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The Relationship between Periodontitis and COPD and the Impact of Periodontal Therapy on COPD Outcomes: A Narrative Review

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Abstract: ***A common ailment, chronic bacterial-initiated inflammatory periodontitis is closely related to several systemic diseases, including chronic obstructive pulmonary disease (COPD). Similar risk factors, pathophysiology, and bacteria are present in both COPD and periodontitis. Clinical and epidemiological studies have found a strong link between the two illnesses. Severe periodontitis increased the likelihood of developing COPD in a person. Recent research suggests that periodontitis is widespread among COPD patients, and it has been shown that periodontal therapy may improve a number of COPD outcomes. The goal of this review is to determine the relationship between COPD and periodontitis as well as how periodontal therapy affects COPD patients.***

Keywords: Periodontitis, COPD, Microbial Colonization, Periodontal therapy, Exacerbations

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder has a history that is consistent with exposure to tobacco smoke and other unpleasant particles or gases as well as a partially reversible airflow restriction [1]. Patients with COPD feel shortness of breath throughout regular activities and even when at rest as a result of recurrent attacks and acute exacerbations of the condition. 10% of those over 40 have COPD, which is a significant cause of morbidity and impairment [2]. Asia and Africa account for 90% of COPD-related fatalities worldwide, which places COPD as the third highest cause of mortality overall [3]. Exacerbations of COPD are difficult events brought on by respiratory viral or bacterial pathogens as well as environmental elements like pollution and ambient temperature, and they frequently call for medication adjustments or even hospitalization. Additionally, they might negatively affect the progression of diseases, the frequency of hospitalizations, and general health, which would result in less favorable results [4, 5].

One of the six non-communicable diseases with the highest prevalence in the world [6.7] is periodontitis, which is characterized by alveolar bone loss, clinical attachment loss, gingival bleeding, periodontal pocketing, and chronic inflammation and polymicrobial plaque biofilms [8]. Teeth may eventually become loose and fall out as a result of immunological reactions brought on by germs adhering to the tooth's surface [9]. Although periodontitis is mostly preventable via routine, self-administered dental hygiene, its incidence is still significant and it is believed to be a primary cause of tooth loss [10]. In addition to leading to tooth loss, periodontitis has a deleterious impact on a number of systemic diseases, including as osteoporosis, chronic obstructive pulmonary disease (COPD), diabetes, rheumatoid arthritis, and cardiovascular disease.

Both COPD and periodontitis are chronic, inflammatory, progressive diseases that lower quality of life [11]. They are all at risk for the same diseases, including diabetes, poor socioeconomic position, microbial infection, environmental pollution, smoking, and bad dental habits [12]. Periodontitis had an odds ratio (OR) of 2.08 for the onset of COPD in a meta-analysis of 14 observational studies [13]. However, COPD patients had a 1.2 times higher chance of acquiring periodontal disease than the general population, and this risk increased to 3.17 times for those who had previously been hospitalized [14]. Additionally, it has been shown that COPD patients with periodontal disease had lower lung function [15, 16]. Routine evaluation and periodontal therapy have been shown to significantly improve the clinical and functional results of COPD patients in number of systematic reviews and meta-analyses. Most recent research indicates that periodontal care, whether surgical or non-surgical, improves patients with COPD and periodontitis' quality of life, lung function, and exacerbations [17].

In addition to emphasizing the impact of periodontal therapy on COPD patients, this review concentrates on the demographic, clinical, pathological, and microbiological relationships between COPD and periodontitis.

2. Associations of COPD and Periodontitis

Periodontitis, a polymicrobial infection, is closely related to lung infections because of the structural relationship between the lungs and the oral cavity, which makes the latter a potential reservoir of the respiratory pathogens [18].

2.1. Epidemiological associations between COPD and periodontitis

The first theory on the connection between COPD and periodontitis was proposed in 1990; however a number of epidemiological studies later verified this association [19]. The first National Health and Nutrition Examination Survey (NHANES I) data were reviewed in 1998 by Scannapieco et al. [20], who found a link between periodontitis and chronic

respiratory disorders. In a follow-up study based on NHANES III carried out three years later, Scannapieco et al. discovered that periodontal attachment loss with a history of COPD was significantly higher than that of patients without a history of COPD [21]. Patients presenting a mean attachment loss of 3.0 mm had a higher risk of COPD. Scannapieco et al. [20] concluded from the two investigations that periodontitis and COPD may be related, and they further hypothesized that periodontitis would hasten the progression of COPD.

