



Periodontal Diseases and COVID-19: A Scoping Review

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Abstract

The aim of this scoping review was to present the existing literature regarding the relationship between periodontal diseases and coronavirus disease 2019 (COVID-19). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping review guidelines was followed. Articles were retrieved from PubMed/MEDLINE and Scopus databases and screened to include studies relating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 to periodontal cells and/or tissues and/or diseases. Twenty-five papers were included; consisting of six reviews, seven original articles, six short reports, four letters to the editor, one commentary, and one case report. The articles were allocated to three different topics: (i) hypotheses on the relationship between periodontal diseases and COVID-19; (ii) risk factors and comorbidities common to periodontitis and COVID-19; (iii) periodontal manifestations of COVID-19. Certain molecules (angiotensin-converting enzyme-2, furin, cathepsin, TMPRSS2...) that are found at a high level in periodontal tissues, particularly in patients with periodontitis, are involved in the mechanism of entry of SARS-CoV-2 into cells. Periodontopathic bacteria could also play a direct role in the mechanism of entry of SARS-CoV-2 by cleaving the S-protein, and the cytokines produced during periodontitis could add to the cytokine storm found in the severe forms of COVID-19. It thus appears that the treatment of periodontitis, which allows a reduction in periodontopathic bacteria and of the local and systemic inflammation state, could be part of a strategy to prevent the development of severe forms of COVID-19.

Keywords

- ▶ coronavirus
- ▶ risk factors
- ▶ oral health
- ▶ periodontitis

*These are the co-first authors for this article.

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Introduction

Coronavirus disease 2019 (COVID-19), a disease that provokes severe acute respiratory syndrome,¹ was first identified in the province of Wuhan, China, in December 2019² and as of February 17, 2021, a total of 109,217,366 confirmed cases, including 2,413,912 deaths, have been reported to the World Health Organization (WHO).³ Among the factors that increase the risk of severe outcomes and mortality,⁴ cardiovascular diseases, cancer, obesity, and diabetes have also been reported to be associated with periodontal diseases.⁵⁻¹⁰ In this context, the potential relationship between COVID-19 and periodontal diseases has become of major interest and many papers have been published on this issue. The aim of the present scoping review was not only to present the published data regarding potential relationships between periodontal diseases and COVID-19 but also to highlight any gaps in the existing literature.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping review have been used as a guideline throughout the manuscript.¹¹ A literature search was performed using two electronic databases (MEDLINE/PubMed and Scopus). Eligibility criteria were studies on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19; relating SARS-CoV-2 or COVID-19 to periodontal cells and/or tissues and/or diseases; published until the December 31, 2020.

The following literature search was conducted using PubMed and adapted to Scopus. The terms used in the search were limited on "Title and Abstract": (Periodont*) AND (COVID OR coronavirus).

Selection of Sources of Evidence

The titles and abstracts of identified records were screened independently by two reviewers (LB and KG) after removal of duplicates; disagreements were resolved through discussion. The full texts of all the abstracts in accordance with the focus question were collected and reviewed; disagreements were resolved through discussion.

Data Charting Process

A data-charting form was jointly developed by two reviewers (LB and KG) to determine which variables to extract. For each paper, the following items were noted: article type, publication date, proposed mechanism of SARS-CoV-2 entry, proposed mechanism of how periodontitis might influence the entry of SARS-CoV-2 into cells or might worsen COVID-19, proposed antiviral targets, risk factors, or comorbidities common to periodontitis and COVID-19.

Two reviewers (LB and KG) independently charted the data and discussed the results.

