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Association between periodontal disease and chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and periodontal disease are chronic inflammatory conditions that significantly affect an individual's overall health and well-being. Generally, the prevalence of periodontitis is higher in patients with COPD than those without COPD, which may partly be attributed to common risk factors in COPD, such as smoking, respiratory infections, and inflammation. In particular, periodontitis may exacerbate the progression of COPD and further deteriorate the respiratory system by promoting inflammatory responses and bacterial infections. Immunocytes, including neutrophils, and microorganisms such as *Fusobacterium nucleatum* originating from oral biofilms are believed to be crucial factors influencing to COPD. Furthermore, the potential benefits of treating periodontal disease in COPD outcomes have been investigated. Although the relationship between COPD and periodontal disease has been preliminarily studied, there is currently a lack of large-scale clinical studies to validate this association. In addition to clinical examinations, investigating biomarkers and microbiology may contribute to explore the underlying mechanisms involved in the management of these conditions. This review aims to contribute to a better understanding of the clinical and basic research aspects of COPD and periodontitis, allowing for potential therapeutic approaches and interdisciplinary management strategies.

1. Information

Over the past few decades, increasing attention has been paid to the association between periodontal diseases and systemic conditions [1]. Many reports have indicated that periodontal disease affects systemic diseases, including diabetes [2,3], cardiovascular diseases [4,5], and non-alcoholic fatty liver disease [6]. The association between periodontal disease and chronic obstructive pulmonary disease (COPD) has attracted increasing attention.

Periodontal disease is an infectious disease caused by periodontal bacteria that trigger chronic inflammation and destruction of tooth-supporting structures [7,8]. Periodontitis is one of the most common diseases in the world, as more than 40% of the world's population suffers from different degrees of periodontitis, and this proportion continues to increase with age [9]. In Japan, at least 49.4% of the population has mild periodontitis [10]. For the clinical diagnosis of periodontitis, probing pocket depth (PPD), clinical attachment level (CAL), and bleeding on probing (BOP) are commonly used indicators [11], oral hygiene index (OHI), plaque index (PI), gingival index (GI), and other oral health examination methods can provide a more comprehensive understanding of a patient's oral condition [12,13].

Chronic obstructive pulmonary disease (COPD) is a group of chronic lung diseases characterized by airflow limitation, including chronic bronchitis and emphysema. According to an epidemiological study, this disease is the third leading cause of death worldwide [14]. Although COPD occurs in all regions of the world, its prevalence varies in different regions [15]. For instance, in Japan, approximately 6.8% of people over 40 years have at least one of the following airflow limitations, chronic

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cough/phlegm and currently treated respiratory diseases [16]. Spirometry has been the most commonly utilized diagnostic test for COPD, which assesses the impairment of forced expiratory volume (FEV_1) and airflow obstruction. The gold standard for COPD diagnosis is the value of FEV_1/forced vital capacity (FVC) [17].

In the early stages of research, the common risk factors between periodontal disease and COPD were investigated, such as smoking and poor oral hygiene habits, etc. [18–20]. However, as research progressed, an increasing amount of evidence suggests that periodontal disease may not only be a risk factor for COPD but also directly affect the pathology processes of COPD. Particularly, studies have suggested that bacteria in the periodontal tissues of patients suffering from periodontal disease can enter the lungs via the oral cavity or respiratory tract and potentially cause lung infections, inflammation, and exacerbate symptoms in patients [21–23]. Furthermore, periodontal disease is chronic oral infections, triggering systemic inflammatory responses associated with the development and progression of COPD [24,25].

Therefore, this review aimed to systematically summarize and analyze previous research findings to comprehensively understand the relationship between periodontal disease and COPD, as well as to explore their possible mechanisms of association. In addition, we investigated the potential role of periodontal disease in the prevention and treatment of COPD and its significance in clinical practice.

2. Cross-sectional study

Cross-sectional studies are based on the results of investigations and examinations. The following indices were used to assess periodontal disease: the gingival index (GI), PPD, CAL, periodontal disease index (PDI), community periodontal index of treatment needs (CPITN), periodontal index for risk of infection (PIRI), and BOP. Additionally, the oral hygiene index-simplified (OHI-S) and PI were used to evaluate oral hygiene status, while the decayed, missing, and filled teeth (DMFT) and significant caries index (SiC) were used for caries assessment. Furthermore, Candida load [26,27] and sputum tests [28] were considered. To assess COPD, researchers have utilized various tools, including the FEV_1 value [29], FEV_1/FVC ratio [30], Gold's criteria [31], spirometer [32], oxygen saturation (SpO_2) [30], Modified Medical Research Council (MMRC) [30] and COPD Assessment Test (CAT) questionnaire [30,31].

2.1. Asia

2.1.1. East Asia

Cross-sectional studies on the relationship between periodontitis and COPD in East Asia have been performed in Japan and China and have shown results of similarities and differences. Studies in both countries have evaluated PI, PPD, BOP, O'Leary's plaque control record (PCR), and alveolar bone level (ABL) as indicators of periodontal disease [33–38]. For indications of COPD, the 6-minute walk test (6 MWT) and evaluation of %FEV were performed [33–36, 38]. Studies in both countries have shown an association between periodontal disease and the severity of COPD, with a higher smoking ratio and prevalence of COPD in men than in women [34,38].

Many Japanese studies have examined the association between periodontal disease and COPD with the aim of predicting the systemic health of patients with COPD by assessing their oral health status. Some studies in Japan have reported that smoking and diabetes are associated with periodontal disease and COPD [34,36]. To examine inflammation and health status, the Body Mass Index (BMI) and blood parameters, including HbA1c, Fasting Blood Glucose (FBG), and serum albumin, were evaluated [36,39]. Periodontal disease exacerbates systemic inflammation and COPD [34]. In another study, poor periodontal health was associated with hypoalbuminemia, suggesting poor nutritional status and inflammation in patients with COPD [39]. Furthermore, PPD, HbA1c, and FBG levels were significantly associated with occlusal force in patients with moderate/severe periodontitis. PPD was significantly associated with occlusal force among employees with moderate COPD, and atherosclerotic cardiovascular disease [36].

Studies conducted in China have aimed to prevent COPD by promoting oral health care and knowledge. Many studies have focused on the concerns about their own health status of patients with COPD [33–35, 40]. Therefore, questionnaires such as the St. George's Respiratory Questionnaire (SGRQ), which examines the quality of life (QOL) [35], BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index, indicating the prognosis of COPD, were used. BODE showed significant associations with periodontal parameters, including the bleeding index (BI), PI, CAL, ABL, and number of teeth. In particular, PI was a major periodontal factor for predicting COPD in Chinese adults [34]. Another report showed that few remaining teeth, high plaque index, low tooth brushing times, and low regular supragingival scaling were significantly associated with exacerbations of COPD [33], suggesting improvement of periodontal health and oral hygiene might be a potential preventive strategy against COPD and that promoting dental care and oral health knowledge might help prevention and treatment for COPD. The contents of this section are summarized in Table 1.

2.1.2. Other Asia

Twelve cross-sectional studies from Asian regions other than East Asia were conducted between 2011 and 2021. Among these, ten reports were from India [26–29, 32, 41–45], and two were from Iran [30,31]. While most of these reports have focused on comparing patients with COPD to healthy individuals without COPD, some have compared healthy individuals with a population that includes not only COPD but also other lung diseases, including tuberculosis and pneumonia [27, 29, 42]. Some reports have also examined the effects of the long-term use of drugs for COPD treatment, such as inhaled corticosteroids [27] and theophylline [26] on oral health.

