Original Article

The oral-lung microbiome dysbiosis: Unravelling its role in implications for chronic obstructive pulmonary disease (COPD) pathogenesis

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Abstract

Background: The impact of the oral flora on the composition of the microbiome in the lungs is substantial in both healthy and diseased conditions, contributing significantly to its intricacy. There is mounting evidence from microbiological research that suggests a major ecological relationship between periodontitis, Chronic Obstructive Pulmonary Disease (COPD), and oral microecosystems. An association has been established between respiratory diseases and disruptions in the symbiotic equilibrium of the oral microbiome. This study aims to explore the intricate connections between oral health and lung microflora, particularly about the pathogenesis of COPD, and to highlight the implications for future research and clinical practice.

Materials and Methods: Subgingival Plaque samples were collected from a total of 120 participants with 30 healthy Control (H group),30 Periodontitis with no COPD (P group), 30 COPD with periodontally healthy (COPD) and 30 individuals with COPD and Periodontitis (COPD+ P). All participants underwent evaluation of periodontal measurements like Pocket Depth (PD), Clinical loss of Attachment (CAL), Gingival Index (GI), and Plaque Index (PI) Bacterial DNA was extracted and quantified using Real-time polymerase chain reaction. Using the One-dimensional Analysis of Variance (ANOVA) and post-analysis test for multiple comparisons, the mean values of all the clinical parameters were analyzed among the four participant groups. Using the Pearson Correlation coefficient, the parameters were correlated.

Results: Statistical relevant relation was shown among Probing Depth (PD), Clinical Loss of Attachment (CAL), Plaque Index (PI) and Gingival Index (GI) in the COPD+P group. Increased prevalence of Pa (*Pseudomonas aeroginosa*) seen among *P* group and COPD+P. A substantial inverse relationship was seen between the absolute levels of Pa, CAL, PI, and lung function measures (Fev1, Fev1/FVC).

Conclusion: The importance of maintaining dental health in the prevention and treatment of respiratory disorders is highlighted by the relationships that exist between the oral microecosystem, oral hygiene, and respiratory pathologies. There is substantial potential to decrease the occurrence of respiratory illnesses by practicing good oral care and strategically managing the balance of the oral microbial flora. Therefore, future research efforts should prioritize the characterization of the precise impact of the oral microbiota

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on pulmonary health and use this knowledge towards developing innovative preventive and treatment measures targeted at combating respiratory infections and related diseases.

Keywords: COPD, dysbiosis, oral microbiome, periodontitis

INTRODUCTION

The connection between lung and oral health is an emerging area of research, with growing evidence suggesting that the microbiota is crucial in connecting these two systems. The mouth contains a complex ecosystem called the oral microecosystem, which includes the oral microbiome, and the anatomical structures of the mouth, such as the teeth, periodontal sulcus, palate, tongue, and periodontium.[1] A wide variety of viruses, protozoa, bacteria, and fungi numbering more than 700 genera, can be found in the human oral space. The interaction of humans with their oral microbiota during growth leads to the progressive formation of solid oral biofilms known as dental plaques.[2] These biofilms are made up of oral microorganisms and an extracellular matrix that surrounds the tooth surface. Dental plaque biofilms under normal circumstances support local oral health and immune system stimulation while shielding the mouth cavity from external pharmacological stimulation and environmental changes. In addition to helping to maintain dental health, the balance of the oral microecosystem may also affect general health. The oral microecosystem's bacteria, via complex interspecies interactions such as mutualism, competition, and antagonism, create an ongoing equilibrium with the host.[3,4] Nevertheless, internal or external causes that produce dysbiosis or imbalance of oral biofilms can result in oral illnesses such as periodontitis, gingivitis, and dental caries. An increasing amount of research indicates that the imbalance of oral microflora not solely worsens the oral diseases listed above, but as well as contributes to the development of systemic conditions including diabetes, negative pregnancy outcomes, cardiovascular disorders, Alzheimer's disease, pneumonia, lung cancer, chronic obstructive pulmonary disease (COPD) and other lung disorders.[5-8]

