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SYSTEMIC DISEASES (N BUDUNELI, SECTION EDITOR)

Periodontitis and Respiratory Diseases: What Does the Recent Evidence Point to?

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Abstract

Purpose of the Paper There is an increase in focus of research to find the relationship between periodontal diseases and systemic illnesses, in particular respiratory diseases. Though numerous literatures have been published to assess the link, the nature of relationship between the two diseases is still unclear. Periodontal diseases and respiratory diseases share a common pathogenesis and risk factors. Periodontal diseases and respiratory diseases including bronchial asthma have an inflammatory nature thus mandate a positive correlation between these. Understanding the relationship can help development of more focused preventive and treatment measures.

Recent Findings and Summary The available link suggests that there could be independent association between periodontitis and respiratory diseases. However, more structured studies are needed to establish the causal relationship between the two entities. The link is stronger between nosocomial and ventilator-associated pneumonia and is stronger than for chronic obstructive pulmonary diseases.

Keywords Periodontitis · COPD · Pneumonia · Oral care · Review

Introduction

The relationship between the oral health and overall health is indisputable. This relationship had been documented in ancient medical practices. It all started with the theory of focal infection that dates to 1900 AD by William Hunter [1]. But this speculation had its basis on personal experiences and anecdotes. Since it lacked strong scientific evidence, it lost its favor around the late 1930s.

Later from the 1980s, more well-designed studies were conducted to explore the link between oral diseases, especially chronic periodontal diseases and systemic diseases. Since then, there has been an exponential rise in the number of studies that have investigated links between periodontal disease and various systemic diseases [2]. This led to the emergence of new term in periodontology, the Periodontal medicine proposed in World Workshop in Periodontics in 1996 [3].

Chronic periodontitis, also known as adult periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tissues that support the teeth, i.e., the gingival, the periodontal ligament, cementum, and the alveolar bone [4•, 5]. The chronic nature of periodontal inflammation, etiology and pathogenesis, and the infection and inflammatory response can cause events elsewhere in the body [6]. Numerous researches in this field have led to understanding the link between periodontitis and systemic diseases [7]. The most studied and linked diseases with periodontitis are cardiovascular diseases, adverse pregnancy outcomes, diabetes mellitus, and respiratory diseases [8].

Numerous studies have been done to establish the link between respiratory diseases and periodontitis. One of the important reasons for development of respiratory diseases is the oral colonization by respiratory pathogens appears. In addition, reduction in oral bacterial load through periodontal therapies has resulted in reduced incidence of these reparatory illnesses. This suggests a strong link between the two entities.

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This review highlights the recent evidence in assessing the evidence between periodontitis and respiratory diseases.

Periodontitis and Chronic Obstructive Pulmonary Diseases—the Shared Link

Chronic periodontitis is one of the commonest inflammatory human diseases and shares its inflammatory mechanism with many other systemic diseases including chronic obstructive pulmonary disease (COPD). The pathophysiology of COPD involves systemic inflammation that is common to periodontitis [9, 10]. The common attributed factor is the alteration in neutrophil function. Periodontitis is associated with hyperactive and hyper-reactive neutrophil. They exhibit reduced movement and accuracy in reacting to chemoattractants [11, 12], and they are induced to produce large amount of pro-inflammatory cytokines that spill into systemic stream and cause alveolar damage in lungs [13–15•].

Another shared mechanism is imbalance between protease and antiprotease levels. Patients with deficiency of α1-antitrypsin were more susceptible to and exhibited more tissue destruction in COPD [16]. Imbalance in elastase and antielastase levels was identified in patients with COPD. Similarly, seven times higher concentrations of collagenase and elastase were identified in gingival crevicular fluid of severe periodontitis cases as compared to those in controls [17].

Another mechanism that is common is the tissue damage by oxidative stress. In response to bacteria and their product inflammatory cells, especially neutrophils and macrophages secrete large amounts of reactive oxygen species (ROS). Excess ROS mediates tissue damage by making them more susceptible to proteolytic degradation [18–20]. In periodontitis, hyperactive neutrophils are identified to produce large amounts of ROS that can damage alveolar tissue in the lung [21, 22•].