CAL was the primary tool in 10 of the 12 reports, showing significantly higher scores in the COPD group [28, 29, 32, 43–45]. Furthermore, while CAL exhibits a significantly positive correlation with CAT [27,31], it showed a significantly negative correlation with FEV_1, FEV index [30], and SpO_2 [30], and no correlation with MMRC [30] or serum cotinine [41]. The GI index showed a significant elevation in patients with COPD and/or other lung diseases compared to healthy individuals [26, 27, 41, 45]. GI also exhibited a significant negative correlation with FEV_1 [45] and SpO_2 [30]. Additionally, PPD was significantly greater in patients with COPD than in the control group [29, 44, 45] and displayed a significant negative correlation with FEV_1 [30]. In contrast, PDI was significantly lower in the study group than in the control group. Although the study population was relatively young (20 – 45 years), inhaled corticosteroids might have limited periodontal disease progression [43].

Furthermore, the Candida load was significantly higher in patients with COPD than in controls [26,43], particularly in those taking theophylline [26]. Meanwhile, the OHI-S score was significantly higher in the COPD group than in the control group [29, 32, 43–45]. Serum and salivary CRP levels showed significant positive correlations and were significantly higher in COPD patients than in healthy control subjects [44]. The contents of this section are summarized in Table 2.

2.2. Out of Asia

Nine studies have been reported in the United States of America and Europe describing the association between COPD and indicators of periodontal disease. Among these studies, two were conducted in the USA. Particularly, a study was conducted on 58 individuals to assess the morbidity of pulmonary pathogens colonized by dental plaques. The COPD incidence was significantly higher in subjects with pathogen colonization than in non-colonized subjects in chronic care facilities [46]. The other study evaluated the association between COPD exacerbation and periodontitis in 136 patients. However, no statistically significant differences were observed between COPD exacerbation and

Table 1
Summary of cross-sectional studies in East Asia.

Ref. No.	Study Country Year Sample Size	Parameters for Evaluated for the Diagnosis of COPD	Parameters for Evaluated for the Diagnosis of Periodontitis	Main Findings
[33]	Zhiqiang Liu et al. China 2012 n = 392	Spirometer FEV1/FVC	PD CEJ BI CAL PLI	Fewer remaining teeth, high PLI scores, and low tooth brushing times are significant correlates of COPD exacerbations, indicating that improving periodontal health and oral hygiene may be a potentially preventive strategy against COPD exacerbations.
[34]	Yan Si et al. China 2012 n = 1019	6MWT, BODE index	CAL PPD BI PI ABL	A strong association between periodontitis and COPD, and PI seemed to be a major periodontal factor for predicting COPD among Chinese adults.
[35]	Xuan Zhou et al. China 2012 n = 306	respiratory function and Respiratory Questionnaire (SGRQ)	missing teeth number, alveolar bone level, PD CAL BI PLI	Poor periodontal health as reflected by missing teeth and plaque index was significantly associated with lower QOL in COPD patients. Promoting dental care and health knowledge helps patients with COPD to prevent and treat COPD.
[36]	Shinsuke Kataoka et al. Japan 2021 n = 1022	FEV1/FVC ratio occlusal force HbA1c FBG	PPD BOP number of teeth	PPD was significantly associated with occlusal force among employees with moderate COPD, and ASCVD, so that future health issues could be accurately predicted from the results of routine dental examinations.
[38]	Jane Harland et al. Japan 2018 n = 1474	Spirometer. 1 s of forced vital capacity	PPD CPI	The association between smoking and COPD was significant for men with periodontitis but was weaker for those without periodontitis, and periodontitis is linked to systemic inflammation in smokers with COPD.
[39]	Takeshi Terashima et al. Japan 2017 n = 136	serum albumin level, Spirometer	BOP PD PCR BMI	Poor periodontal health was associated with hypoalbuminemia, suggesting poor nutritional status and inflammation in COPD.
[40]	Zuomin Wang et al. China 2009 n = 634	Respiratory function questionnaire	PD CAL BI PLI, number of remaining teeth, alveolar bone level	Poor periodontal health, dental care, and oral health knowledge were significantly associated with an increased risk of COPD and promoting dental care improved QOL with COPD patients.

non-exacerbation cases for any periodontitis examination parameters, and the odds ratios for periodontal examination measurements were not significantly different between the two groups [47].

In Norway, Leuckfeld *et al.* evaluated the association between severe COPD and periodontitis using orthopantomograms of 180 adults. They found that chronic periodontitis with a mean marginal bone level of ≥ 4 mm was significantly associated with patients with a prevalence of COPD, suggesting that periodontitis may be an independent risk factor for COPD with considering age and smoking [48]. Another association between periodontal pockets and COPD was observed in 3360 Greek outpatients. In the study, an increase in clinical attachment loss ≥ 6 mm was positively related to COPD (OR = 1.054, 95% CI = 0.244 – 1.523) after adjusting for sex, smoking, and CAL [49]. The significant association between CAL and predicted FEV_1 in 1380 adults was also observed after adjusting for other confounders [50]. Moreover, patients with COPD have significantly worse periodontitis indices than healthy individuals, except for gingival inflammation. Multiple logistic regression analysis adjusting for other risk factor variables showed a significantly higher odds ratio (OR) in the COPD group for periodontitis with CAL $\geq$ 4 mm at $\geq$ 60% of sites (OR: 3.2, 95% CI: 1.0 – 9.8) [51]. Similarly, a Spanish research group reported that the prevalence of periodontitis in patients with COPD was higher compared to those without COPD (adjusted OR: 1.21, 95% CI: 1.12 – 1.30) [52]. Conversely, some studies have reported little direct association between COPD and periodontitis. An epidemiological study of 80 individuals divided into smokers with COPD, smokers without COPD, and healthy nonsmoking groups reported that periodontitis was strongly correlated with smoking, and no association was found between the risk of developing COPD and oral health problems, including periodontitis [53]. Furthermore, according to a German study of 206 adults, periodontitis was significantly correlated with age and smoking but not with pulmonary function [54].

Based on the above, although many epidemiological studies have reported a relationship between COPD and periodontitis, a variety of confounding factors involving both diseases should also be considered. The contents of this section are summarized in Table 3.

3. Cross-sectional study with biomarkers

In addition to clinical examinations, laboratory testing may offer new perspectives for assessing the association between periodontitis and COPD, as inflammatory biomarkers are another major research focus. In a Swedish study, the saliva was found to be the most suitable for the assessment of COPD biomarkers compared to serum-induced sputum and bronchoalveolar lavage fluid [55]. A study in Turkey showed that serum high-sensitive C-reactive protein (hs-CRP) levels and gingival crevicular fluid (GCF) levels of hs-CRP, interleukin-1 (IL-1b), and prostaglandin-E2 (PGE2) were significantly higher in patients with COPD compared to the controls [56]. The salivary and serum levels of matrix metalloproteinases (MMP)– 8 and – 13, and matrix

Table 2
Summary of cross-sectional studies in Other Asia.