Severe periodontal disease has been ranked as the eleventh most common ailment worldwide in the Global Disease Burden analysis (2016).[9] Gingivitis in addition to periodontitis together make up periodontal disease, a common mouth infection that damages the tissues supporting around the teeth. When gingivitis, which is characterized by bleeding, swollen gums, and pain, is not treated, it can progress into periodontitis, leading to supporting bone loss and periodontal loss of attachment. It is one of the main reasons for tooth loss that could have an undesirable outcome on living standards, self-confidence, mastication, as well as appearance. The bacteria in dental plaque create chronic periodontitis, an infectious inflammatory disease that gradually destroys the tissues. Recent literature has highlighted the implication of the oral-lung microbial flora axis, where shifts in oral microbial communities can influence the composition of lung microbiota.[10] Greater than 750 taxa of bacteria can be detected in the oral cavity. Of these, three Gram-negative species collectively known as the red complex including *Porphyromonas gingivalis* (Pg), *Tannerella forsythia* (Tf), and *Treponema denticola* (Td) exhibit strong associations with periodontitis. Periodontitis was found to have a close relationship with respiratory system diseases, among which the association between periodontitis and COPD has become an area of intense interest. Prolonged restriction of airflow and prolonged inflammation of the airways are the defining features of COPD. This condition is often associated with various environmental factors, including smoking and exposure to pollutants, which contribute to the dysbiosis of the lung microbiome. Being the third most common cause of mortality worldwide, it has a significant influence on both life expectancy and quality of life. Both COPD and periodontal diseases contribute to many predisposing factors, including smoking, pathogenic bacteria, genetics, and socioeconomic status. They are chronic inflammatory disorders, particularly involving neutrophil-mediated inflammation and cytokine responses. The presence of periodontal pathogens can exacerbate lung inflammation, leading to worsened respiratory symptoms and increased frequency of COPD exacerbations. Direct inhalation of harmful disease-causing microbes is one of the proposed mechanisms by which periodontal disease and poor dental health contribute to the onset and progression of COPD. Because of the biological connection between the lungs and the mouth cavity, potential respiratory pathogens (PRPs) have been known to inhabit the oral region. During periodontitis, periodontal pathogens can enhance the oral colonization of respiratory pathogens, promoting the aspiration of more pathogens.Therefore, dental biofilm could serve as a source of respiratory organisms.[11,12] Periodontitis-associated pathogens could damage respiratory epithelium and promote respiratory

pathogen infection by elevating the expression of a core mucin protein, Mucin 5AC (MUC5AC), in bronchial epithelial cells. Several studies have demonstrated microbial communication between periodontitis and COPD. Periodontal bacteria such as *Aggregatibacter actinomycetemcomitans, Capnocytophaga sputigena, P. gingivalis, T. forsythia,* and *T. denticola* have been identified in the tracheal aspirates of patients experiencing severe acute exacerbations of COPD. This finding suggests that oral bacteria may play a role in the development and progression of severe COPD exacerbations. Periodontal pockets, dental biofilms, and saliva have been found to contain an array of respiratory pathogens, comprising *Streptococcus pneumonia* (Sp), *Klebseilla pneumonia (Kp), Pseudomonas aeruginosa* (Pa), and *Haemophilus influenza* (Hi). Among the most common organisms causing COPD exacerbations, Pa is the most frequently isolated in severe COPD patients as it can generate resistance against first-line antibiotics used to treat exacerbations and may persist in the airways after appropriate antibiotic treatment in severe COPD patients.[13] The bacteria can also induce apoptosis in pulmonary epithelial cells by disrupting cell junctions, inhibiting cellular growth, and triggering toxic cell death. This occurs through its type III secretion system, which injects effector proteins directly into host cells, and by releasing toxic factors such as pyocyanin.[14] Respiratory pathogens that colonize the oral microecosystem create the groundwork for their afterward invasion and infection of the lower airways when the immune network of the body is compromised. The adaption and colonization of respiratory infections in the oral microecosystem are influenced by both the organic traits of the pathogenic microbes and dysbiosis in the oral microrecosystem.[15] Nevertheless, there is currently a lack of etiological data about the oral microecosystem's contribution to the emergence of respiratory disorders.

