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Infectious and Immunological Links Between Periodontitis and COVID-19: A Review

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Emerging evidence suggests a potential association between periodontitis and adverse outcomes in COVID-19. Both conditions share risk factors and exhibit similar immune dysregulation, including elevated pro-inflammatory cytokines, altered myeloid compartments, and T-cell dysfunction. SARS-CoV-2 uses angiotensin-converting enzyme type 2 and transmembrane protease serine 2 membrane proteins, highly expressed in the oral cavity, for cellular entry. Periodontitis may exacerbate COVID-19 through mechanisms such as oral microbe aspiration, increased viral receptor expression, and systemic inflammation. The shared immunopathogenesis, characterized by cytokine storms and perturbed immune profiles, suggests periodontitis can predispose patients to more severe COVID-19 outcomes. This article aims to review the associations between periodontitis and the severity of COVID-19 and the possible immune mechanisms involved.

Keywords: Periodontitis • COVID-19 • Immunity • Microbiota

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Introduction

In late 2019, SARS-CoV-2, a highly contagious virus that causes severe acute respiratory syndrome, was discovered in Wuhan, China, and quickly spread throughout the world, causing the COVID-19 pandemic [1]. As of October 2023, the recorded incidence of COVID-19 exceeded 676 million cases, resulting in a total of 6.8 million fatalities [2]. While mild symptoms are commonly observed in most cases, the disease can advance to severe pneumonia and multi-organ failure, ultimately resulting in mortality, which is contingent upon factors such as the patient's age and pre-existing comorbidities, including diabetes mellitus, immunosuppression diseases, chronic obstructive pulmonary disease (COPD), asthma, obesity, hypertension, chronic kidney disease, cardiovascular disease, and cancer [3,4].

The oral and nasal cavities have been identified as principal entry points for the SARS-CoV-2 virus, with a pathogenicity of COVID-19 appearing to be significantly affected by the oral cavity [3,5]. The angiotensin-converting enzyme type 2 (ACE2) and transmembrane protease serine 2 membrane proteins (TMPRSS2) used by SARS-CoV-2 for cellular infection were found to be highly expressed within the oral cavity, namely on the tongue epithelial cells, oral mucosa, salivary glands, gingiva, and periodontal pockets [6]. Saliva also plays a role as a retaining medium, as it holds the virus particles and can further contribute to COVID-19 transmission [7].

Periodontitis is defined as a chronic, multifactorial, inflammatory disease that is associated with the presence of plaque biofilms, resulting in progressive deterioration of the tooth-supporting tissues [8]. Around 50% of adults worldwide are affected by periodontitis, making it the sixth most common chronic inflammatory non-communicable disease, and approximately 11% of the global population are affected by its most severe manifestation [9]. Several risk factors to periodontitis were correlated also to COVID-19 severity, such as smoking, increased age, obesity, diabetes, hypertension, and cardiovascular disease [3,10-13]. The presence of periodontitis has been investigated as a significant comorbidity among major risk factors associated with severe symptoms of COVID-19 that elevate the risk of contracting the infection and, perhaps, of developing severe symptoms [5,14,15]. Various mechanisms have been proposed to suggest that the susceptibility for SARS-CoV-2 infection could be heightened by periodontal inflammation, including (1) the capability of periodontal pockets to serve as a reservoir for viral replication, (2) the increased expression of viral receptors in the respiratory tract and oral cavity, (3) aspiration of bacteria into the lower respiratory tract, and (4) translocation of pathogens to the bloodstream, resulting in bacteremia [5]. These identified direct and indirect pathways may contribute to heightened vulnerability of contracting SARS-CoV-2 and experiencing exacerbated COVID-19 symptoms in patients with periodontitis.

Because of the contemporary significance and widespread prevalence of periodontitis and COVID-19, this review aimed to review and correlate the existing evidence regarding a potential association between periodontitis and the risk of COVID-19 complications.

Periodontitis and Respiratory Diseases

The association between periodontitis and several chronic respiratory conditions is hypothesized to arise from 2 primary mechanisms: aspiration of oral microbes into the respiratory tract and hematogenous dissemination of pro-inflammatory mediators from the inflamed periodontium. Both mechanisms can contribute to increased susceptibility to respiratory inflammation and infection [16,17].

Gomes-Filho et al validated previous findings demonstrating a moderate to strong association between periodontitis and respiratory diseases such as asthma, pneumonia, and COPD [16]. Several studies have confirmed a direct link between oral pathogens and respiratory diseases, highlighting the role of aspiration in the development of these conditions [18-20].