The relationship between COPD and periodontitis was the subject of several epidemiological studies that looked at bone loss, clinical attachment loss, OHI-S, and plaque adherence [22].

2.1.1. Cross sectional study

According to Jae Ho Chung, et al., COPD patients had considerably fewer teeth overall and a higher Decayed-Missing-Fill (DMF) tooth index [23]. In comparison to COPD participants without periodontitis, those with periodontitis experienced more frequent furcation involvement, less teeth, and marginal bone loss [24]. Additionally, there is a strong correlation between the severity of periodontitis and the number of days a patient needs to stay in the hospital for a respiratory issue. In a different study, Zhou et al. [25] discovered that COPD patients' quality of life was significantly decreased when they had more missing teeth and a high plaque index, both indicators of poor periodontal health. A cross-sectional study demonstrated that mean CAL was substantially linked with variables of mobile dynamic and static lung capacities, airflow limitation, and hyperinflation (P 0.05) after accounting for all relevant factors.

The amount of the CAL/probing depth, mean probing depth, and the number of missing teeth all had associations. Recent cross sectional investigations show that participants with missing teeth had lower absolute values for FEV1, FVC, and FEV1/ FVC, and that higher mean CAL levels were related to lower FVC and FEV1 levels and higher RV/ TLC ratio levels, as well as higher RV/TLC levels were connected with missing teeth [26, 27]. To estimate the risk of periodontal disorders, Shen et al. conducted a large population-based longitudinal cohort study with 22,332 COPD patients and two randomly chosen matching adults without COPD for each case. After 11 years of observation, it was discovered that the COPD group had a 1.19-fold higher total incidence of periodontal illnesses [28]. This implies that periodontitis and COPD have a close relationship.

2.1.2. Case Control Study

According to a study by Takeshi Terashima, COPD patients had fewer surviving teeth, bleeding when they were probed, deeper probing, and lower blood albumin levels. A risk factor for COPD was poor periodontal health on its own [29]. The incidence of COPD exacerbations was shown to be lower in the group receiving periodontal therapy compared to the control group in a different case-control research by Meric et al. that looked at the effects of periodontal therapy on COPD patients [30]. There was a strong correlation between inadequate oral health awareness and COPD in all populations. Patients with COPD appeared to have lower periodontal health than people with normal lung functions. Promoting oral health, teaching people how to wash their teeth properly, and giving COPD patient's expert periodontal care may help to slow the progression of the disease.

2.1.3. Longitudinal Study

Periodontitis and COPD have a substantial association, with the risk of COPD rising by 60% for every 20% increase in alveolar bone loss, according to a longitudinal study by Hayes et al. [31].

3. Common Pathophysiological process in COPD and Periodontitis

Both COPD and periodontitis shares common, complex pathophysiological events.