This research was done to assess the incidence of respiratory pathogen *Pseudomonas aeroginosa* in the subgingival plaque of subjects with COPD, chronic periodontitis, and COPD with periodontitis thereby exploring the specific mechanisms by which the oral microecosystem contributes to the pathogenesis of respiratory diseases, to inform strategies for prevention and treatment.

MATERIALS AND METHODS

The Institution ethical board committee approved the current study, which was carried out conforming to the principles outlined in the Declaration of Helsinki. Before the collection and sampling of clinical data, all participants provided written informed consent.

SAMPLE GROUPING: The study involved 120 patients overall, 30 of whom were healthy controls (H group),30 with Periodontitis with no COPD (P group), 30 with COPD with periodontally healthy (COPD), and 30 participants with COPD and Periodontal diseases (COPD+ P). All COPD cases were recruited from the respiratory ward of the medical hospital, in Chennai. The recommendations set by the Global Initiative for Chronic Obstructive Airway Disease (GOLD) panel were followed in the analysis and severity evaluation of COPD. Mild to moderate COPD cases in stages II and III were recruited. (Fev1/Fvc, which represents the ratio of forced vital capacity to forced expiratory volume in one second, is less than 80% of the predicted value). Tonetti *et al*.[16] classification of diseases and conditions related to periodontal and peri-implant health served as the basis for the periodontitis diagnosis and evaluation. (Stage II grade B periodontitis- interdental Clinical loss of Attachment (CAL) ≥ 3–4 mm, Probing Depth (PD) ≥ 4–5 mm, and radiographic evidence of bone loss extending to the middle-third of the tooth). The use of antibiotics for the period of 3 months before the commencement of the study, any systemic disorders, any periodontal interventions administered within the same time frame, worsening of pulmonary symptoms, pneumonectomy, and any lung procedures performed in the last 6 months were the exclusion criteria. Periodontal parameters like Pocket Depth (PD), Clinical loss of Attachment (CAL), Gingival Index (GI), and Plaque Index (PI) were measured by a single examiner.

Sample acquisition

The participants were instructed to rinse their mouths to get rid of food remnants before the sample was collected. For every participant, Dental plaque samples were obtained from four of the patients' primary incisor teeth and four of their primary molar teeth. Using sterile Gracey curettes, subgingival plaque samples were extracted from each tooth's buccal and lingual surfaces following the removal of supragingival plaque. Each participant's sample was taken and confined in a tube of Eppendorf and kept at a temperature of −80°C.

Genomic DNA isolation and real-time polymerase chain reaction sample processing

The GenElute™ DNA Miniprep kit ((GIN70—Sigma–Aldrich)) was used to isolate the whole bacterial DNA according to the kit's specific directions. The sample is then lysed using a lysis buffer included in the kit along with proteinase K releasing the DNA into the solution. Extracted DNA was subjected to Real-time PCR, also known as quantitative PCR (qPCR), for the amplification and quantification of DNA.

The process began with the preparation of a master mix, which included DNA (the template), primers specific to the *P. aeroginosa*, a DNA polymerase enzyme, dNTPs, and a fluorescent probe (SYBR Green -TaKaRa, Shiga, Japan). The precise sequences of the forward primer, reverse primer, and probes for pathogens are displayed in Table 1. The fluorescent dye binds to double-stranded DNA and emits fluorescence during amplification, enabling the real-time monitoring of the reaction. The master mix is then placed in a real-time PCR machine, which thermally cycles through three main phases: denaturation (95°C for 15–30 seconds), annealing, (50–65°C for 30 seconds), and extension at (72°C for 30 seconds). This cycle repeats typically 30–40 times, amplifying the target DNA exponentially. Data analysis is conducted by comparing Ct values of the unknown samples to a standard curve or reference, enabling precise quantification of Pa. gene expression using Quantstudio™ Real-time PCR (Thermo Fischer, Scientific).

