to be increased in COVID-19 infections (Table 3). These biomarkers besides being associated with other systemic conditions have effects on the periodontium leading to increased probing depths and clinical attachment loss. There is an increased risk of morbidity and accompanying undesirable complications from COVID-19 in patients with periodontitis. Patients with periodontitis that are infected with COVID-19 have been reported to have more gingival inflammation and abnormal bleeding after the SAR-CoV-2 infection which diminished after recovery. Furthermore, periodontal disease increases biomarkers released in COVID-19 that are linked to increased COVID-19 severity, morbidity and mortality. In addition, COVID-19 increases biomarkers released in periodontitis that are linked to increased probing depths and attachment loss. Herpesviruses reactivation linked with aggressive periodontal disease are also reported to increase COVID-19 severity. Herpesvirus reactivation and COVID-19 infections release similar cytokines that may have an additive effect on the disease severity of periodontitis and COVID-19. Therefore, proper periodontal management with periodontal therapy and oral health maintenance may reduce death from COVID-19 infections and complications. Better management of COVID-19 patients with periodontitis and periodontitis patients with COVID-19 may reduce the morbidity and mortality from COVID-19.

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