Ref. No.	Study Country Year Sample Size	Parameters for Evaluated for the Diagnosis of COPD	Parameters for Evaluated for the Diagnosis of Periodontitis	Main Findings
[26]	Khijmatgar et al. India 2021 n = 212	clinical diagnosis	DMFT, SiC, CPITN, and OHI-S. Candida	The prevalence of Candida was notably elevated in the COPD patient cohort; within the realm of COPD patients, those under theophylline treatment exhibited a higher incidence of Candida colonization.
[27]	Parashar et al. India 2018 n = 98	clinical diagnosis	PI, GI, AL, PPD, CPI	The results pertaining to the PI, and GI exhibited a marked elevation among patients in the test diseases group when compared to the control group.
[28]	Vadiraj et al. India 2013 n = 100	Sputum	CAL, BOP	Improve oral health status may prove to lower the severity of lung infection in susceptible populations.
[29]	Sharma et al. India 2011 n = 200	SES	PI, OHI, GI, PPD, CAL	Patients with respiratory conditions exhibited inferior OHI and PI scores, along with notably elevated GI, PPD, and CAL values compared to the control group.
[30]	Moeintaghavi et al. Iran 2018 n = 50	FEV1/FVC ratio, CAT, MMRC, SpO2	PPD GI PI AL	The relationship between periodontal variables and respiratory indices in the course of COPD, early treatment of periodontal diseases, might considerably reduce the severity of COPD.
[31]	Javaheri et al. Iran 2020 n = 71	CAT	PPD, BOP, AL	Periodontal problems are positively associated with COPD severity as determined by GOLD criteria and negatively associated with quality of life of patients with COPD.
[32]	Bomble et al. India 2020 n = 117	Spirometer	PPD, CAL, OHI	The mean scores for PPD, CAL, and OHI were higher in the COPD group compared to the non-COPD group; furthermore, the COPD group exhibited a higher proportion of smokers in comparison to the non-COPD group.
[41]	Kedlaya et al. India 2021 n = 80	Serum cotinine level, smoking history	GI, CAL	Increased smoking with COPD causes a higher chance of progression of periodontal destruction but it is not statistically significant.
[42]	Rastogi et al. India 2019 n = 700	clinical diagnosis	PDI, PIRI	A survey of patients with various pulmonary diseases (TB, COPD, pneumonia) led to the diagnosis of periodontitis in the majority of the study cohort, with a significant proportion being classified in the high-risk category by their PIRI scores.
[43]	Raj et al. India 2018 n = 340	clinical diagnosis	DMFT, OHI, PDI, Candida	The need for regular oral health maintenance for those under COPD treatment and for greater research into the possible protective role of inhaled corticosteroids in limiting periodontal disease among patients.
[44]	Bhavsar et al. India 2015 n = 200	clinical diagnosis	PI, OHI, PPD, CALs CRP level	The frequency of brushing was notably reduced in COPD patients as compared to the control group. Additionally, the GI, PI, OHI-S, PPD, and CAL exhibited elevated levels in the COPD group.
[45]	Peter et al. India 2013 n = 501	FEV1	PI, OHI, GI, PPD CAL,	A marked elevation in CAL, PD, and OHI was

(continued on next page)

Table 2 (*continued*)

Ref. No.	Study Country Year Sample Size	Parameters for Evaluated for the Diagnosis of COPD	Parameters for Evaluated for the Diagnosis of Periodontitis	Main Findings
				observed in the patients with respiratory in comparison to the control group, revealing a trend towards augmented severity of pulmonary obstruction as these periodontal parameters worsen.

metalloproteinase-1 (TIMP-1) in saliva and serum were not significantly different between the 36 participants with mild COPD and 20 non-COPD Turkish individuals through an enzyme-linked immunosorbent assay; however, serum levels of MMP-8 and MMP-8/TIMP-1 by immunofluorometric assay showed significant differences ($p < 0.005$) between the two groups. These findings indicated that the immunodetection of MMP-8 is dependent on the selected technique [57]. Alpha-1 antitrypsin deficiency (AATD) is a rare disease and the only robust genetic risk factor for COPD. The study assessed the severity of periodontitis indicated that COPD and AATD patients exhibited a high prevalence of periodontitis (COPD: 95%; AATD: 88%), whereas neutrophil migratory accuracy was reduced in patients with stage II–IV periodontitis with COPD or AATD [58]. Additionally, periodontitis severity was associated with lung disease severity (AATD, periodontitis vs. no periodontitis; FEV_1 = 56% vs. 99% predicted; transfer factor for carbon monoxide = 59% vs. 81% predicted; $p < .0001$ for both) [59].

A study about the toll-like receptor 4 (TLR4) genotype showed that CP patients carrying the AG polymorphism in TLR4 rs1927907 were more susceptible to concomitant COPD than those carrying the GG genotype ($p = 0.005$, OR = 1.94, 95% CI: 1.22 – 3.03) after adjusting for age, sex, smoking status, and oral hygiene habits [60]. Transcriptomic analysis of chronic periodontitis (CP, GSE156993) and COPD (GSE42057, GSE94916) datasets indicated that EPB41L4A-AS1, INSR, and R3HDM1 were potential crosstalk genes between COPD and periodontitis that correlated with different infiltrating immune cells. INSR was positively correlated with hepatocytes in CP ($r = 0.6714$, $p = 0.01679$) and COPD ($r = 0.5209$, $p < 0.001$). R3HDM was positively correlated with Th1 cells in CP ($r = 0.6783$, $p = 0.0153$) and COPD ($r = 0.4120$, $p < 0.01$) [61].

Furthermore, salivary sialic acid levels were significantly higher in patients with COPD and periodontitis than in those with only periodontitis in a study that included 90 Indian participants [62]. Another case-control study from China suggested that lower serum 25-hydroxyvitamin D (25(OH)D) concentrations were significantly associated with poor periodontal health and an increased risk of COPD [63]. Corticosteroids are widely used to treat COPD and asthma [64]. Although there is no evidence to show that corticosteroid intake affected periodontal health, significantly lower levels of osteocalcin ($p < 0.0001$), calcium ($p = 0.004$), and cortisol ($p = 0.03$) were observed in 30 Turkish patients who were treated with corticosteroids for > 1 year [65].

Specific biomarkers and immune cells present in saliva and serum are useful in explaining the relationship between the two diseases. However, the accuracy of laboratory testing may be affected by changes in testing methods, and further research is required. The contents of this section are summarized in Table 4.

4. Cross-sectional study with pathogens

The lung microbiome was shown to be important in the etiology and progression of chronic respiratory diseases [66]. The oropharynx–lung continuum represents a potential gateway for bacterial exchange because of its close anatomical proximity, and research has shown that subclinical aspiration of oropharyngeal contents occurs universally in humans [67,68]. A significant negative correlation was found between the abundance of *Porphyromonas gingivalis* and FEV_1% in patients with COPD in a cross-sectional study of 80 COPD and 80 non-COPD participants in China. Additionally, an increased prevalence of *P. gingivalis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Streptococcus pneumonia* was observed in the subgingival plaques of patients with COPD in another study [69]. However, in another case-control study with 120 participants from China, the average levels of *P. gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola*, and *Haemophilus influenzae* in the subgingival plaques of patients with both COPD and periodontitis tended to be higher than those in participants with only periodontitis, but the

Table 3
Summary of cross-sectional studies in other countries.