Statistical analysis

Statistical analysis of the data was done using IBM SPS Software. A One-way ANOVA was conducted to assess the mean values of all clinical parameters between the four participant groups, followed by Tukey's Honestly Significant Difference (HSD) test for pairwise comparisons. The relationship between clinical, lung function, and bacterial data within the study groups was assessed using the Pearson correlation coefficient. The present investigation maintained a statistical significance at $P < 0.05$.

RESULTS

When comparing COPD+P to the other Groups, the mean values of PD, GI, CAL, and PI were higher, and there was a significant difference [Table 2]. The multiple comparisons of clinical parameters between the H Group and the COPD group did not yield statistically significant [Table 3]. Mean Ct levels of Pa were higher in *P* Group and COPD+P Group compared to other groups and multiple comparisons between the groups revealed a significant difference [Tables 4 and 5]. Furthermore, a notable inverse relationship was seen between pathogen Pa, periodontal parameters CAL, and PI with mean lung function parameters (Fev1, Fev1/Fvc) among the tested groups. Thus, it is inferred that an increase in the relative values of Pa is linked to a decrease in lung function measures [Table 6].

DISCUSSION

Over the past few years, there has been a lot of research focused on how individuals with systemic disorders affect their oral microecosystem. Recent research has highlighted the intricate oral microbial ecosystem, which comprises the microflora, morphological features, saliva, and their host interactions, by focussing more on the connection between the oral microbiota, periodontal disorders, and lung diseases. This study focused on the significance of oral microbe dysbiosis in increasing the adherence of respiratory microbe within the dental biofilm of individuals with chronic periodontitis, COPD, and COPD with periodontitis. The physical relationship between the lungs and mouth affords lots of possibilities for oral microflora to affect lung microflora in disease and health. Exacerbations of chronic obstructive lung disease can be attributed, in part, to the acquisition of novel bacterial strains, as demonstrated by molecular characterization of the bacteria and assessments of the host immune response. In our study investigations, all periodontal parameters were increased in the COPD +P group with a decline in lung function parameters indicating poor periodontal health led to aggravation of COPD. This is in consistent with a survey study involving 501 participants, by Peter *et al*.[17] assessed the health of periodontium in 399 healthy controls, 102 people with chronic obstructive pulmonary disease. The investigation revealed a considerable negative correlation between lung function, measured by forced expiratory volume in 1 second (FEV1), and periodontal health indicators, including pocket depth, dental hygiene index, and clinical loss of attachment. This suggests that poor oral health may be linked to worsened lung function in COPD patients. Similarly, studies have shown that COPD patients tend to have worse periodontal health, including more severe inflammation of the gingiva and increased periodontal pockets or clinical attachment loss (CAL) compared to non-COPD individuals.[18] Prospective and longitudinal studies, such as those by Takeuchi *et al*.,[19] also confirm Increased vulnerability to COPD in individuals with severe periodontitis. Cumulative analysis of investigations from 14 studies further supports the interrelationship between periodontal diseases and COPD, with reports indicating that COPD patients tend to retain fewer teeth, reinforcing the link between oral health and respiratory function.[20] Studies have reported that *P.*

Table 1: Primers for real-time Quantitative Polymerase Chain Rection

Bacteria	Sequence (5′–3′)	Annealing temperature (°C)	Fragment length (bp)
Pseudomonas Aeroginosa (Pa)	F: ATGGAAATGCTGAAATTCGG R: CTTCTTCAGCTCGATGCGAC	55.0	134

F=Forward Primer, R=Reverse Primer

Table 2: Comparison of mean clinical parameters (PD, GI, CAL, PI) among the groups

Variables	Groups	*n*	Mean±.Std. Deviation	*F*	*P*
PD	H	30	2.15±0.444		
	P	30	6.30±0.657	346.120	0.000
	COPD	30	3.10±0.858		
	COPD+P	30	7.45±0.686		
	H	30	0.89±0.0.23	137.678	0.000
GI	P	30	2.15±0.0.34		
	COPD	30	0.88±0.0.33		
	COPD+P	30	2.14±0.0.45		
CAL	H	30	2.25±0.366	349.069	0.000
	P	30	7.50±0.1.046		
	COPD	30	3.10±0.858		
	COPD+P	30	9.25±0.988		
PI	H	30	0.20±0.227	162.682	0.000
	P	30	2.55±0.527		
	COPD	30	0.80±0.417		
	COPD+P	30	3.12±0.446		