The inflammatory milieu generated within periodontal tissues, characterized by the release of potent immunoinflammatory mediators, such as interleukin (IL)-1α, IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, is implicated in the pathogenesis of chronic pulmonary diseases, including COPD and asthma [16,19,21,22]. Systemic inflammatory markers, such as serum fibrinogen and C-reactive protein (CRP), further mediate the association between periodontal inflammation and compromised lung function [20]. This link was further investigated in a case-control study with a longitudinal arm, which demonstrated a significantly higher prevalence of periodontitis and poorer periodontal health in patients with COVID-19 than in controls [23]. Notably, patients with severe COVID-19 exhibited elevated levels of inflammatory markers (high-sensitivity CRP, ferritin, neutrophil/lymphocyte ratio), and these levels decreased after treatment. The study also found that periodontitis was associated with increased odds of SARS-CoV-2 infection, suggesting a potential causal relationship mediated by local and systemic inflammatory responses. This association is consistent with findings from Holtfreter et al, which showed periodontitis was independently associated with reduced lung volumes and airflow limitation [20]. However, it is crucial to acknowledge that smoking, a well-established risk factor for periodontitis and respiratory infections, confounds these associations [24]. Smoking alters the subgingival microbiome, promotes periodontal pathogen colonization, and impairs host immune responses and vascularization, thereby exacerbating pulmonary disease progression in susceptible individuals [25]. Collectively, these studies underscore the potential

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Table 1. Features of oral bacterial species detected in patients with COVID-19.

Species	Virulence	Significance	References
Leptotrichia buccalis	Produces endotoxin with a high potency	• Associated with periodontitis and oropharyngeal abscesses • Increasingly isolated in systemic and deep-seated infections, including bloodstream infection	[135,136]
Prevotella melaninogenica	Expresses Dipeptidyl peptidase-4 endopeptidase that hydrolyzes the penultimate proline or alanine dipeptides from the N-terminal polypeptide chains	• Modulates blood glucose and chemokine levels • Tumor marker • Strong association with the severity of disease and comorbidity in patients with COVID-19	[38,137-140]
Capnocytophaga gingivalis	Secretes trypsin-like protease which is an endo- peptidase capable of degrading proteins and large peptides Also secretes aminopeptidase involvement in bradykinin formation	Associated with periodonttitis, bone infections and oral squamous cell carcinoma development	[141-143]
Veillonella parvula	Catalase-positive Able to eliminate H_2O_2, which rescues the growth of these anaerobic periodontopathogens produces heme, which is the preferred iron source of the periodontopathogenic *P. gingivalis*	• Commonly associated with periodontitis • Rare association with meningitis, osteomyelitis, prosthetic joint infection, pleuropulmonary infection, endocarditis, and bacteremia	[144,145]

for periodontitis to contribute to respiratory dysfunction and increased susceptibility to infections, including SARS-CoV-2, potentially through shared inflammatory pathways; however, further research is needed to disentangle the complex interplay between periodontitis, smoking, and respiratory health.

Oral Microbiome and SARS-CoV-2 Infection

The oral cavity, a complex microbial ecosystem, maintains homeostasis through a delicate balance of commensal bacteria and microbial diversity [26]. However, disruption of this balance, leading to dysbiosis with increased pathogenic bacteria, initiates and perpetuates inflammatory conditions, such as periodontitis [27,28]. Periodontitis, driven by microbial biofilms, triggers a cascade of immune reactions, ultimately leading to the destruction of periodontal tissues [28,29]. Specific pathogens, including *Prevotella intermedia*, *Porphyromonas gingivalis*, *Fusibactereum nucleatum*, *Treponema denticola*, and *Aggregatibacter actinomycemetcomitans*, are strongly associated with periodontitis and contribute to systemic diseases, highlighting the systemic implications of oral dysbiosis [30-34]. Notably, oral dysbiosis can also facilitate viral infections, as viruses exploit bacterial co-inhabitants to enhance host cell entry, suggesting a potential role for viral-bacterial co-infections in periodontitis pathogenesis [35,36].

The pathogenic potential of oral bacteria, particularly periodontal pathogens, in the development and exacerbation of respiratory diseases, such as aspiration pneumonia [19], influenza [37], and COPD [21], has become increasingly recognized. Conversely, the intricate interactions between viral pathogens, host immune responses, and the oral microbiome, as observed during influenza infections and currently with SARS-CoV-2, can also induce oral microbiome dysbiosis, predisposing to secondary infections [38].