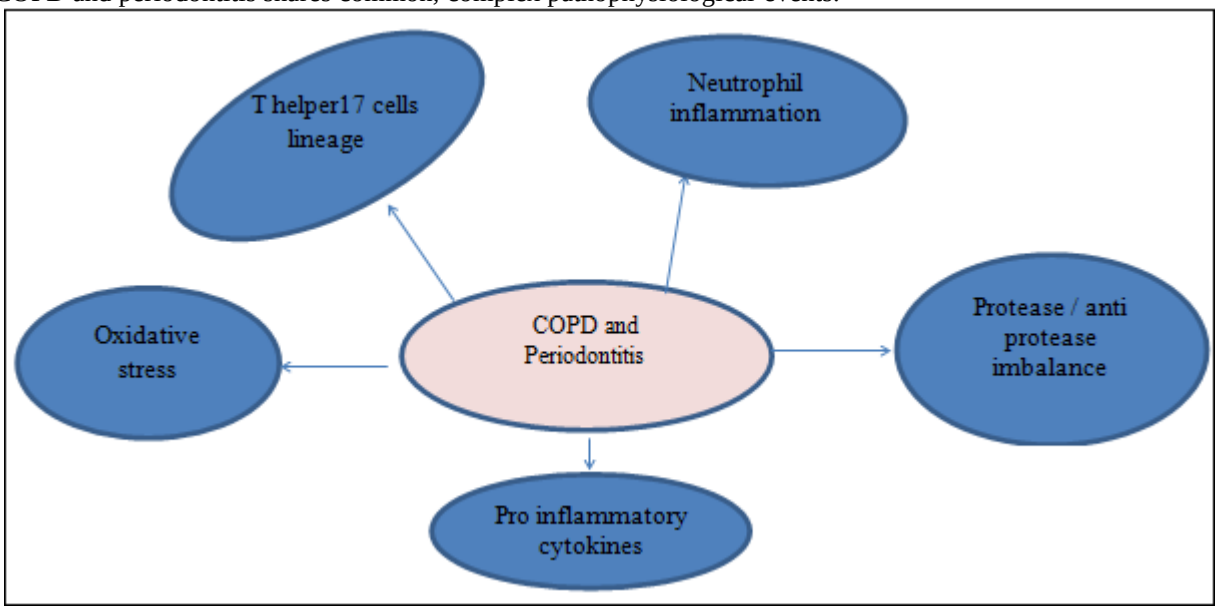

Figure 1: Shows the common pathophysiological events

3.1. T helper 17 cells lineage

Both the degenerative processes of periodontitis and COPD are significantly influenced by Th17 and the cytokines that it secretes and induces. Chronic inflammation is one of the key clinical characteristics of COPD and periodontitis, and it is fueled by the pro-inflammatory cytokine interleukin-17 (IL-17), which is generated by Th17 cells [32]. As a result of IL-17 stimulation, periodontal ligament (PDL) cells and primary gingival epithelial cells highly express the proinflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-alpha), stromelysin, prostaglandin E2 (PGE2), and others [33]. By stimulating the production of CXCL1, CXCL5, Chemokine (C-X-C motif) ligand 8 (CXCL8), Granulocyto-colony-Stimulating-Factor (G-CSF), and Granulocyte-macrophage colony stimulating factor (GM-CSF) by airway epithelial cells, IL-17 enhances lung tissue inflammation and damage in a manner similar to this. Similar to this, IL-17 increases the production of CXCL1, CXCL5, Chemokine (C-X-C motif) ligand 8 (CXCL8), Granulocyto-colony-Stimulating-Factor (G-CSF), and Granulocyte-macrophage colony stimulating factor (GM-CSF) by airway epithelial cells, which promotes lung tissue inflammation and damage and worsens COPD [34]. Environmental factors including Porphyromonas gingivalis (P. gingivalis) or cigarette smoke may induce the expression of Th17 cell differentiation-inducing cytokines, particularly IL-1, IL-6, IL-23, and Transforming growth factor- (TGF-) [35,36]. Periodontitis and COPD may eventually be brought on by these circumstances. In general, a pathogenic pathway involving the Th17 lineage is involved in both COPD and periodontitis. This pathway leads to Th17 differentiation and recruitment, followed by the production of IL-17, which promotes periodontitis and COPD. IL-6, IL-1, IL-23, and TGF- are the agents that trigger this process.

3.2. Protease / anti protease imbalance

Widespread consensus supports the protease/anti-protease imbalance theory as the primary pathogenic mechanism behind tissue damage in COPD patients. One typical protease/anti-protease combination is neutrophil elastase and 1-antitrypsin (AAT). AAT deficiency and chronic respiratory disorders are tightly connected [37]. Elastase was also discovered to cause emphysema [38]. The degree of emphysema in persons with COPD was found to be correlated with the elastase/anti-elastase imbalance, with elastase load and anti-elastase capability having a direct and inverse connection with emphysema, respectively [39]. The pathologically destructive process of COPD has also been found to be induced by matrix metalloproteinases (MMPs), although in a healthy state, these enzymes are inhibited by certain tissue metalloproteinases [40]. In terms of periodontitis, this imbalance concept has received little research. However, it was found that persons with chronic gingivitis had a substantially greater level of neutrophil elastase in their crevicular fluid [41]. Since then, numerous investigations have shown a connection between periodontitis and a imbalance between neutrophil elastase and AAT. Similar to COPD, [41] MMPs were also reported to be associated with periodontal damage [42].

3.3. Neutrophilic inflammation and damage

Periodontitis and COPD both frequently have neutrophil-mediated tissue destructions and neutrophilic inflammations. It has been established that COPD patients' neutrophils exhibit significantly higher chemotaxis and extracellular proteolysis, which suggests a stronger capacity for destruction [43, 44]. Additionally, it was found that COPD neutrophils migrated more quickly and generated fewer pseudopods [43]. Similar to gingivitis, neutrophil infiltration is a sign of periodontitis and neutrophils are the main inflammatory cells in gingivitis [45]. Increased prevalence of periodontitis was linked to abnormal neutrophil function [46]. Hajishengallis et al.'s study found that neutrophils from people with chronic periodontitis showed reduced speed, velocity, and accuracy [46]. The treatment for periodontitis may, however, enhance this bizarre behavior [47]. Neutrophilic damage is therefore a major factor that both COPD and periodontitis share.