Results

A total of 119 records were identified from the databases and 3 from other sources; of these 41 were duplicates and were removed. The title and abstract of 81 records were assessed, 50 were excluded. The remaining 31 underwent full-text examination; 25 studies were finally included in the review (► Fig. 1).¹²⁻³⁶ Among the six articles excluded after full-text assessment, one focused on the association between periodontitis and respiratory diseases in general and was not specific to COVID-19,³⁷ one focused on the oral manifestations in COVID-19 but was not specific to periodontal diseases,³⁸ one reviewed the risks of periodontal procedures in terms of aerosolization and transmission of the SARS-CoV-2,³⁹ and two illustrated the association between periodontitis and COVID-19 through a study included in the review^{40,41}; the full-text of the sixth article was not available and the authors were contacted but have not provided the paper at the time of writing.⁴²

To give structure to this review, the papers were classified into three topics: (i) hypotheses on the relationship between periodontal diseases and COVID-19, (ii) risk factors and comorbidities common to periodontitis and COVID-19, and (iii) periodontal manifestations of COVID-19.

Hypotheses on the Relationship between Periodontal Diseases and COVID-19 Study Characteristics

Among the 22 studies related to this topic, 15 were nonexperimental studies^{12,15-19,21,23-25,27,28,30,32,35}; there were seven experimental reports.^{13,14,26,31,33,34,36} For 16, the type of article was

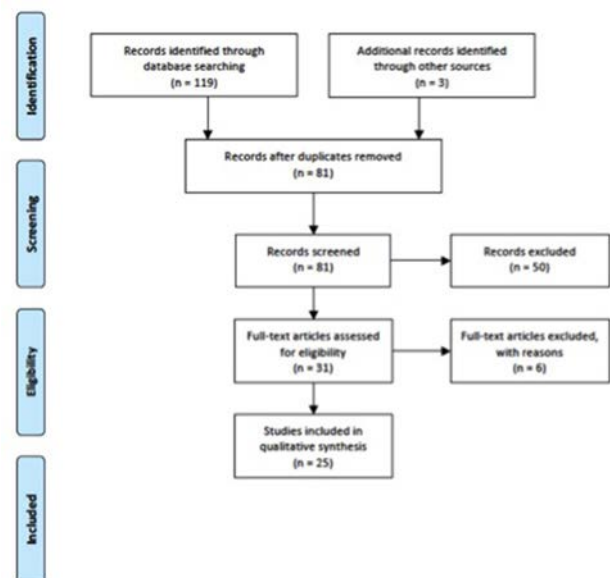


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

clearly indicated; seven were original articles,^{13,14,26,31,33,34,36} four were letters to the editor,^{17,18,25,30} four were reviews,^{24,28,32,35} and one was a “commentary.”²⁷ Among the six for which this was not clearly indicated, we considered that five were short reports^{12,15,16,19,21}—one of which reported an ongoing clinical trial,¹⁶ and one was a review.²³ The information relating to the topic found in the papers was the SARS-CoV-2 entry mechanism,^{12-14,16,18,21,24-28,30,32,36} the mechanism of how periodontitis might influence the entry of SARS-CoV-2 into cells or might worsen COVID-19,^{15-19,21,23-28,30,32-36} and antiviral targets to treat COVID-19 (► **Table 1**).^{14,18,24,27}

SARS-CoV-2 Entry Mechanism

The main reported receptor allowing SARS-CoV-2 for entry in to human cells is angiotensin-converting enzyme-2 (ACE-2).^{13,14,16,18,21,24-28,30,32,36} The latter is present in several tissues including lungs, nasopharyngeal mucosa, salivary glands, and oral mucosa.^{13,14,16,18,24,27,30,36} Within the oral mucosa, ACE-2 is mainly expressed not only by epithelial cells but also by fibroblasts,¹⁶ T cells, and B cells; it is not only detected in the lip, tongue, and buccal mucosa but also in the gingival (stratified squamous epithelium) and palatal tissue.^{13,14,18,26}

Table 1 Characteristics of the studies hypothesizing a relationship between periodontal diseases and COVID-19 (n = 22)