Incoming evidence from several studies confirm that SARS-CoV-2 infection results in altering oral bacterial species, thereby enhancing opportunistic pathogens in the oral cavity [38]. Dysbiosis of the oral microbiome in patients with SARS-CoV-2 reflects a notable increase in the abundance of *Streptococcus*, *Prevotella*, *Bacillus*, *Acinetobacter*, *Arenibacter*, *Gemella*, *Veillonella*, *Klebsiella*, *Idiomarina*, *Chryseobacterium,* and *Capnocytophaga*. The diminution of species, including *Neisseria*, *Haemophilus*, *Pseudomonas*, *Lautropia*, *Rothia*, *Leptotrichia*, *Porphyromonas*, *Actinobacillus*, *Granulicatella*, *Fusobacterium*, *Aggregatibacter*, *Alloprevotella,* and *Selenomonas,* was seen in infected patients [26]. Sequencing data from earlier studies during the pandemic revealed high levels of *Leptotrichia buccalis*, *Veillonella parvula*, *Capnocytophaga gingivalis*, and *Prevotella melaninogenica* in the bronchoalveolar lavage fluid in patients with COVID-19 [39,40]. These species are normal

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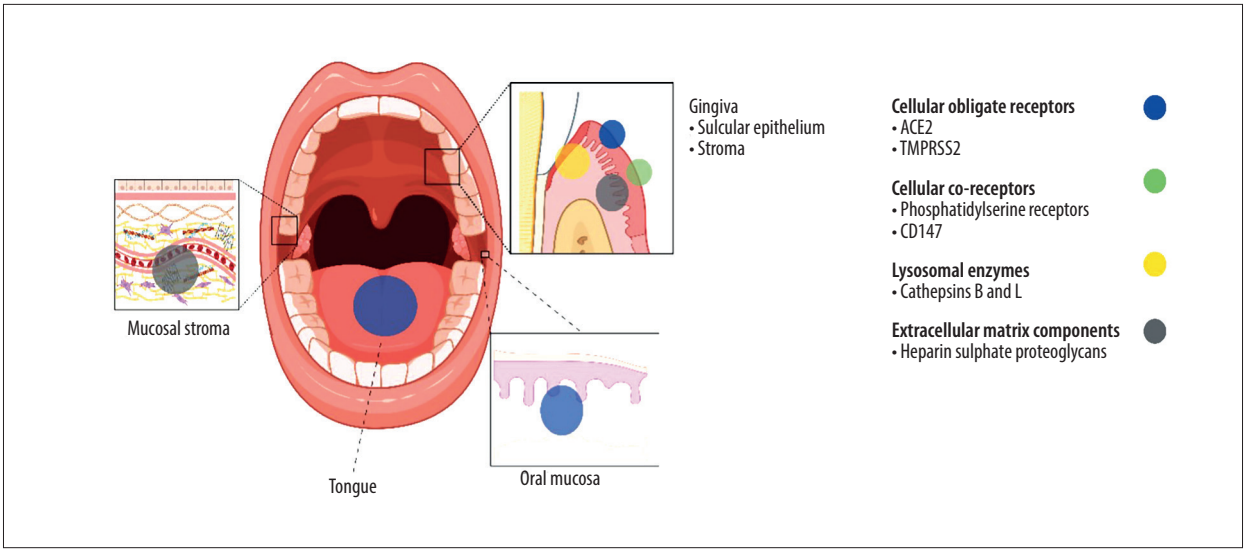

Figure 1. Expression profile SARS-CoV-2 entry factors in the oral cavity. The different factors include receptors, enzymes, and extra cellular matrix components, which are represented by colored circles. The size of the circle is representative of the expression intensity [53]. ACE2 – angiotensin-converting enzyme type 2; TMPRSS2 – transmembrane protease serine 2 membrane protein; CD – cluster of differentiation

oral flora habitants but can surface as opportunistic pathogens in the dysbiotic state (**Table 1**).

SARS-CoV-2 infection in which symptoms persist for 8 weeks or more are termed long COVID-19 cases [41]. The presence of prolonged symptoms reflects a disconcerted and frustrated immune response, which would inadvertently affect oral microbiota [42]. The extent of oral microbiome dysbiosis in patients with prolonged symptoms is important to understand, as it can reveal the association between periodontitis and SARS-CoV-2 infection. Haran et al examined the link between the oral microbiome and the duration of long COVID-19 symptoms using tongue swabs [43]. In line with previous findings, they detected high numbers of *Prevotella* and *Veillonella* species in patients with prolonged symptoms.