Release of neutrophil extracellular traps (NETs) has been implicated in lung inflammation and plays a vital role in degradation of lung tissue and pathogenesis of COPD [23, 24]. Extracellular DNase production by periodontal bacteria like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can degrade NETs and release them [25].

Periodontitis and Chronic Obstructive Pulmonary Diseases—the Recent Clinical Evidence

Garcia et al. 2001 [26•] reviewed the epidemiologic and clinical evidence for the association between periodontitis and COPD. They found that worse periodontal health status is associated with increased risk of COPD. Hyman et al. [27] studied 7625 participants, and found no significant association between periodontitis and COPD after adjustments for smoking status. Kowalski et al. [28] assessed 100 subjects with grade II COPD and 100 age matched controls without COPD. The frequency and severity of periodontal diseases in COPD patients were demonstrated to be greater than those in the control group.

Scannapeico et al. [29••] in NHANES III cross-sectional retrospective survey surveyed 13,729 subjects in the USA and reported that subjects with COPD had more periodontal loss than subjects without COPD. Azharapooh et al. [30••] investigate evidence for a possible etiological association between oral health and pneumonia or other respiratory diseases. After investigating all published articles, they concluded that there is poor evidence of a weak association (OR < 2.0) between COPD and oral health.

Leuckfeld et al. [31] evaluated 40 patients with and without COPD for periodontal status. After adjusting for age, gender, and smoking status, marginal chronic periodontitis was more pronounced in COPD cases than that in the non-COPD controls. Fatemi et al. [32] in a case-control study evaluated 30 patients with COPD and without COPD and found that periodontal disease was significantly higher in case group. Wang et al. [33] evaluated the associations of oral health behaviors with COPD. Around 600 patients with and without COPD were assessed. After adjustments for age, gender, body mass index (BMI), smoking, supra-gingival scaling, etc., poor oral health knowledge and periodontal status were significantly higher among COPD group.

Doe et al. [34] attempted to correlate the severity of periodontal disease with COPD. A total of 200 patients with and without COPD were compared. Subjects with COPD had significantly more attachment loss. It was also noted that lung function diminished as the amount of attachment loss increased. Prasanna et al. [35•] in an observational study assessed the relationship between periodontal diseases and COPD. He found a significant association between the both disease entities. Si et al. [36] explored the association between periodontitis and COPD in a Chinese population. They examined 581 COPD cases and 438 non-COPD controls and concluded that strong association existed between periodontitis and COPD, and periodontal disease is a major for predicting COPD among Chinese adults.

Zeng et al. 2012 [37••] conducted a comprehensive meta-analysis to assess the relationship between periodontitis and COPD. He reported that periodontal diseases significantly increase the risk of COPD, with the increase being likely independent of conventional COPD risk factors.

Ledik et al. [38] explored whether periodontal disease could be a risk indicator for a chronic obstructive pulmonary disease. In this case-control study, COPD subjects had significantly worse periodontal conditions than controls. Their data suggested that periodontal disease could be a risk indicator for COPD. Peter et al. [39] conducted an observational study

including 501 individuals. This study concluded that severity of lung obstruction increased as these periodontal indices worsened.

Oztekin et al. [40] evaluated effects of periodontal health on COPD. He stated that COPD may be associated with periodontal disease as manifested by lower number of teeth and higher levels of inflammatory mediators especially C-reactive proteins in gingival crevicular fluid (GCF). Chun et al. [41] evaluated the risk of periodontal disease in patients with COPD in a nationwide population in Taiwan. They found that patient with COPD had more periodontal diseases than the controls.

A compiled data is represented in Table 1.

Periodontitis and Pneumonia—the Shared Link

Pneumonia is a life-threatening infection especially of the old and immune compromised with high morbidity and mortality rates [42]. The lower respiratory tract can get infected by one of the four causes: aspiration of oropharyngeal contents, inhalation of infectious substances, spread of infections from extrapulmonary sites, and hematogenous spread [43, 44]. In bacterial pneumonia, tissue destruction is mainly caused by aspiration of oropharyngeal contents that result in adhesion and multiplication of bacteria. They are termed as potential respiratory pathogens (PRPs) [45]. The common PRPs are *Streptococcus pneumoniae*, *Mycoplasma pneumonia*, and *Haemophilus influenza*. Important periodontal pathogens associated with acute pneumonia are *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Fusobacterium* species [46••].