Authors	Article type	Publication date	SARS-CoV-2 entry mechanism	Influence of periodontitis	Antiviral targets
Roganovic ³⁶	Original article	December 14, 2020	Micro-RNA-146a and -155 may enhance expression of ACE-2	Micro-RNA-146a and -155 increased in the oral cavity during periodontitis	–
Gofur ³⁵	Review	November 30, 2020	–	Periodontopathic bacteria could increase the severity of COVID-19 (risk of bacterial superinfection) Periodontal pockets may be a reservoir for SARS-CoV-2	–
Fernandes Matuck et al ³⁴	Original article	November 26, 2020	–	Presence of SARS-CoV-2 in periodontal tissue in deceased COVID-19 patients	–
Larvin et al ³³	Original article	November 23, 2020	–	Periodontitis may be associated with COVID-19 and increase the risk of death	–
Takahashi et al ³²	Review	November 12, 2020	Binding of the S protein to ACE-2 S protein cleaved by TMPRSS2 and furin, and may also be cleaved by the proteases produced by periodontopathic bacteria	Aspiration of periodontopathic bacteria induces ACE-2 expression, cytokines production in the lower respiratory tract and degradation of the S protein	–
Gupta et al ³¹	Original article	November 2, 2020	SARS-CoV-2 identified in the gingival crevicular fluid	–	–
Elisetti ³⁰	Letter to the editor	November 1, 2020	Presence of ACE-2 and TMPRSS2 in salivary glands	Presence of SARS-CoV-2 in saliva; breach of the periodontal pocket epithelium may be an entry point for the virus	–
Mancini et al ²⁸	Review	September 8, 2020	ACE-2	Low ACE-2 levels in periodontal patients as for COVID-19 patients (reduced ACE-2 levels at the cell surface due to an ACE-2-SARS-CoV-2 connection)	–
Kara et al ²⁷	Commentary	August 24, 2020	Presence of ACE-2 in oral mucosa Gal-3 may increase immune response and viral attachment	Increased level of Gal-3 associated with the severity of periodontitis	Inhibition of Gal-3 may disrupt the SARS-CoV-2 attachment
Sakaguchi et al ²⁶	Original article	August 20, 2020	Presence of ACE-2, TMPRSS2 and furin in the oral cavity (tongue epithelium, taste buds, gingiva and sulcus epithelium, submandibular glands)	Periodontal pocket epithelium may be a focal point of infection to SARS-CoV-2	–

(Continued)

Table 1 (Continued)

Authors	Article type	Publication date	SARS-CoV-2 entry mechanism	Influence of periodontitis	Antiviral targets
Pedrosa and Neves Nogueira ²⁵	Letter to the editor	August 7, 2020	ACE-2 and TMPRSS2	Oxidative stress, as a link between diabetes and periodontal disease, may play a part in COVID-19 infection	–
Bertolini et al ²⁴	Review	July 6, 2020	Presence of ACE-2 in the nasopharyngeal mucosa, salivary cells and oral epithelial cells. Role of furin and cathepsin L in enabling the SARS-CoV-2 to bind ACE-2	High viral load of SARS-CoV-2 in the crevicular fluid	TMPRSS2 inhibitor is able to block the SARS-CoV-2 entry into cells
Sampson et al ²³	Review	June 26, 2020	–	Periodontopathic bacteria (Prevotella, Staphylococcus, Fusobacterium) present in the metagenome of patients severely infected with SARS-CoV-2	–
Pfützner et al ²¹	Short report	June 7, 2020	ACE-2 highly expressed in oral cavity	Detectable SARS-CoV-2 concentrations found in saliva; ulceration of the gingival epithelium during periodontitis may increase the risk of invasion	–
Gupta and Sahni ¹⁹	Short report	June 7, 2020	–	Interferon α implicated in the stimulation of NETs release (higher in periodontal patients); NETs may be implicated in the “cytokine storm” described in advanced stages of COVID-19	–
Madapusi Balaji et al ¹⁸	Letter to the editor	June 1, 2020	Presence of ACE-2 in oral mucosa including tongue, buccal mucosa and gingiva. Role of furin, cathepsin B/L and TMPRSS2 in SARS-CoV-2 entry into cells	Furin and cathepsin L levels elevated in patients with periodontitis	Melatonin inhibits cathepsin L
Sahni and Gupta ¹⁷	Letter to the editor	May 30, 2020	–	Cytokines levels elevated in both periodontitis and COVID-19	–
Badran et al ¹⁶	Short report	May 30, 2020	Presence of ACE-2 in salivary glands cells, gingival and periodontal ligament fibroblasts. Presence of furin in oral epithelial cells. SARS-CoV-2 could infect cells by binding to CD147 instead of ACE-2	Periodontal pocket may be a favorable environment for SARS-CoV-2 replication; virus could reach the oral cavity and mix with saliva, or migrate systemically via the capillary periodontal complex. Gingival epithelium expression of CD147 increased in patients with periodontitis	–
Botros et al ¹⁵	Short report	May 29, 2020	–	Secretion of pro-inflammatory cytokines during periodontitis can promote adhesion to lung epithelium and lung colonization by respiratory pathogens	–