These bacterial species produce lipopolysaccharides (LPS), which can induce local as well as systemic inflammation [44,45]. Alongside inflammation, bacteria-derived LPS can also be involved in the expression of SARS-CoV-2 entry receptors and influence the amount of tissue infection. Such an involvement was reported by Sena et al, who showed how *P. gingivalis*-derived LPS increased gingival fibroblast expression of ACE2 and TMPRSS, potentially enhancing SARS-CoV-2 infectivity [46]. *P. gingivalis* is a gram-negative, anaerobic bacterium that forms part of the subgingival microbiome and is well known for its pathogenic role in periodontitis, as it can promote dysbiosis [29]. Another previous study reported the induction of *P. gingivalis*- and *E. coli*-derived LPS in fibroblasts obtained from healthy and periodontally inflamed tissue samples from mice and humans [47]. Deep periodontal pockets harbour bacteria and LPS units with very high levels of endotoxins. Amongst these are the *Veillonella parvula* species, which have been identified in respiratory infections (**Table 1**) [48]. Gupta et al detected coronavirus accumulation in gingival crevicular fluid from patients with asymptomatic and mildly symptomatic COVID-19 [49]. Building upon these findings, Badran et al hypothesized that periodontal pockets might also act as reservoirs for SARS-CoV-2, thereby contributing to increased viral load in infected individuals [50]. This potential for periodontal pockets to serve as viral reservoirs, coupled with the LPS-mediated upregulation of SARS-CoV-2 entry receptors, suggests a complex interplay between periodontal dysbiosis and COVID-19 pathogenesis.

Expression Profile of SARS-CoV-2 Entry Factors in the Oral Cavity

SARS-CoV-2 enters human cells via its obligate receptor ACE2 [51]. The expression profile of ACE2 in oral tissues is not uniform,as they are found to be much higher in tongue than buccal and gingival tissues [52]. The ACE2-positive cells in the oral cavity include epithelial cells, immune cells (B and T cells), and fibroblasts, the majority being epithelial cells [50]. The sulcular epithelium, which extends into the base of periodontal pockets, co-expresses ACE2 and TMPRSS2, making periodontal pocket lining a high-risk site for infection [53]. The strong expression of TMPRSS2 in the tongue coating increases the surface area available for viral particles to engage with host cells, as reported by Sakaguchi et al [53]. In addition to ACE2, other co-receptors have been implicated in the entry of

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SARS-CoV-2 into host cells. They include cathepsins B and L (CatB/L) [54], cluster of differentiation 147 (CD147) [55], phosphatidylserine receptors (tyrosine-protein kinase receptor UFO (AXL) and T-cell immunoglobulin and mucin domain 1 [TIM-1]) [56], and heparin sulphate proteoglycans [57]. The expression of SARS-CoV-2 entry and transmission factors in the oral cavity are summarized in **Figure 1**.

Cathepsin B and L

Cathepsins are protease enzymes, categorized into serine protease, cysteine protease, or aspartyl protease. They are active in low pH and found within lysosomes. They play a vital role in regulating the physiological functions ion channel activity, apoptosis, vesicular trafficking, autophagy, angiogenesis, and innate immunity [58]. In chronic diseases, including periodontitis, dysregulated cathepsins are known to contribute and sustain these pathological states. CatB/L are cysteine proteases that promote matrix degradation, cell invasion (promoting cancer), and viral entry into cells [58]. Entry of coronaviruses into host cells necessitates proteolytic processing of the viral spike (S) protein by host proteases. This priming process involves cleavage at the S1/S2 boundary, resulting in the dissociation of the S1 subunit from S2, thereby enabling S2 subunit-mediated membrane fusion between the viral envelope and the host cell membrane [59]. A previous study reported that SARS-CoV-2 S protein can be primed at the S2' site by host cell membrane-associated TMPRSS2 [60], endosomal CatB/L [61], and other trypsin-like proteases [62]. While TMPRSS2 is a plasma membrane protease, CatB/L are endosomal proteases that prime the virus after it is endocytosed [59]. Furthermore, pharmacological inhibition of either TMPRSS2 or CatB/L has been shown to attenuate entry of SARS-CoV-2 S-pseudotyped vesicular stomatitis virus or lentivirus [62,63].