Ref. No.	Study Country Year Sample Size	Parameters for Evaluated for the Diagnosis of COPD	Parameters for Evaluated for the Diagnosis of Periodontitis	Main Findings
[46]	Russel et al. USA 1999 n = 58	Clinical diagnosis	Dental plaque	Pulmonary pathogens formed from oral plaque were associated with COPD morbidity.
[47]	Baldomero et al. USA 2019 n = 136	SGRQ	PD, BOP, CAL, PI, GI	Periodontitis index was not associated with COPD exacerbations.
[48]	Leuckfeld et al. Norway 2008 n = 180	Clinical diagnosis	Marginal bone level	Chronic periodontitis defined as mean marginal bone level ≥ 4 mm was significantly associated with severe COPD.
[49]	Chrysanthakopoulos et al. Greece 2016 n = 3360	Self-administered questionnaire	PPD, CAL	Clinical attachment loss was significantly associated with COPD.
[50]	Winning et al. Northern Ireland 2019 n = 1380	Spirometry	PPD, CAL	Chronic periodontitis was significantly associated with decreased respiratory function, after adjusting for other confounders.
[51]	Ledić et al. Croatia 2013 n = 136	Spirometry	PI, PBI, RE, PPD, CAL	An association with severity of periodontitis and COPD. (OR 3.2, 95% CI 1.0–9.8)
[52]	MLopez-de-Andrés et al. Spain 2018 n = 51142	Self-reported questionnaire		The prevalence of periodontitis in COPD patients was higher compared to that without COPD subjects.
[53]	Bergström et al. Sweden 2013 n = 80	Spirometry, Pulmonary X - ray, computed Tomography, and SGRQ	Remaining teeth, PPD, BOP, RE, Dental plaque	Periodontitis is strongly associated with smoking, but not with the development of COPD in smokers.
[54]	Henke et al. Germany 2016 n = 206	Spirometry	PPD, Alveolar bone loss	No association was observed between periodontitis and pulmonary function, and periodontitis was associated with age and smoking habits.

Table 4
Summary of cross-sectional studies with biomarkers.

Ref. No.	Study Country Year Sample Size	Samples	Methods	Main Finds
[55]	Ji et al. Sweden 2014 n = 80	Saliva, induced sputum, bronchoalveolar lavage fluid and serum	ELISA, flow cytometry and RT-PCR	The mRNA and protein expression of TNF-α in smoking patients were lower than those in non-smokers. Negative correlations between lung function and saliva IL-8 and matrix metalloproteinase-9 (MMP-9) were found in smokers with COPD.
[56]	Öztekin et al. Turkey 2014 n = 90	Gingival crevicular fluid and serum	ELISA and latex-enhanced immuneturbidimetric assay	COPD may be associated with periodontal disease as manifested by lower number of teeth and higher levels of inflammatory mediators especially CRP in GCF.
[57]	Yıldırım et al. Turkey 2013 n = 56	Saliva and serum	Immunofluorometric assay (IFMA) and ELISA	Higher MMP-8 and MMP-8/TIMP-1 levels were detected by IFMA in COPD patients, but ELISA did not show a difference.
[59]	Sapey et al. United Kingdom 2020 n = 156	Saliva and serum	ELISA and neutrophil migration	Moderate-to-severe periodontitis was associated with elevated salivary inflammatory markers and reduced accuracy of systemic neutrophil chemotaxis towards CXCL8.
[60]	Yu et al. China 2017 n = 712	Serum	Real-time quantitative PCR	CP patients with TLR4 gene rs1927907 polymorphism may be more susceptible to COPD.
[61]	Liu et al. China 2022 n = 160	Peripheral blood mononuclear cells	Transcriptomic analysis	EPB41L4A-AS1, INSR and R3HDM1 are potential crosstalk genes between COPD and periodontitis.
[62]	Rathod et al. India 2018 n = 90	Saliva	Combined modification of the thiobarbituric acid method of Skoza and Mohos.	The mean salivary sialic acid levels were least in the healthy group followed by the periodontitis group, and it was highest in the COPD group.
[63]	Zhou et al. China 2012 n = 374	Serum	ELISA	Lower serum 25(OH)D concentrations were significantly associated with poor periodontal health and an increased risk of COPD.
[65]	Komerik et al. Turkey 2018 n = 60	Serum	Immulite immunometric assay and immulite chemiluminescence immunoassay	Significantly lower levels of osteocalcin, calcium and cortisol were observed in the patients on corticosteroid treatment.

differences were not statistically significant [70]. Owing to the limitations of these studies, the role of periodontal pathogens in the etiology and progression of COPD remains unclear.

Furthermore, a subgingival and pulmonary isolate from one patient with COPD was identified as a genetically identical *Veillonella parvula* strain [71]. Several studies have reported that the microbiome of the lungs more closely resembles that of the oropharynx rather than that of the nasopharynx or the lower gastrointestinal tract in healthy individuals [72–74]. Moffatt and Cookson described that the healthy lung microbiome was characterized by the presence of *Actinobacteria*, *Bacteriodetes*, *Firmicutes*, *Fusobacteria*, and *Proteobacteria* at the family level, whereas *Prevotella*, *Streptococcus*, and *Veillonella* were characterized at the species level according to studies using 16 S rRNA gene sequencing [75].

Alterations in bacterial diversity or abundance in the lung microbiome have been associated with several chronic respiratory diseases, including COPD, asthma, and bronchiectasis [76]. Disorders in the lung microbiome and abnormal inflammatory reactions are the two leading causes of acute COPD exacerbation [77]. While a significant feature of the lung microbiome in lower airway diseases was the reduced abundance of phylum *Bacteroidetes*, the abundance of the class *Gammaproteobacteri*, which contains many common lung-associated gram-negative pathogens, was increased in the lung microbiome of patients with lower airway disease [73]. Periodontitis is a major condition that disturbs the oral microbiome [78]. The exacerbation of periodontitis and increased diversity of microbiota lead to the deterioration of respiratory function [79]. Wu *et al.* compared the bacterial composition of subgingival plaques among COPD patients with periodontitis, COPD patients without periodontitis, periodontitis patients without COPD, and healthy individuals using 16 S rRNA gene sequencing. They reported an increase in *Dysgonomonas*, *Desulfobulbus*, and *Catonella* at the genus level and in *Porphyromonas endodontalis*, *Dysgonomonas wimpennyi*, *Catonella morbi*, and *Prevotella intermedia* at the species level in the COPD with periodontitis group, suggesting that an increase in the periodontitis-associated microbiota may be related to COPD. Additionally, the decrease in the genera *Arcanobacterium*, *Oribacterium*, and *Streptomyces* in the COPD group indicated that these three genera might be health-associated, suggesting that the decrease in these genera might exacerbate COPD [80]. Similar to the study by Wu *et al.* [80], Liu *et al.* [81] compared the microbiota of subgingival plaque and gingival crevicular fluid samples among four groups using 16 S rRNA gene sequencing. Using gingival crevicular fluid samples, the abundance of the genera *Mogibacterium* was increased in a COPD group without periodontitis. On the other hand, the abundance of the genera *Phocaeicola* and *Schwartzia* was higher in the COPD with periodontitis group. Based on the predicted functional analysis using gingival crevicular fluid samples, the COPD without periodontitis group showed significantly enriched protein families, such as genetic information processing, translation, replication and repair, metabolism, and glycan biosynthesis and metabolism. The COPD with periodontitis group showed significantly enriched protein families, such as genetic information processing, metabolism, translation, glycan biosynthesis and metabolism, and metabolism of cofactors and vitamins. Interestingly, subgingival plaque has the potential to reflect the differences in subgingival microbiota in patients with COPD compared to gingival crevicular fluid [81]. Tan et al. reported the homology of bacterial species between the oral cavity and lungs from the same patient with acute exacerbations of COPD using homology analysis utilizing 16 S rRNA gene sequencing. Bacteria that showed homology between the oral cavity and lungs were dental plaque pathogens such as *Aggregatibacter actinomycetemcomitans*, *Capnocytophaga sputigena*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* and lung pathogens such as *Acinetobacter baumannii, Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and *Streptococcus pneumoniae* [82].