(Continued)

Table 1 (Continued)

Authors	Article type	Publication date	SARS-CoV-2 entry mechanism	Influence of periodontitis	Antiviral targets
Zhong et al ¹⁴	Original article	April 22, 2020	Presence of ACE-2 and furin in oral mucosal tissues (epithelial layers, partly expressed in fibroblasts) Two possible routes for SARS-CoV-2 invasion: binding to the ACE-2 receptor and fusion with cell membrane activated by furin protease	–	Furin
Xu et al ¹³	Original article	February 24, 2020	Expression of ACE-2 on the mucosa of oral cavity (higher in tongue than buccal or gingival tissues); the oral cavity might be a potential risk route of SARS-CoV-2 infection	–	–
Kadkhodazadeh et al ¹²	Short report	January 10, 2020	SARS-CoV-2 identified in the saliva of infected patients	–	–

Abbreviations: ACE-2, angiotensin-converting enzyme-2; COVID-19, coronavirus disease 2019; Gal-3, galectin-3; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

One of the hypotheses is that furin, cathepsin, and TMPRSS2 proteases allow the entry of SARS-CoV-2 into cells.^{14,16,18,24–26,30,32} Furin is thought to precleave the spike protein (S-protein) of coronavirus into two subunits (S1 and S2) allowing S1 to attach itself to ACE-2.^{18,24} Then, the virus fuses with the host cells in two ways: endosomal fusion mediated by cysteine protease cathepsin B/L and plasma membrane fusion mediated by serine protease TMPRSS2.¹⁸ In addition, Roganovic, who constructed an in silico model around the mechanism involving ACE-2 and furin/TMPRSS2, reported that microRNA-146 and -155 seem to be widely involved in the regulation of SARS-CoV-2 oral cellular entry factors and may enhance expression of ACE-2 and modulate genes involved in host immunity.³⁶ Another infection route that has been suggested also involves the S-protein but through binding to the cluster of differentiation 147 (CD-147).¹⁶

How Do Periodontal Diseases Worsen COVID-19?

Multiple papers try to explain the mechanism of how periodontitis worsens COVID-19.^{15–19,21,23–28,30,32–36} Among these, three mention the impact of cytokine release during periodontitis that may worsen the cytokine storm described in some symptomatic COVID-19 patients.^{17,19,32} Moreover, the cytokines produced during periodontitis can promote adhesion to lung epithelium and lung colonization by respiratory pathogens; in parallel, aspirated periodontopathic bacteria may also induce secretion of cytokines in the lower respiratory tract aggravating the symptoms of COVID-19.^{15,32}

Other molecules or inflammatory mediators involved in periodontitis could also contribute to worsen COVID-19. For instance, the level of osteopontin is directly related to that of furin and cathepsin L, and thus could impact the mechanism of entry of SARS-CoV-2 into cells.^{18,24}

Galectin-3 (Gal-3) is also suggested to play a role in both the severity of COVID-19 and periodontal diseases; an increased level in Gal-3 is associated with the level of severity of periodontal diseases and, as Gal-3 may cause an increased immune response and viral attachment, it could substantially impact the severity of COVID-19.²⁷ Moreover, in periodontitis patients, gingival epithelium expression of CD-147 is increased¹⁶ potentially increasing SARS-CoV-2 entry into cells. Likewise, microRNA-146a and -155 are increased in the oral cavity during periodontitis, modulating host antiviral response.³⁶