Cathepsins are dysregulated in periodontitis, such that their activities and concentrations are both increased. They have been shown to correlate positively with periodontal parameters on patient and site levels [64]. Considering the established role of CatB/L in SARS-CoV-2 entry, the observed upregulation of CatB/L during periodontal inflammation may contribute to increased infection susceptibility. This effect is likely due to the activation of viral processing and the promotion of viral envelope fusion with endocytic membranes.

Cluster of Differentiation 147

CD147, also known as basigin, a transmembrane glycoprotein of the immunoglobulin superfamily, plays a functional mediator role in immune-inflammatory responses [65]. Wang et al reported a direct interaction between SARS-CoV-2 and CD147, with CD147 inhibition resulting in reduced viral replication. Furthermore, CD147-spike protein interactions facilitate viral entry via endocytosis [66]. In the oral mucosa, CD147 is expressed on the basal epithelial cell layer in healthy and inflamed states, with notable upregulation observed during inflammation, extending to the underlying connective tissue, primarily synthesized by fibroblasts and inflammatory cells [67]. Immunohistochemical analyses have revealed intense and widespread CD147 immunoreactivity in periodontitis, spanning epithelial and connective tissue layers [68]. Consistent with this, chronic periodontitis tissue samples exhibit elevated CD147 mRNA expression [69]. Given the role of CD147 in SARS-CoV-2 entry and replication, the observed CD147 upregulation in periodontal inflammation can potentiate infection risk.

Phosphatidylserine Receptors

Virion-associated phosphatidylserine enables a range of enveloped viruses to bind to host phosphatidylserine receptors, thereby facilitating viral binding and internalization [70]. This interaction involves the TAM tyrosine kinase receptor family (Tyro3, AXL, Mertk), which binds phosphatidylserine indirectly via ligands growth arrest specific 6 (Gas6) and Protein S (Pros1), and the TIM receptor family (TIM-1, TIM-4), which binds phosphatidylserine directly [71,72]. A study by Bohan et al [56] highlighted AXL as a key receptor for SARS-CoV-2 infection. Additionally, TIM-1 and TIM-4 potentiated SARS-CoV-2 infection in HEK 293T cells under conditions of low ACE2 expression; however, this effect was diminished with increasing ACE2 levels [73]. TAM receptors also play crucial roles in immune regulation, modulating innate inflammatory responses by macrophages, promoting antigen-presenting cell phagocytosis, and influencing natural killer cell maturation [73].

AXL and its ligands, Gas6 and Pros1, have been identified in healthy gingival tissues. Oral microbiota can induce the expression of Gas6, which subsequently modulates mucosal immune responses to colonizing bacteria [74]. The upregulation of AXL and Gas6 involves toll-like receptor (TLR) signaling [75]. Surface proteins of diverse viruses, including SARS-CoV-2, can activate TLR-2 signaling. This ligand engagement with TLRs is sufficient to elicit an immune response independent of viral internalization [76]. As a pattern recognition receptor, TLR-2 functions as a constant monitor for pathogenic microorganisms. Consequently, TLR-2 receptors are upregulated in periodontitis, a condition characterized by significant and sustained microbial dysbiosis [77]. In an in vitro study, Scheres et al reported that *P. gingivalis*-derived LPS stimulates human gingival fibroblasts, resulting in increased TLR-2 expression [78]. Furthermore, inflamed gingival tissues in periodontitis express TIM-1 on various cell types, including mast cells [79]. The elevated expression of TIM-1 and TLR-2 in periodontitis, coupled with the upregulation of AXL and Gas6, may contribute to the increased COVID-19 risk observed in these patients,

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as these receptors facilitate SARS-CoV-2 viral protein engagement and initiate robust immune responses.

Immuno-Inflammatory Mechanisms Underlying Periodontitis and COVID-19

The innate immune system, including natural killer cells, serves as the initial defense against viral pathogens by limiting viral entry, replication, and eliminating infected cells [80,81]. In periodontitis, while natural killer cells exhibit cytotoxic activity [82-84], they primarily contribute to pro-inflammatory responses, releasing interferon (IFN)-γ, TNF-α, and IL-15, which can exacerbate bone destruction [85]. The paradoxical role of IFN-γ is evident, as it both amplifies pro-inflammatory cytokine production, contributing to disease manifestations, and facilitates viral clearance by inducing chemokine production for B-cell infiltration [86]. Recent in vitro research on airway epithelial cells indicates that ACE2 is an IFN-stimulated gene, suggesting that SARS-CoV-2 can exploit IFN-driven ACE2 upregulation to enhance infection [87]. Consequently, the elevated IFN-γ levels observed in periodontitis may potentiate COVID-19 severity in infected patients. However, the mechanisms by which IFN regulates ACE2 expression in extrapulmonary tissues, including the oral cavity, remain to be fully elucidated.

The Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes Pathway

IFNs are crucial mediators of both antimicrobial and antiviral immunity [88]. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, activated by intracellular receptors (TLRs, RIG-I-like receptors), recognizing pathogen-derived cytosolic double-stranded DNAs and cyclic dinucleotides, culminates in IFN production via IFN regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB) activation [89-91]. Notably, SARS-CoV-2 manipulates this pathway, favoring NF-κB over IRF3, leading to diminished IFN production and enhanced pro-inflammatory cytokine release during early infection [92,93]. This reduction in IFN levels reflects a viral strategy to antagonize innate immune activation through IRF3 inhibition. Conversely, later COVID-19 stages exhibit elevated IFN and ACE2 expression in airway epithelial cells, potentially facilitating increased viral uptake [94]. This complex interplay between IFN signaling and viral manipulation raises questions regarding its role in extrapulmonary tissues, particularly the oral cavity. In periodontitis, a condition characterized by increased bacterial DNA release from biofilms and damaged host cells [95], immune receptors are expected to be activated against bacterial DNA. Immunohistochemical analyses reveal strong STING accumulation in inflamed gingival basal epithelium, compared with in healthy tissue [95]. Furthermore, *P. gingivalis*, a key periodontal pathogen, upregulates cGAS and STING expression, resulting in increased pro-inflammatory cytokine release (IL-6, IL-8, CCL2) in vitro [96]. Thus, the observed STING activation and pro-inflammatory cytokine release in periodontitis, coupled with the potential for IFN-mediated ACE2 modulation, suggests a complex relationship between periodontal inflammation and SARS-CoV-2 susceptibility, warranting further investigation.

Perturbations of Immune Cells

Severe COVID-19 is characterized by a systemic immunopathogenesis involving hematological perturbations (lymphopenia, coagulation disorders, thrombocytopenia) and a profound dysregulation of quantitative and qualitative immune responses [97-100]. This dysregulation manifests as a significantly altered myeloid compartment, featuring peculiar monocyte clusters (HLA-DRloS100Ahi, HLA-DRloCD163hi) and an emergency myelopoiesis-driven hyperinflammatory state mediated by calprotectin release [100-104]. Notably, periodontitis exhibits a parallel immunopathogenic profile, characterized by elevated neutrophil infiltration, impaired neutrophil function (chemotaxis, phagocytosis, ROS synthesis), and an immunosuppressive transition marked by T-cell depletion and increased calprotectin levels in gingival crevicular fluid [105-108]. This shared myeloid and lymphoid dysfunction suggests a potential link between periodontitis and increased susceptibility to severe COVID-19, potentially through similar mechanisms of immune dysregulation.

The convergence of pro-inflammatory macrophage activity further underscores this connection. These macrophages, which express high levels of ACE2, are abundant in COVID-19 and periodontitis tissues [109-111]. Upon SARS-CoV-2 infection, they amplify inflammation through cytokine and chemokine release, creating a positive feedback loop that exacerbates disease [110]. This amplification is particularly relevant in periodontitis, in which a sustained inflammatory microenvironment, driven by bacterial products and excessive pro-inflammatory macrophage infiltration, favors disease progression and potentially enhances viral infectivity through increased ACE2 engagement [111].

Furthermore, both conditions exhibit T-cell dysfunction, including lymphopenia, T-cell exhaustion (characterized by programmed cell death 1 upregulation), and altered T-cell differentiation and cytotoxicity [112-115]. The chronic antigenic exposure in periodontitis leads to T-cell exhaustion and systemic immunosuppression, mirroring the T-cell abnormalities observed in severe COVID-19 [114,115]. This shared T-cell dysregulation, coupled with altered B-cell populations and a potentially compromised humoral response in both conditions [116-119], suggests that the systemic immune skewing observed in periodontitis can predispose patients to more severe