These data support the hypothesis that COPD is correlated with periodontitis via these significantly altered specific bacteria, and treatment of periodontitis may reduce the exacerbation frequency of COPD. However, further studies are required to determine the role of periodontopathic bacteria in COPD. The contents of this section are summarized in Table 5.

5. Retrospective study

A retrospective study of the association between periodontal disease and COPD was conducted in the early 2000 s. Some studies reported in the United States were based on the analysis of the National Health and Nutrition Examination Survey III (NHANES III), which was conducted by the National Center for Health Statistics and documented the general

Table 5
Summary of the effect of periodontitis pathogens in COPD using 16 S rRNA gene sequencing.

Ref. No.	Study Country Year Sample Size	Type	Methods	Main Finds
[69]	Tan et al. China 2019 n = 160	cross-sectional study	Real-time polymerase chain reaction	*Porphyromonas gingivalis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa,* and *Streptococcus pneumonia* prevalence was increased in participants with COPD compared with control group. A significant negative association was noted between the relative content of Pg and forced expiratory volume in one second in participants with COPD.
[70]	Zhou et al. China 2020 n = 120	cross-sectional study	Real-time polymerase chain reaction	The average levels of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Treponema denticola,* and *Haemophilus influenzae* in subgingival plaque of patients with both COPD and periodontitis were found to tend to be higher than that in the participants with only periodontitis.
[79]	Winning et al. Northern Ireland 2023 n = 507	cross-sectional study	16 S rRNA gene sequencing	Subgingival microbial diversity was associated with reduced respiratory function.
[80]	Wu et al. China 2017 n = 105	cross-sectional study	16 S rRNA gene sequencing	An increase in the genera *Dysgonomonas*, *Desulfobulbus*, and *Catonella* and in four species (*Porphyromonas endodontalis*, *Dysgonomonas wimpennyi*, *Catonella morbi*, and *Prevotella intermedia*) in both COPD with periodontitis patients suggests that an increase in these periodontitis-associated microbiota may be related to COPD.
[81]	Liu et al. China 2023 n = 112	cross-sectional study	16 S rRNA gene sequencing	Significant differences in the bacterial community and functional characterization of oral microbiota in COPD without periodontitis, COPD with periodontitis group. Compared to gingival crevicular fluid, subgingival plaque may be more appropriate for reflecting the difference of subgingival microbiota in periodontitis patients with COPD.
[82]	Tan et al. China 2014 n = 53	cross-sectional study	16 S rRNA gene sequencing	Dental bacteria may contribute to the pathology of acute exacerbation of COPD.
[110]	Sundh et al. Sweden 2021 n = 101	longitudinal study	16 S rRNA gene sequencing	Dental cleaning treatment is associated with a reduced frequency of COPD exacerbations.

health and nutritional status of individuals randomly selected from sampling areas that encompassed the continental United States from 1988 to 1994 [83,84]. Scannapieco *et al.* reported that participants with a history of COPD had greater periodontal attachment loss than those without a history of COPD. Especially, patients with mean attachment loss (MAL) $\geq$ 3.0 mm had a higher risk of COPD than those with MAL $<$ 3.0 mm (OR: 1.45, 95% CI: 1.02 – 2.05) [83]. Hyman *et al.* reported a relationship between smoking, periodontal disease, and COPD [84]. They reported no significant relationship between periodontal disease and COPD in former smokers and nonsmokers. However, current smokers with $\geq$ 4 mm MAL had an OR of 3.71 (95% CI: 1.74 – 7.89). These results suggest that cigarette smoking may be a cofactor in the association between periodontal disease and COPD. Another study conducted in 2005 included a subset of 860 well-functioning elderly individuals [85]. This study could not provide direct inference of cause and effect, it reveals a significant association between periodontal disease and airway obstruction, an early stage of compromised pulmonary function. Chen *et al.* conducted research based on the latest data from the 2009–2012 NHANES in the United States, and included a total of 6313 participants aged 30 years or older [86]. Compared to those without periodontitis, the multivariate-adjusted OR of airflow obstruction for moderate and severe periodontitis were 1.38 (95% CI: 1.01 – 1.75) and 1.47 (95% CI: 1.06 – 2.01). This study suggests that moderate-to-severe periodontitis may be associated with a decline in lung function in the United States.

In Sweden, a retrospective study was conducted on older Caucasian dentate individuals from Karlskrona between the ages of 60 and 93 years, and it revealed that periodontitis was independently associated with airflow limitation. This relationship was independent of known confounders, such as smoking, BMI, exercise, systemic diseases, educational level, and living conditions [87].

In China, more than 1385 permanent residents aged over 75 years who were referred for periodontal treatment at the Shanghai Ninth People's Hospital between 2010 and 2014 were analyzed [88]. The study showed that mortality from respiratory diseases was significantly associated with periodontal disease. After adjusting for relevant confounding factors, the hazard ratio (HR) for patients with periodontitis was 2.72 (95% CI: 1.04 – 7.11). However, the number of teeth lost was not significantly associated with total respiratory disease or mortality due to COPD. Three studies were conducted in South Korea based on the Sixth Korean National Health and Nutrition Examination Survey

(KNHANES). Chung *et al.* revealed that periodontitis (CPI 3 or 4) was associated in males with COPD after adjusting for confounding factors (CPI 3: relative risk [RR] = 1.38, 95% CI: 1.12 – 2.05; CPI 4: RR = 1.23, 95% CI: 1.06 – 1.56) [89]. Lee *et al.* conducted a study based on the Sixth KNHANES 2014 [90]. The assessment of reduced pulmonary function data was classified as "normal," "restrictive impairment," or "obstructive impairment." For pulmonary function assessments, obstructive pulmonary impairment, but not restrictive pulmonary impairment, was a significant predictor of periodontitis based on the univariate analysis (unadjusted OR = 1.729, 95% CI: 1.344 – 2.233). However, the associations between periodontitis and restrictive pulmonary impairment (adjusted OR = 1.059, 95% CI: 0.829 – 1.540) or obstructive pulmonary impairment (adjusted OR = 1.140, 95% CI: 0.849 – 1.530) were not statistically significant. Likewise, Jung *et al.* also used data from the Sixth KNHANES 2013 – 2015 (N = 7719) [91]. This report revealed that poor periodontal status exhibited a higher prevalence of COPD. Moreover, patients with COPD had more missing teeth than those without COPD. The logistic regression model, adjusted for demographic, socioeconomic, health, and oral health-related factors, showed that periodontal status was not significantly associated with COPD, whereas participants with more missing teeth had a significantly increased risk of having COPD. Recently, artificial intelligence (AI)-based statistical analysis was applied to the NHANES III dataset [92]. AI-based analysis revealed that a high CAL appeared to increase the risk of COPD; however, causal relationships could not be determined in this study.

Although some studies have reported that periodontal disease associated with COPD is a risk factor, especially in current or former smokers, others have reported no significant or limited relationship between periodontal disease and COPD. As a result, most studies have concluded that large prospective and longitudinal studies are required to examine this relationship in greater detail. The contents of this section are summarized in Table 6.