3.4. Oxidative stress

Oxidative stress, another feature of both COPD and periodontitis, is likely to constitute a significant pathogenic factor in both illnesses. The importance of oxidative stress in COPD has been highlighted by the discovery of numerous indicators of oxidative stress that are much higher in COPD patients. These markers include lipid peroxidation products, superoxide dismutase 3 gene polymorphism, markers for oxidant-induced DNA damage, hydrogen peroxide levels, and others [48]. It's interesting that periodontitis had some of the same consequences. The periodontitis-related pathogen Fusobacterium nucleatum (F. nucleatum) stimulated human gingival fibroblasts, drastically increasing their production of intracellular reactive oxygen species (ROS) [49]. This suggests that oxidative stress, the main etiology of periodontitis, may also be present.

3.5. Pro – inflammatory cytokines

Inflammatory diseases like COPD and periodontitis are made worse by pro-inflammatory cytokines. In COPD patients' blood samples or lung secretions, there is a similar rise in a number of pro-inflammatory cytokines, including TNF-, IL-6, C-reactive protein (CRP), IL-1, etc., demonstrating that periodontitis and COPD share an inflammatory process to some extent. [50,51].

4. Mechanism of action of COPD and periodontitis

The mechanism between COPD and periodontitis is basically an imbalance in the microbial community and dysregulated host responses. Various mechanisms include:

4.1. Oral bacteria that enter the lungs by aspiration can cause lung inflammation.

There is microbiological connection between COPD and periodontitis, according to numerous researches. The tracheal aspirate of COPD patients with severe acute exacerbations contained periodontal bacteria Aggregatibacter actinomycetemcomitans, Capnocytophaga

sputigena, Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, suggesting that dental bacteria may be involved in the pathology of severe acute exacerbations of COPD [52]. Furthermore, it was discovered that P. gingivalis, Treponema odontocera, and Forsytanella were homologous in subgingival plaque and respiratory secretions of patients with acute exacerbations of COPD [53], indicating that aspiration of periodontal pathogens into the lung promoted exacerbation of COPD symptoms. According to Tian et al. [54], the periodontal infection P. gingivalis might spread to lung tissue, where it would then cause lung inflammation and impair lung function. Furthermore, it was discovered that P. gingivalis, Treponema odontocera, and Forsytanella were homologous in subgingival plaque and respiratory secretions of patients with acute exacerbations of COPD [53], indicating that aspiration of periodontal pathogens into the lung promoted exacerbation of COPD symptoms. More evidence reports that the detection of higher levels of inflammatory factors such as TNF-, IL-17, and G-CSF in lung tissue suggests that periodontal infection could trigger the secretion of inflammatory factors to cause lung injury after entering the lung. According to Parashar et al. [55] and Budden et al. [56], P. gingivalis causes lung damage by stimulating the nuclear factor kappa-B (NF-B) signaling pathway and the toll-like receptor-2 (TLR-2).

4.2. Promote oral colonization of respiratory pathogens

The closest reservoir for respiratory infections is the mouth cavity [57]. Before colonizing the lungs, several respiratory infections can be breathed through the mouth and upper respiratory tract. Periodontal pathogens can facilitate the oral colonization of respiratory pathogens during periodontitis, facilitating the aspiration of more pathogens [57]. Lung pathogens like Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, and S. pneumoniae were found in subgingival plaque biofilm in patients with severe acute exacerbations of COPD [52]. According to Tan et al.'s research [58], there is a significant negative correlation between P. gingivalis and FEV1/FVC in COPD patients. They also found that P. gingivalis and several respiratory pathogens, such as Klebsiella pneumoniae, Pseudomonas aeruginosa, and Streptococcus pneumoniae, are more prevalent in the subgingival plaque of COPD patients than in the non-COPD group.