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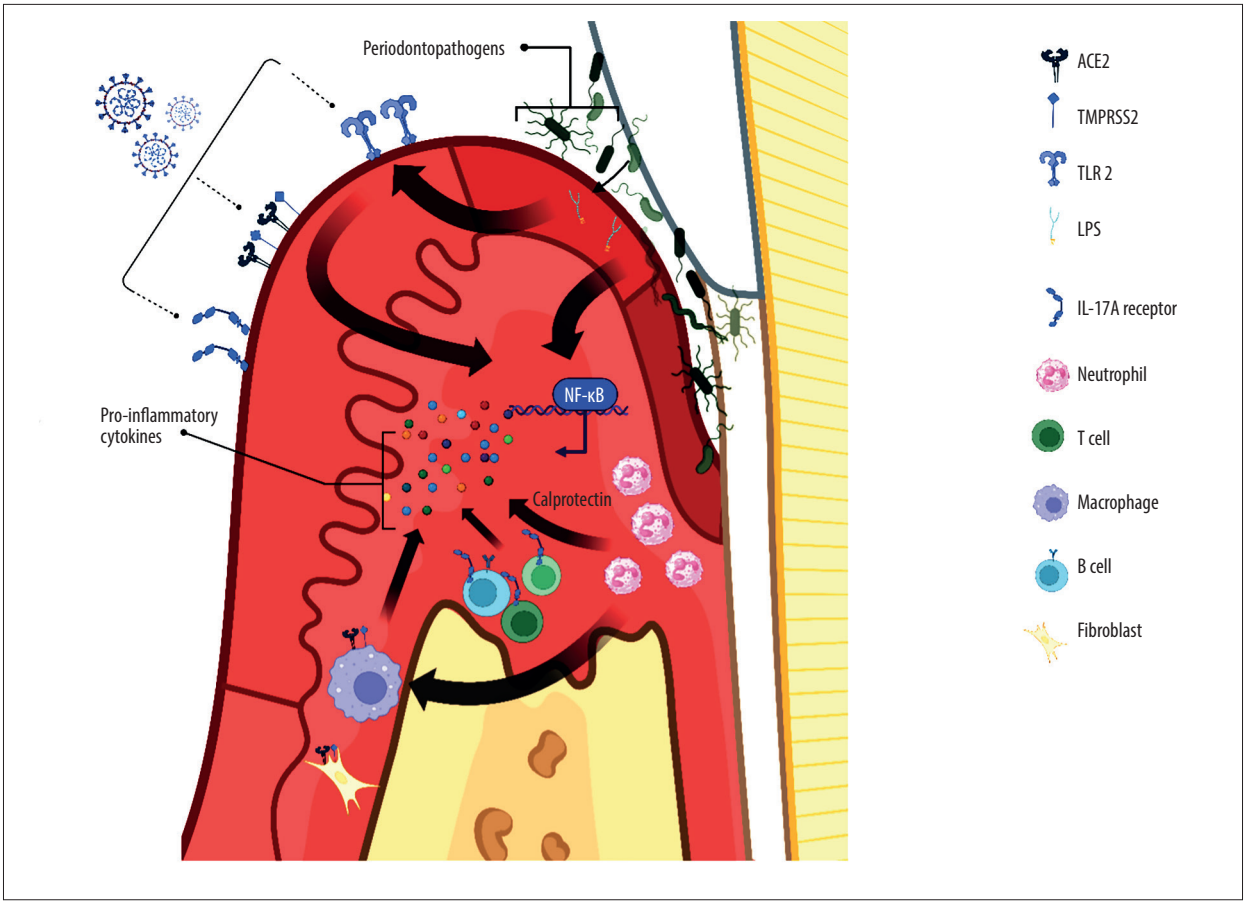

Figure 2. Periodontal pathogenesis providing a milieu of facilitation for SARS-CoV-2. The expression of receptors that engage SARS-CoV-2 are more abundant in the inflamed periodontium, as TLRs are upregulated due to bacterial stimulation. Microbial lipopolysaccharides also upregulate pro-inflammatory transcription factors (NF-κB), which cause the release of pro-inflammatory cytokines, including IL-1, IL-6, IL-8, IL-17, TNF-α, and IFN-v.

COVID-19 outcomes. Specifically, the observed delayed and abnormal B-cell maturation, along with decreased regulatory B cells and increased activated B cells, in periodontitis, mirror some B-cell abnormalities seen in COVID-19, potentially contributing to a less effective antiviral response.