One of the included articles focused on periodontal pathogens and their relationship with the severity of COVID-19; it was noted that periodontal pathogens increase the expression of ACE-2 and therefore offer more points of entry for the virus, and hypothesized that proteases of periodontopathic bacteria may cleave the S-protein of the viral envelope of SARS-CoV-2 facilitating its entry into cells.³² In another paper, it is hypothesized that bacterial pathogens present in the oral cavity, in particular in the periodontal region, could increase the severity of COVID-19 due to the risk of bacterial superinfection.³⁵

Five papers present the potential role of periodontal pockets as a reservoir for SARS-CoV-2.^{16,24,26,30,35} For some authors, ulceration of the gingival epithelium occurring during periodontitis could increase the risk of SARS-CoV-2 invasion.^{21,30} This may be supported by a postmortem study that found SARS-CoV-2 in periodontal tissue in COVID-19 patients.³⁴

From a more clinical point of view, a cohort study (UK Biobank cohort) found an increased risk of mortality following COVID-19 infection in people with periodontal disease, suggesting that periodontitis may be associated with the severity of COVID-19.³³

Table 2 Risk factors and comorbidities hypothesized to be common to periodontitis and COVID-19

Authors	Article type	Publication date	Risk factors and comorbidities
Botros et al ¹⁵	Short report	May 29, 2020	Chronic kidney disease, diabetes, liver disease, obesity
Pfützner et al ²¹	Short report	June 7, 2020	Age, diabetes
Pitones-Rubio et al ²²	Review	June 19, 2020	Age, asthma, cancer, cardiovascular disease and hypertension, chronic obstructive pulmonary disease, diabetes, human immunodeficiency virus, liver disease, obesity, oral dysbiosis, pregnancy, rheumatoid arthritis, sex, smoking
Pedrosa and Neves Nogueira ²⁵	Letter to the editor	August 7, 2020	Diabetes
Räisänen et al ²⁹	Short report	September 12, 2020	Cancer, cardiovascular disease and hypertension, chronic kidney disease, diabetes, respiratory disease
Takahashi et al ³²	Review	November 12, 2020	Cardiovascular disease, chronic obstructive pulmonary disease, diabetes, pneumonia

Abbreviation: COVID-19, coronavirus disease 2019.

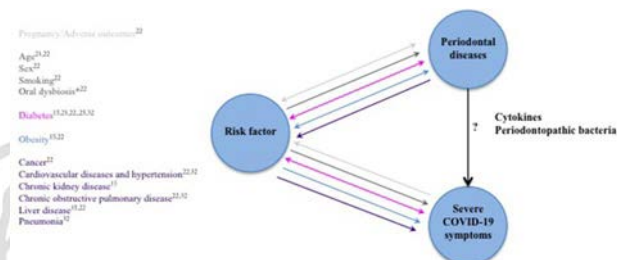


Fig. 2 Relationship between periodontal diseases and severe coronavirus disease 2019 (COVID-19) symptoms through suggested risk factors. Arrows indicate the onset or aggravation of diseases. * Oral dysbiosis is the principal etiological factor of periodontitis.

Antiviral Targets for COVID-19

Antiviral targets have been proposed; these are involved in cellular entry mechanism of SARS-CoV-2, such as TMPRSS2, furin, and Gal-3,^{14,24,27} and others are involved in regulation of inflammation and oxidative stress, such as melatonin.¹⁸

Periodontitis and COVID-19: Common Risk Factors and Comorbidities Report Characteristics

Six articles mentioned risk factors or comorbidities that may be common to COVID-19 and periodontal diseases.^{15,21,22,25,29,32} One was a letter to the editor,²⁵ three were short reports,^{15,21,29} and two were reviews (► **Table 2**).^{22,32}