PD=Probing Depth, CAL=Clinical Attachment Level, PI=Plaque Index, *P* value=probability value

Table 3: Multiple comparison of Clinical Parameters between the groups

Dependent Variable	Groups	Groups	Mean Difference (I–J)	Sig.
	H	P	−4.540*	0.000
PPD		COPD	−0.650*	0.830
		COPD+P	−4.600*	0.000
	P	COPD	−3.710*	0.000
		COPD+P	−1.430*	0.000
	COPD	COPD+P	−4.680*	0.000
	H	P	−4.560*	0.000
GI		COPD	−0.750*	0.980
		COPD+P	−5.700*	0.000
	P	COPD	3.700*	0.000
		COPD+P	−1.250*	0.000
	COPD	COPD+P	−4.950*	0.000
	H	P	−5.450*	0.000
CAL		COPD	−0.850*	0.172
		COPD+P	−7.000*	0.000
	P	COPD	4.600*	0.000
		COPD+P	−1.550*	0.000
	COPD	COPD+P	−6.420*	0.000
	H	P	−1.934*	0.000
PI		COPD	−0.4800*	0.405
		COPD+P	−2.350*	0.000
	P	COPD	1.570*	0.000
		COPD+P	−0.7800*	0.000
	COPD	COPD+P	−2.655*	0.000

PD=Probing Depth, CAL=Clinical Attachment Level, PI=Plaque Index, *P* value=probability value

gingivalis, Treponema odontocera, and *T. forsythia* were identified in both subgingival plaque and respiratory secretions of patients experiencing acute exacerbations of COPD. The homology between these bacteria suggests that the aspiration of periodontal pathogens into the lungs may contribute to worsening COPD symptoms.[21] Additionally, elevated levels of inflammatory mediators such as TNF-α, IL-17, and G-CSF in lung tissue were observed, indicating that these periodontal pathogens can stimulate the production of inflammatory factors. This response likely contributes to lung injury and exacerbation of COPD after these pathogens invade the respiratory system.

Table 4: Comparison of mean values of *Pseudomonas aeuroginosa* (Pa) among the Groups

	Groups	*n*	Mean±Std. Deviation	Std. error Mean	*F*	Sig. (2-tailed)
Pa/Ct value	H	30	30.525±0.70004	0.15653		
	P	30	18.974±1.8292	0.40903	589.960	0.000
	COPD	30	22.798±0.96244	0.21521		
	COPD+P	30	16.248±1.0055	0.22485		

Table 5: Multiple group comparison of *Pseudomonas aeuroginosa* (Pa) between the groups

	Groups	Groups	Mean Difference (I–J)	Std. Error	Sig.
Pa/Ct value	H	P	9.98750*	0.37992	0.000
		COPD	11.811*	0.36982	0.000
		COPD+P	13.33750*	0.57990	0.000
	P	COPD	1.72350*	0.76984	0.000
		COPD+P	4.75000*	0.27392	0.000
	COPD	COPD+P	2.82650*	0.16983	0.000

The presence of harmful microbes such as Pa is inhibited by a healthy oral microbiota. On the contrary, disruptions in oral microecology provide possibilities for opportunistic respiratory infections to colonize and invade the mouth. It has been extensively documented that alterations in the oral micro biosystem, such as denture stomatitis, periodontitis or the existence of dentures, or imbalances in oral microbiota's nutritional composition encourage *P. aeruginosa, S. aureus,* and Acinetobacter spp. colonisation of the mouth and may facilitate the extend of additional virulent strains.[22] This is on par with our results which showed an increased prevalence of Pa and a negative correlation of lung function parameters (Fev1 and Fev1/FVC) in the P group and COPD+P group. Inhalation of enzymes, cytokines, and physiologically active compounds emitted by oral bacteria and inflammatory periodontal tissues can impact the respiratory mucosal epithelium in the lower respiratory tract. Proteases and other enzymes, such as sialidase, fucosidase, and mannosidase produced by oral bacteria, may modify the mucosal surfaces or expose adhesion receptors, facilitating respiratory microbial colonization. Additionally, the protective salivary pellicle can be effectively destroyed by degradative enzymes produced by periodontal bacteria allowing respiratory pathogens to adhere more easily, while microbial components like LPS and cytokines further alter the respiratory epithelium, promoting COPD exasperation.[23] Numerous commensal bacteria in the mouth have been shown to have antagonistic effects on respiratory infections by preventing their invasion and colonization, hence preserving the equilibrium of oral microecology. Consequently, the reduction in oral commensal bacteria also resulted in an increase in Pa adhesion.[24] Additionally, data indicates that the co-infection of respiratory and periodontal