Consequently, the cumulative effects of dysfunctional myeloid cells, pro-inflammatory macrophage activity, and impaired T- and B-cell responses in periodontitis may create a microenvironment conducive to enhanced viral entry, replication, and prolonged retention, thereby increasing COVID-19 severity. This shared immunopathogenesis underscores the potential for periodontitis to act as a significant comorbidity in COVID-19, warranting further investigation into the underlying mechanisms and potential therapeutic interventions.

Cytokine Storm

The pathogenesis of severe COVID-19 is significantly influenced by the cytokine storm, a state of excessive cytokine production that contributes to life-threatening complications, including acute respiratory distress syndrome, hemophagocytic lymphohistiocytosis, and multi-organ failure [120]. This hypercytokinemia involves a complex interplay of pro-inflammatory mediators, such as IL-1, IL-6, TNF-α, and IFN-γ, primarily driven by innate immune activation, as evidenced by lymphopenia and subsequent diminished adaptive immune responses [121]. The initiation of this cytokine cascade is attributed to the recognition of viral RNA by TLRs and RIG-I-like receptors, leading to the activation of IRF3/7 and NF-κB transcription factors. However, SARS-CoV-2 effectively suppresses the initial IFN-I response while leaving NF-κB-mediated pro-inflammatory cytokine production unchecked [92].

A pivotal factor in the COVID-19 cytokine storm is the SARS-CoV-2 open reading frame 8 protein, a virokine that structurally mimics IL-17A, thereby engaging and activating the IL-17 receptor [122,123]. This interaction triggers a signaling cascade involving ACT1 and TNF receptor-associated factor 6, ultimately leading to NF-κB activation and enhanced pro-inflammatory

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cytokine release [124]. Furthermore, open reading frame 8 protein is implicated in the activation of the NLRP3 inflammasome, contributing to elevated IL-1β levels [125,126]. Clinical studies corroborate these findings, demonstrating a strong correlation between IL-17A, IL-6, and TNF-α levels and COVID-19 severity, even after adjusting for comorbidities [127,128].

Notably, periodontitis, as a chronic inflammatory disease, also presents with systemic inflammation characterized by elevated circulating levels of IL-1, IL-6, and TNF-α [129-131]. The chronic nature of periodontitis leads to sustained pro-inflammatory cytokine production, potentially exacerbating the cytokine storm observed in patients with COVID-19. Furthermore, diminished levels of soluble TNF receptors (TNFR1 and TNFR2) in patients with periodontitis suggest a reduced capacity to modulate TNF-α activity [132]. Similarly, increased IL-17-producing cells and elevated serum IL-17 levels are observed in periodontitis [133,134]. Therefore, the pre-existing pro-inflammatory milieu in periodontitis may synergistically amplify the COVID-19 cytokine storm, potentially leading to more severe clinical outcomes. Clinical evidence supports this hypothesis, demonstrating that COVID-19 patients with advanced periodontitis exhibit higher serum levels of pro-inflammatory cytokines and increased white blood cell counts than do those without periodontitis [15]. This suggests a dose-response relationship between the severity of periodontitis and the intensity of the COVID-19 cytokine storm (**Figure 2**).

Future Directions

To solidify the observed association between periodontitis and increased COVID-19 severity, future research should prioritize longitudinal cohort studies, employing omics to clarify molecular interactions, and mechanistic studies to elucidate how periodontal pathogens exacerbate COVID-19, using in vitro and in vivo models. Clinical trials are vital to evaluate the impact of periodontal interventions on respiratory diseases outcomes, alongside investigations into the effect of long COVID-19 on oral microbiota and periodontal health. Finally, developing targeted therapies addressing shared immunopathogenic pathways offers a promising avenue for improving patient care and outcomes.

Conclusions

Periodontitis is known to impact systemic health, as evidenced from findings of experimental, clinical, and epidemiological studies. Sustained immunological effects due to periodontal bacteria or locally dysregulated host response with pro-inflammatory cytokines disseminating to extra-oral tissues may explain attendant co-morbidities, including pulmonary diseases and infections. A detailed understanding of mechanisms linking dysbiosis, increased viral receptor expression, and low-grade systemic inflammation may explain increased COVID-19 susceptibility in patients with periodontitis. Further research of mechanistic propagation in periodontitis may help identify novel markers for therapeutic interventions, which can reduce the susceptibility of infectious and non-infectious co-morbidities.

Declaration of Figures' Authenticity

All figures submitted have been created by the author who confirms that the images are original with no duplication and have not been previously published in whole or in part.

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