6. Longitudinal study

There are seven papers on longitudinal studies. The oldest study on this topic was conducted in 1988. Hayes *et al.* reported that logistic regression analysis examined the independent contribution of bone loss measured at baseline to the subsequent risk of developing COPD over a 25-year follow-up period. Approximately 23% of the participants happened COPD, although they were healthy at baseline. Alveolar bone loss status at baseline was an independent risk factor for COPD, with patients in the worst population quintile of bone loss found to be at significantly higher risk [93].

Another report focused on the IgG antibody titer against *P. gingivalis;* 93 individuals were prospectively followed up for over one year to detect exacerbations. The number of exacerbations and their frequencies were significantly lower in patients with higher IgG titers than in those with normal IgG titers [94]. There has also been a large cohort study with over 20,000 subjects. The overall incidence of periodontal diseases was 1.19-fold greater in the COPD group than in the non-COPD group (32.2 vs 26.4 per 1000 person-years; CI: 1.15 – 1.24). Compared with non-COPD patients, the adjusted HRs of patients with COPD increased with the number of emergency room visits (from 1.14 [95% CI:1.10 – 1.19] to 5.09 [95% CI: 4.5 – 5.72]) and admissions (from 1.15 [95% CI: 1.10 – 1.20] to 3.17 [95% CI: 2.81 – 3.57]) [95].

Several studies in Japan have indicated that periodontitis is a risk factor for worse status in patients with COPD. Takeuchi *et al.* reported that there was a tendency for the adjusted risk ratio of developing rapid lung function decline (≥160 mL/3 years, the highest quartile of the distribution of FEV_1 declines) to increase as mean clinical attachment levels increased (p = 0.039) [96]. In addition, the analysis was performed using a 5-year follow-up population-based cohort study. After adjustment for potential confounders, including smoking intensity, the relationship between severe periodontitis and the risk of COPD remained significant. Moreover, periodontitis severity was positively

Table 6
Summary of retrospective study.

Ref. No.	Study Country Year Sample Size	Parameters for Evaluated for the Diagnosis of COPD	Parameters for Evaluated for the Diagnosis of Periodontitis	Main Findings
[83]	Scannapieco et al. America 2001 n = 13792	FEV1/FVC ratio	Mean attachment loss (MAL), gingival bleeding, Dental health index	Patients with MAL ≥ 3.0 mm had a higher risk of COPD than those with MAL < 3.0 mm.
[84]	Hyman et al. America 2004 n = 7625	FEV1/FVC ratio	Loss of Attachment	Cigarette smoking may be a cofactor in the association between periodontal disease and COPD.
[85]	Katancik et al. America 2005 n = 860	FEV1/FVC ratio	GI, PPD, Loss of Attachment	While this study cannot provide direct inference of cause and effect for COPD, it revealed a significant association between periodontal disease and airway obstruction, particularly in former smokers.
[86]	Chen et al. America 2022 n = 6313	FEV1/FVC ratio	PPD, AL	After adjusting for relevant confounding factors, the hazard ratio (HR) for patients with periodontitis was 2.72 (95% CI: 1.04 – 7.11), while the number of teeth lost was not significantly associated with total respiratory disease or mortality.
[87]	Winning et al. Sweden 2020 n = 826	FEV1/FVC ratio	radiographical assessment, missing teeth	Periodontitis was independently associated with airflow limitation.
[88]	Qian et al. China 2020 n = 1385	respiratory disease mortality	alveolar bone loss	Mortality from respiratory diseases was significantly associated with periodontal disease after adjusting for relevant confounding factors.
[89]	Chung et al. South Korea 2016 n = 5878	FEV1/FVC ratio	CPI, Questionnaire for oral hygiene	Periodontitis (CPI 3 or 4) was significantly associated in males with

(*continued on next page*)

Table 6 (*continued*)

Ref. No.	Study Country Year Sample Size	Parameters for Evaluated for the Diagnosis of COPD	Parameters for Evaluated for the Diagnosis of Periodontitis	Main Findings
				COPD and participants with more missing teeth had a significantly increased possibility of having COPD.
[90]	Lee et al. South Korea 2019 n = 4004	FEV1/FVC ratio	CPI	The association between periodontitis and restrictive impairment or obstructive impairment was not significant.
[91]	Jung et al. South Korea 2020 n = 7719	FEV1/FVC ratio	CPI	There was no statistically significant association between periodontal disease and COPD among former or non-smokers.
[92]	Vollmer et al. America 2022 n = 15868	Pulmonary function tests	Database extraction attachment loss	Based upon AI-based analyses, high CAL appears to increase the risk of COPD, although causal relationships cannot be concluded.

associated with the risk of developing COPD (p = 0.043) [97]. A recent study examined the relationship between the incidence of COPD and periodontitis and smoking by A Cox proportional hazard model. Both periodontitis and heavy smoking had significant effects on COPD development in a multivariable analysis [98]. In addition, a cohort study was conducted on the impact of tooth loss and periodontal disease on respiratory events in patients with COPD. After adjusting for potential confounders, the study demonstrated that the risk of COPD-related events might be attributable to both edentulism and elevated serum IL-6 levels [99]. Another study also reported that individuals with greater bone resorption exhibited more comorbidities than their counterparts. However, the study showed no significant association between periodontitis and COPD [100].

Almost all studies mentioned above reported that periodontal disease was a risk factor for COPD exacerbation. However, further studies are needed to clarify the association between periodontal disease and COPD. The contents of this section are summarized in Table 7.

Table 7
Longitudinal studies regarding the relationship between COPD and periodontal disease.

Ref. No.	Study Country Year Sample Size	Methods	Main Finds
[93]	Hayes et al. America 1998 n = 1231	ABL FEV1	ABL status at baseline was an independent risk factor for COPD, with patients in the worst population quintile of bone loss (mean ABL > 20% per site) found to be at significantly higher risk (OR = 1.8; 95% CI = 1.3 – 2.5)
[94]	Takahashi et al. Japan 2012 n = 109	IgG antibody titer against *Porphyromonas gingivalis*	The number of exacerbations and their frequencies were significantly lower in patients with higher IgG titers than in those with normal IgG titers (0.8 vs.1.2 per year, p = 0.045, and 14.3 vs. 38.6%, p = 0.009, respectively).
[95]	Shen et al. China 2015 n = 22,332	index date to the current date of periodontal diseases	Patient with COPD are at a higher risk of developing periodontal diseases than the general population.
[96]	Takeuchi et al. Japan 2018 n = 2557	CAL PPD FEV1	A positive association was observed between mean PPD levels and RR of developing rapid lung function decline (*P* trend = 0.047).
[97]	Takeuchi et al. Japan 2019 n = 1585	PPD , CAL , FEV1/FVC	The adjusted Relative Risk of development of COPD was significantly higher in subjects with severe periodontitis than in those with no/mild periodontitis (RR = 3.51; 95% CI, 1.15–10.74).
[98]	Saito et al. Japan 2023 n = 50,333	Community Periodontal Index and pulmonary function tests	Periodontitis has no interaction with smoking but has an independent effect on developing COPD.
[99]	Barros et al. America 2013 n = 15,792	Respiratory and periodontal conditions	A statistically significant association was found between oral health status and COPD-related events, even adjusting for conditions such as hypertension, smoking and diabetes.
[100]	Zhao et al. China 2019 n = 17,400	community periodontal index, BL, bone loss/age and number of remaining teeth	Periodontal disease experience to some extent reflects the host susceptibility to onset of common systemic comorbidities.