4.3 Respiratory infection is brought on by periodontal microorganisms that harm the respiratory epithelium.

When mucin is produced excessively, it might cause COPD patients' respiratory function to progressively decline [59]. P. gingivalis, a periodontal pathogen, has the ability to greatly increase the expression of Mucin 5AC (MUC5AC), a key mucin protein, in bronchial epithelial cells [60]. The amount of Goblet cell metaplasia (related with mucin hypersecretion) and MUC5AC expression were also markedly increased after intratracheal administration of the periodontal pathogen F. nucleatum [61]. Furthermore, it has been hypothesized that F. nucleatum aggravates COPD by expressing MMP12 more frequently, which encourages the breakdown of alveolar walls [61].

A key initiator of COPD exacerbation is platelet-activating factor receptor (PAFR)-mediated pneumonia-causing bacterial infection [59]. The pneumonia-causing pathogen S. pneumoniae became more adherent as a result of the periodontal pathogen P. gingivalis promoting the production of PAFR by alveolar epithelial cells [62]. In brief, aspiration of periodontal pathogens may cause epithelial damage and, at the same time, encourage infection with pathogens that cause pneumonia, which would hasten the course of COPD.

4.4 Periodontitis down regulate the immunity and promotes COPD

Immune dysregulation is crucial to the development of COPD. In addition to disrupting the equilibrium of neutrophils, inflammatory cytokines, and macrophages, periodontitis may also have an impact on the circulatory system's immunological and inflammatory state [12].

4.5 Periodontitis increases the severity of COPD by causing an imbalance in the numbers and functions of neutrophil

Both periodontitis and COPD share the pathogenic trait of neutrophil-mediated inflammation. More importantly, earlier research showed that periodontitis may influence pulmonary inflammation by disrupting neutrophil function and quantity. It has been demonstrated that ligature, in conjunction with periodontitis brought on by P. gingivalis, can cause pulmonary inflammation by increasing the levels of cytokines and neutrophils in blood and lung tissue [54]. Furthermore, with worsening periodontitis in COPD patients, neutrophil migratory speed and accuracy decreased, regardless of the patient's alpha-1 antitrypsin deficiency (AATD) status [63]. Therefore, the way periodontitis affects COPD depends heavily on an imbalance in neutrophil quantity and function.

4.6 The Pro-inflammatory cytokines in lung tissue are increased by periodontitis.

Supernatants of the periodontal pathogen P. gingivalis elevate the expression of inflammatory cytokines like TNF-, Macrophage inflammatory protein 2 (MIP-2), IL-1, and IL-17 in the lung tissue of mice infected with S. pneumoniae, which further exacerbated the pneumonia inflammation [64]. The expression of TNF- and IL-6 in lung epithelial cells may be induced by extracellular vesicles of macrophages infected with P. gingivalis, leading to further lung damage and inflammation [65]. Additionally, it has been noted that F. nucleatum can cause COPD by raising the levels of IL-8 and IL-6 expression in a variety of human respiratory epithelial cells and mouse lung tissue [66]. In the F. nucleatum-exacerbated COPD animal model, the production of inflammatory cytokines such as IL-6, CXCL-1, CXCL-5, Monocyte chemoattractant protein-2 (CCL-2), and CXCL-10 was also considerably increased in lung tissue [61].

4.7 Alters the macrophage polarization

The actions of macrophages are crucial to the development and spread of COPD. The most prevalent immune cells in lung tissue, macrophages play both pro- and anti-

inflammatory roles [67] and can display a variety of polarization phenotypes in response to micro environmental change. Immune responses linked to macrophage polarization are crucial in the development of COPD. In COPD lung tissue, the phenomena of macrophage polarization and the co-expression of M1 and M2 polarization are markedly increased [68]. Both M1 and M2 macrophage polarization can be induced by periodontal infections [69]. Additionally, periodontitis may have some influence over the microphage polarization, which may have an impact on systemic illnesses. Through the activation of macrophages' classical polarization, periodontitis increased the development of diabetes, according to an in vivo investigation by Xu et al. using obese rats. Numerous studies have demonstrated that periodontitis may enhance the expression of M1- or M2-related (CCL-2, IL-17, and MMP-12) inflammatory factors in COPD lung tissue. As a result, we hypothesize that, similar to other systemic diseases, periodontitis may slow the progression of COPD by influencing the polarization of local macrophages. The particular effects, however, need more research.

4.8 The severity of COPD is exacerbated by periodontitis, which changes the inflammatory mediators in the circulatory system.