Table 6: Correlation of clinical parameters, *Pseudomonas aeuroginosa* (Pa) with mean lung function parameters (Fev1, Fev1/Fvc) among the groups

		Fev1	Fev1/FVC
PPD	Pearson Correlation	−0.508	−0.534
	Sig. (2-tailed)	0.283	0.346
	n	120	120
CAL	Pearson Correlation	−0.809**	−0.682**
	Sig. (2-tailed)	0.000	0.000
	n	120	120
GI	Pearson Correlation	−0.032	−0.066
	Sig. (2-tailed)	0.279	0.321
	n	120	120
PI	Pearson Correlation	−0.743**	−0.584**
	Sig. (2-tailed)	0.01	0.05
	n	120	60
Pa	Pearson Correlation	−0.738**	−0.678**
	Sig. (2-tailed)	0.000	0.000
	n	120	120

**Correlation is significant at the 0.01 level (2-tailed)

Infectious microbes in lung epithelium induces apoptosis and the release of inflammatory mediators. It has been found that perio pathogens such as *Fusobacterium nucleatum, P. gingivalis,* and *A. actinomycetemcomitans* facilitate *P. aeruginosa* incursion of human epithelial (HEp-2) respiratory epithelial cells and increase the release of MMP and cytokines generated from host cells (IL-6, IL-1, and TNF-α). Subsequent research revealed that *P. gingivalis* controlled the programmed cell death of respiratory cells produced by *P. aeruginosa* via the signal transducer and activator of the transcription 3 (STAT3) cellular signaling route and their co-penetration resulted in a higher amount of cell death than isolated P. aeruginosa infection.[25] In addition to this Tan L also identified that species common to both subgingival plaque and tracheal aspirate samples included well-known dental pathogens such as *P. gingivalis* (Pg), Tannerella forsythia (Tf), and *T. denticola* (Td), as well as respiratory pathogens like *K. pneumoniae* (Kp), *P. aeruginosa* (Pa), and *S. pneumoniae* (Sp). This overlap highlights the potential role of oral bacteria in contributing to respiratory infections through aspiration or migration into the lungs.[15] Culture studies have also identified species like Staphylococcus aureus and *Streptococcus viridans* in COPD patients' respiratory tracts, further supporting the connection between oral and respiratory microbiomes.[26]

More comprehensive research including a wider range of participants could yield an additional understanding of the consequences of oral health on COPD outcomes and overall well-being.

CONCLUSION

The correlation between lung infections and microbiome in the oral cavity has important implications for public health and therapeutic procedures. This research indicates that dysbiosis in the oral microbiome, often exacerbated by conditions such as periodontitis, facilitates the colonization of opportunistic pathogens like Pseudomonas aeruginosa. This pathogen can be inhaled into the lungs, causing increased inflammation and respiratory complications that worsen COPD symptoms. Additionally, the interplay between the oral and lung microbiomes suggests that maintaining oral health is crucial for preventing respiratory infections and managing COPD effectively. As studies continue to explore the intricate relationships between these microbiomes, it is clear that therapeutic strategies aimed at restoring oral microbiome balance may hold promise for improving outcomes in COPD patients. Future research should focus on larger, multicenter studies to further elucidate these connections and develop targeted interventions that consider the oral-lung axis in COPD management.

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Conflicts of interest

There are no conflicts of interest.

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