7. Intervention study

There are six papers on intervention studies. Generally, COPD is exacerbated by bacterial or viral infections. Oral hygiene procedures and dental treatments also cause transient bacteremia [101–103]. Successful periodontal treatment improves systemic inflammation and positively affects other diseases, including diabetes [104–106]. Periodontal debridement performed with ultrasonic or hand instruments for chronic periodontitis has no negative effect on the quality of life or illness in patients with COPD [107]. The initial periodontal treatment group received oral hygiene instructions and full-mouth scaling and root planning using hand instruments and showed a significant reduction in the exacerbation frequency during the follow-up period (p = 0.01). Although the median exacerbations declined from three to two times in the treatment group, patients with no treatment showed an increase in exacerbations from two to three times [108]. In Taiwan, the effects of periodontal treatment on COPD were investigated in a retrospective cohort study using data from a large population. Shen *et al.* reported that periodontal treatment for COPD patients could reduce the risk of

adverse respiratory events and mortality. During the 5-year follow-up period, the incident adverse respiratory events were lower in the treatment group than in the comparison group for ER uses and hospitalizations [109]. Periodontal treatment for COPD patients decreased COPD exacerbations and improved the ratio of FEV1 to FVC [110–112]. A Swedish study investigated whether dental cleaning was associated with improved health status, lung function, or periodontal status and whether specific components of the plaque microbiome at baseline were associated with changes in exacerbation frequency. They found that the risk of new exacerbations was significantly lower in patients both in the total population (regression coefficient 0.36 (95% CI: 0.25 – 0.52), $p < 0.0001$) and in the population with repeated dental cleaning (0.16 (0.10 – 0.27), $p < 0.0001$) compared with the no treatment group. Additionally, the FEV_1 percentage of the predicted value was also decreased in periodontal treatment patients with COPD [110].

In the present, periodontal treatment may be effective in preventing COPD exacerbation. Therefore, well-designed randomized clinical trials are required. The contents of this section are summarized in Table 8.

8. Mechanism study *in* vitro and *in vivo*

Although the above studies have demonstrated an association between periodontal disease and COPD, the specific cause of this phenomenon remains to be elucidated for further clinical application. COPD is a disease characterized by emphysema and chronic bronchitis, long-term dyspnea, poor airflow, recurrent mucosal inflammation, and peribronchiolar fibrosis, mainly triggered by viruses, bacteria, or pollutants [113]. As periodontitis is a bacterial infectious disease with increased oral plaque, the transfer of proliferating bacteria (e.g. by aspiration) has been seen as a bridge between the two diseases [114].

Table 8
Intervention studies regarding the relationship between COPD and periodontal disease.

Ref. No.	Study Country Year Sample Size	Methods	Main Findings
[107]	Agado et al. America 2012 n = 30	Respiratory Questionnaire	Periodontal debridement for chronic periodontitis has no effect on quality of life and illness in patients with COPD.
[108]	Kucukcoskun et al. Turkey 2013 n = 40	Number of exacerbations	Initial periodontal therapy showed a significant reduction in the exacerbation frequency during the follow-up period ($P = 0.01$).
[109]	Shen et al. China 2016 n = 126,251	Adverse respiratory event	During the 5-year follow-up period, all three types (acute exacerbation, pneumonia, and acute respiratory failure) of incident adverse respiratory events were lower in periodontal treatment group than in the comparison group for ER uses and hospitalizations.
[110]	Sundh et al. Sweden 2021 n = 101	16 S rRNA gene sequencing	Advanced dental cleaning is associated with a reduced frequency of COPD exacerbations.
[111]	Zhou et al. China 2014 n = 306	Periodontal indexes, respiratory function, and COPD exacerbations	FEV1 were significantly higher in both Scaling and SRP groups compared with the control group during the follow-up ($p < 0.05$).
[112]	Sharma et al. India 2021 n = 75	PI, GI, PPD, CAL, and BOP and spirometry (FEV1/forced vital capacity (FVC)) values	COPD patients have poorer periodontal health as compared to systemically healthy counterparts.

8.1. Studies focusing on *Fusobacterium nucleatum*

Periodontal pathogens have been studied for a century, and *P. gingivalis* (Pg), *Tannerella forsythia,* and *Treponema denticola* have been defined as the most harmful (red complex) pathogens, while other pathogens are considered milder than them, such as *Prevotella intermedia*, *Prevotella nigrescens* and *Fusobacterium nucleatum* (Fn) [115]. Interestingly, the research performed by Hayata *et al.* showed that heat-inactivated Fn was the most inflammation-inducible bacterium among various periodontal pathogens when infecting the BEAS-2B (human bronchial cell) and human pharyngeal (Detroit 562) cell lines [116]. Although the inflammatory response of the A549 (human alveolar epithelial) cell line was questionable in their study, respiratory inoculation of heat-inactivated Fn into healthy mice demonstrated its pathogenicity, which has also been confirmed by others, accompanied by the upregulation of MMP-9 [117]. Meanwhile, a more obvious involvement of several types of immune cells and chemokines was observed when COPD was simultaneously induced by elastase injection. Compared with healthy mice, their results demonstrated a much greater deterioration of pulmonary function and upregulation of MMP-12, perforin, and mucin, indicating an exacerbation of the inflammatory response when Fn infection and COPD coexist [118]. To clinically verify these findings, Li *et al.* detected Fn and *Pseudomonas aeruginosa* (Pa) in sputum samples from patients with acute exacerbation of COPD, and the results showed a correlation between the detection of Fn and worsening of lung function [119]. With regard to the specific mechanism by which Fn exacerbates COPD, Fn was co-cultured with Pa, and it was found that the addition of Fn accelerated proliferation and plaque formation and even reduced the antibiotic susceptibility of Pa. The authors explained that enhanced proliferation and plaque formation were possibly caused by the upregulation of *pelB* and *pslA* induced by Fn-produced *Fusobacterium* adhesin A, and its pathogenic effect was confirmed in a subsequent study infecting the A549 cell line [120]. Furthermore, heat-inactivated Fn infection in the A549 cell line also increased the expression of angiotensin-converting enzyme 2, but the addition of the main virulence factor of Fn (butyric acid) did not affect the inflammatory response, suggesting that the pathogenic factor of Fn in COPD is something else [121].

8.2. Other studies

Only a few studies have taken a sensible approach from different perspectives, as direct evidence suggests the crucial role of Fn in this relationship. To reduce the influence of specific types of bacteria, Rosa *et al.* induced periodontitis by ligature placement and COPD by smoking in mice and then analyzed bronchoalveolar lavage fluid, blood, and lung samples [122]. Notably, the induction of periodontitis in mice with pre-existing COPD did not exacerbate the disease, and in fact may have relieved the progress of COPD. Given that the ligature model lacks traditional periodontal pathogens [123], and that COPD was not induced by infection, it is reliable and suggests that the key to explaining the relationship between the two diseases remains human-associated bacteria. Han *et al.* also performed experiments in rats to investigate this relationship but used a submucosal injection of Pg to induce periodontitis [124]. Due to the lack of COPD control group, their results can only discuss the effect of COPD on periodontitis and conclude that there was no effect; however, the evidence could be used to deny the influence of COPD on periodontitis. Moreover, since treating BEAS-2B cell lines with other heat-inactivated periodontal pathogens still stimulated the inflammation, some researchers discussed bacteria other than Fn. Since Pg and *Acinetobacter baumannii* (Ab) are both present in the oral cavity and pulmonary system, they discussed the differences between

monoculture and co-incubation by comprehensive analysis, which resulted in several alterations in gene expression and enhanced colonization [125]. However, their conclusion was over-interpreted and needs to be confirmed by further studies due to the lack of evidence for the detection of the two bacterial species in COPD patients.