Hypothesized Common Risk Factors and Comorbidities

Various parameters and diseases are presented as being able to constitute common risk factors, such as for example diabetes, obesity, or cardiovascular diseases (► **Table 2**); as are hypotheses of the relationships between these and periodontal diseases or severe COVID-19 symptoms suggesting a link between periodontal diseases and COVID-19. The most frequently proposed mechanism for this related to the cytokines released in response to periodontitis^{15,21,29,32} that could add to the cytokine storm encountered in severe forms of COVID-19.^{15,29} In addition, the presence of periodontopathic bacteria (oral dysbiosis) is presented as being able to facilitate cellular entry of SARS-CoV-2 (degradation of the

S-protein)^{22,32} (► **Fig. 2**) and known as being the principal etiological factor of periodontitis in the literature,⁵ and this is potentiated by a poor swallowing function in the elderly that increases the risk of periodontal pathogen aspiration.³²

Periodontal Manifestations of COVID-19

One study was a case report of periodontal manifestations of COVID-19.²⁰ A 35-year-old woman complained of gingival pain and bleeding characterized as edematous gingivae and necrotic interdental papillae; the final diagnosis was necrotizing gingivitis. Moreover, she had a fever and was a suspected case of COVID-19, but as testing was not available at the time, they could not confirm that she was positive for SARS-CoV-2. Another study, including 33 COVID-19 positive patients (including 20 who were asymptomatic), reported that 14 patients presented gum disease.³¹ However, it is not possible to determine whether gum disease was present prior to SARS-CoV-2 infection or whether it is a consequence of the infection.

A review article hypothesized that mild cases of COVID-19 might not show any oral manifestations, but in severe cases, persistent inflammatory responses trigger inflammatory oral cavity manifestations, especially in periodontal tissue leading to coagulation cascade and increased fibrinogen degradation confirming that COVID-19 could have an impact on periodontal tissue.³⁵

Discussion

The papers included in this scoping review underline the role of certain molecules (ACE-2, furin, cathepsin, TMPRSS2...) in the mechanism of entry of SARS-CoV-2 into cells; these molecules are found at a high level in periodontal tissues, particularly in patients with periodontitis. In addition, periodontopathic bacteria could play a direct role in the mechanism of entry of SARS-CoV-2 by cleaving the S-protein, and the cytokines produced during periodontitis⁴³ could add to the cytokine storm found in the severe forms of COVID-19. Several authors also note that the periodontal pockets could constitute a reservoir for SARS-CoV-2 allowing the virus to enter at the systemic level and to be present at the

salivary level. Taken together, this suggests a link between periodontitis and COVID-19. This leads us to wonder whether or not periodontal diseases should be considered as a risk factor for COVID-19, at the same level as diabetes, cardiovascular diseases, etc. More generally, given that periodontal treatment allows a reduction in periodontopathic bacteria and in the local and systemic inflammation state,⁴⁴⁻⁴⁶ it could consequently reduce the inflammation state in COVID-19 patients. It thus appears that the treatment of periodontitis could be part of a strategy to prevent the development of severe forms of COVID-19.

Regarding clinical periodontal manifestations of COVID-19, as of today, there is an insufficient number of clinical cases with confirmed COVID-19 to draw any conclusions. Gingival inflammation appears to be common in patients suspected of having COVID-19, but there is insufficient evidence that this gingival inflammation is secondary to CoV-2 SARS infection and it is widely known that gingivitis is very common.⁴⁷ However, lesions of the oral cavity have been reported in COVID-19, such as vesiculobullous lesions.^{12,48} In this context, the potential risk of periodontal manifestations related to COVID-19 needs to be further explored.

Overall, this scoping review, although being mostly composed of hypotheses, presents possible biological mechanisms behind the relationship between SARS-CoV-2 and periodontal diseases that seem promising for future studies, especially clinical or experimental research. In addition, it should be noted that published data currently does not include new variants and these should be investigated to better understand their impact at the periodontal level.

Conflict of Interest

None declared.

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