Inflammatory mediators and bacterial toxins in the circulatory system are altered by periodontal disease and indirectly lead to the progression of COPD. According to research by Wang et al, periodontitis can worsen COPD by raising levels of the inflammatory cytokines TNF-, IL-1, and RANKL in the blood. However, periodontitis therapy can lower these levels, alleviating the exacerbation of COPD [70]. The levels of KC (an IL-8 homologue neutrophil chemoattractant) and IL-6 were dramatically elevated in the COPD mice model induced by the periodontal infection F. nucleatum [66]. In contrast to those in the periodontitis, acute exacerbation of COPD, and healthy control groups, the levels of IL-8 and IL-6 in the serum were clearly higher in the patients with periodontitis and acute exacerbation of COPD [71] suggesting periodontitis increases the severity of COPD.

5. Common risk factors shared between COPD and periodontitis

Poor oral hygiene, diabetes, smoking, a low socioeconomic level, growing older, and stress are all risk factors for periodontitis.

The incidence and prevalence of COPD is more in older patients, less education, low Socio income status, smokers and alcoholics. Although they both share common risk factors like

5.1. Smoking: Around 80% of COPD patients smoke presently or in the past, making smoking a known major risk factor for the condition. Smoking is one of the most important independent risk factors for periodontitis that can have an impact on the host immune-inflammatory response. Studies on the impact of smoking on IL-1 levels in saliva or GCF have produced inconsistent results, with some pointing to higher levels, others to decreased levels, and still others showing no difference [72]. Chronic respiratory conditions like chronic obstructive pulmonary disorders (COPD) and lung cancer can develop as a result of prolonged exposure to cigarette smoke's harmful effects on the host.

5.2. BMI: The severity of periodontitis and BMI were significantly correlated. Ex-smokers had a much higher BMI than current smokers, according to research by Berne Eriksson. Subjects with diabetes, asthma, and respiratory symptoms other than a chronic productive cough had higher BMIs. Subjects with COPD had a somewhat lower mean BMI than the general population [73, 74].

5.3. Age: Periodontitis is a chronic condition whose effects worsen as people age. Therefore, it makes sense to assume that elderly patients would be more affected by unmanaged periodontitis than younger individuals. Elderly people with COPD are extremely common, especially those living in facilities like nursing homes and those who have a number of serious risk factors. In a study of Japanese individuals aged 80, it was discovered that those with periodontal pockets—those with 10 or more teeth and a probing depth greater than 4 mm—had a 3.9 times higher adjusted mortality from pneumonia than those without periodontal pockets [75].

5.4. Smoking: The prevalence of the disease has increased in females over the past several years, which is a result of rising smoking rates and makes the disease more evenly distributed across the sexes.

5.5. Diabetes: Major risk factor for COPD and periodontitis. Elevated blood sugar level alters the host immune responses and triggers the pro inflammatory cytokines in turn develop the diseases.

6. Effects of periodontal therapy on COPD

Numerous epidemiological studies have linked periodontitis to COPD, leading researchers to investigate if periodontal therapy can reduce COPD patients' symptoms. Interestingly, there is research that suggests treating periodontitis may help COPD patients' lung function. After reviewing the available data from the past four decades, Gupta et al. [12] came to the following conclusion: the risk of developing COPD was influenced by periodontal attachment loss, and periodontal therapy helped reduce COPD flare-ups. Three groups of 60 COPD patients with periodontitis received different modes of treatment like scaling and root planing (SRP), supragingival scaling, or just oral hygiene advice without any periodontal therapy, according to Zhou et al. [12]. FEV1/FVC and FEV1 values were considerably higher in the treatment groups compared to the control group (which did not get periodontal treatment). The study concluded that, two treatment groups had considerably lower COPD exacerbation rates than the control group, indicating that periodontal therapy may be able to manage COPD patients' acute exacerbations. Another study by Sharma et al. shown that non-surgical treatment can enhance lung function in COPD patients. This gives true evidence that periodontal therapy has strong beneficial effects on the improvement of COPD.

7. Conclusion

COPD and periodontitis have a strong relationship. Similar risk factors, microbial interactions, and pathologies, as well as demographic and clinical characteristics, exist for both COPD and periodontitis. In addition to affecting the structure of the respiratory epithelium and causing imbalances in neutrophils, macrophages, and inflammatory cytokines, periodontitis can promote the colonization of the mouth by pneumonia-associated bacteria. To reduce the risk of developing COPD and enhance outcomes for those who already have the condition, it is essential to address oral health concerns and inflammation. Another method to lower the prevalence of respiratory disease and enhance quality of life is to treat periodontitis (either by recurrent antibiotic prescriptions or by clinical interventions).

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