8.3. Summary

Taking all the relevant studies together, the mechanism by which periodontitis exacerbates COPD is mainly related to the transfer of bacteria in oral plaque to the respiratory system, and Fn is its strongest "candidate" so far. However, most studies have used inactivated bacteria, which do not reflect all the viral factors of the pathogen. To verify the objective link between the two diseases, further studies using live bacteria are needed to confirm the existing view and a comprehensive analysis of samples co-infected with several periodontal pathogens or whole plaques should be performed. The contents of this section are summarized in Table 9.

9. Conclusion

This review summarized the relationship between COPD and periodontal disease (Fig. 1). While the incidence of both diseases is closely related to social factors, such as geographical location and economic development, epidemiological studies across various countries and regions still indicate a positive correlation between the prevalence and severity of periodontal disease and the onset and progression of COPD. Through 16 S rRNA gene sequencing and various laboratory testing methods, researchers have discovered that COPD may be associated with periodontal disease through significant alterations in specific bacteria and biomarkers. Moreover, in vitro and in vivo studies have suggested that periodontal disease exacerbates COPD by transferring Fn in the oral biofilm. Longitudinal research and intervention studies have indicated that periodontal disease is a risk factor for COPD and that periodontal treatment may effectively improve COPD symptoms.

The association with COVID-19 has recently gained attention as new research [126–128] field. Similar to the relationship between COPD and periodontal disease, oral infections from periodontitis may enter the respiratory system through the oral-lung pathway, potentially increasing the risk of COVID-19 infection and/or symptoms [129–131].

In summary, an increasing number of studies have confirmed the association between periodontitis and COPD. However, smoking is a common risk factor for both disease, which make it difficult to find out the direct relationship between these two diseases. Most of the previous studies were cross-sectional or case-control studies and lacked direct evidence from randomized controlled clinical studies. To confirm whether periodontal disease promotes the progression of COPD, and whether periodontal treatment prevents COPD exacerbation, more direct evidence, as well as larger samples and more rigorous epidemiologic study designs, are needed. Moreover, the related mechanisms of influence need to be further investigated.

The association between periodontitis and COPD is complex and multifaceted. Inflammation and the microbiome appear to be the key factors influencing the development of both diseases through shared inflammatory pathways. Understanding these interconnections may provide valuable insights for the prevention and management of periodontitis and COPD as well as for addressing similar pandemics such as COVID-19 more effectively.

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Table 9
Summary of studies on mechanisms.

Ref. No.	Study Country Year	Experimental type	Main Findings
[116]	2019 Hayata et al.	In vivo and In vitro	Among several periodontal pathogens, exposure to elevated levels of Fn was the most potent in inducing the production of pro-inflammatory cytokines by human bronchial and pharyngeal epithelial cells, which may lead to exacerbation of COPD.
[117]	2022 Suzuki et al.	In vivo and In vitro	Fn may contribute to the onset of pulmonary diseases via MMP-9 expression through extracellular-regulated kinase 1/2 and NF-κB activation.
[118]	2022 Suzuki et al.	In vivo	The administration of Fn to elastase-treated mice enhanced inflammatory responses, production of alveolar wall destruction factors, progression of emphysema, and recruitment of mucin.
[119]	2020 Li et al.	In vitro	Fn frequently coexisted with Pa in the respiratory tract of AECOPD patients, and co-culturing the two bacteria promoted bacterial proliferation and induced antibiotic tolerance by forming a dense biofilm surrounded by excessive Pel and Psl polysaccharides, which might be induced by FadA.
[120]	2021 Li et al.	In vitro	Fn could co-aggregate with Pa to synergistically invade into pulmonary epithelial cells and transiently resist P. aeruginosa-induced cytotoxic damage to amplify IL-6 and TNF-α associated inflammation in pulmonary epithelial cells simultaneously infected with P. aeruginosa and F. nucleatum.
[121]	2021 Takahashi et al.	In vitro	The culture supernatant of the Fn upregulated the SARS-CoV-2 receptor angiotensin-converting enzyme 2 in A549 alveolar epithelial cells, and induced IL-6 and IL-8 production by A549 alveolar epithelial cells, BEAS-2B bronchial epithelial cells, Detroit 562 pharyngeal epithelial cells, and primary alveolar epithelial cells.
[122]	2020 Rosa et al.	In vivo	The association COPD and periodontitis decreased macrophages, TNF-α and INF-γ in BAL, when compared to the COPD group maintaining emphysema levels by alveolar enlargement reorganization of collagen fibers and also mean linear intercept and mucus.
[124]	2019 Han et al.	In vivo	Although COPD had no effect on periodontitis, 25-OHD3 treatment significantly reduced inflammation by decreasing serum levels of RANKL, TNF-α and IL-1 and increasing that of IL-10, while reducing alveolar bone loss and slightly improving lung function in the periodontitis group or COPD+periodontitis group.
[125]	2018 Miller et al.	In vitro	The presence of Ab increased the abundance of Pg in model dual-species communities,suggesting that both Pg and Ab adapt to each other and have synergistic potential for increased pathogenicity.

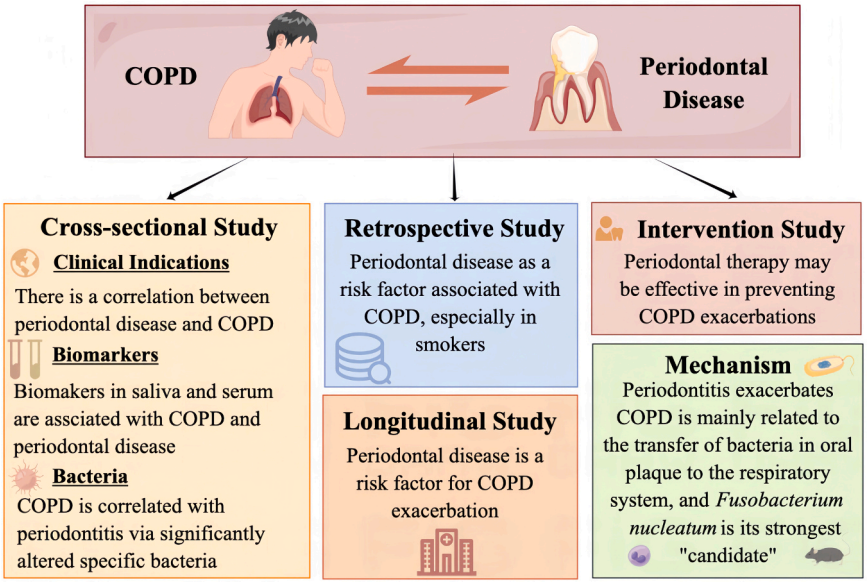

Fig. 1. The summary of this review. Periodontal disease has an association with COPD.

CRediT authorship contribution statement

Literature collection, P.L and S.K.; writing, P.L., A.L., Yosuke.T., K. N., Y.O., K.T., Yuta.T., T.S., and S.K.; revision, H.N., A.A., T.I., and S.K. All authors have read and agreed to the published the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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