Table 1 Recent research related to periodontitis and COPD

Author	Study design	Odds ratio
Scannapeico et al. 2001	Cross-sectional	1.45
Garcia et al. 2001	Cross-sectional	1.75
Hyman et al. 2004	Cross-sectional	1.48
Kawalski et al. 2005	Case-control	3.59
Leuckfeld et al. 2009	Cross-sectional	10.03
Fatemi et al. 2009	Case-control	1.08
Wang et al. 2009	Case-control	1.00
Deo et al. 2009	Case-control	1.11
Prasanna et al. 2011	Case-control	3.12
Si et al. 2011	Case-control	9.01
Zhou et al. 2012	Case-control	1.34
Chun et al. 2015	Cross-sectional	1.19
Azharapooh et al. 2006	Meta-analysis	< 2.0
Zeng et al. 2012	Meta-analysis	2.08
Ledik et al. 2013	Case-control	3.2

Dental plaque acts as major reservoir for the PRPs, especially in patients with periodontitis. Periodontal bacteria like *A. actinomycetemcomitans*, *Actinomyces israelii*, *Capnocytophaga* species [47–49], *Eikenella corrodens*, *Prevotella intermedia*, and *Streptococcus constellatus* have been isolated in patients with severe pneumonia [50, 51]. These bacteria can become part of normal oral flora in periodontitis patients.

The question is how do these PRPs colonize to oral cavity? Certain individuals are at more risk like alcoholics whose oropharynx contained more PRPs as compared to controls. In addition, they are also prone to periodontitis [52, 53]. It is also suggested that the oral surface modifies to express receptors for PRPs, especially in hospitalized patients [54]. Another mechanism is that an enzymatic alteration in the mucosa by periodontal bacteria can increase the colonization of the PRPs [55, 56].

Normally, the respiratory tract will itself defend against the invading bacteria. But in conditions like esophageal reflex and swallowing disorders, the chances are high for risk of pulmonary infection. The commonest pathogenesis of oropharyngeal bacteria causing pneumonia is that the oropharyngeal bacteria are aspirated into respiratory tract and lowered immune response fails of eliminate the bacteria [57•]. More oral anaerobic bacteria are also found in patients who are mechanically ventilated. Important reasons for this are aspiration of the saliva and colonization of bacteria during intubation [58].

Periodontitis and Pneumonia—the Recent Clinical Evidence

Not many recent case-control studies are available in recent literature as the relationship between the two diseases is well established.

Scannapeico et al. [59•] in a systematic review stated that nosocomial pneumonia positively associated with periodontal diseases and poor oral hygiene. Awano et al. [60•] evaluated a relationship between oral health and mortality in older Japanese population with pneumonia. He found that morbidity due to pneumonia was 3.9 times higher in persons with ten or more teeth with periodontal pocket than in those without periodontal pockets.

Pace et al. in 2010 [61] did a review of literature with search terms aspiration pneumonia, oral health, and periodontitis. He found that there is a direct relationship between periodontal diseases and aspiration pneumonia. Oliveria et al. in 2011 [62] conducted study to find factors associated with nosocomial pneumonia in patients admitted to a public hospital and found that arterial hypertension, length of stay at hospital, and poor oral hygiene had strong association with the disease.

Melo neto et al. [63] conducted a study to evaluate if the presence of periodontal infections (PI) is associated with

community-acquired pneumonia. He found that the presence of moderate or severe chronic periodontitis increased the risk for community-acquired pneumonia [odds ratio (OR) = 4.4, 95% confidence interval (CI) = 1.4–13.8], even when adjusted for age, ethnicity, gender, and smoking. Gomes-Filho et al. [64••] conducted a case-control study to find the influence of periodontitis on nosocomial pneumonia. The study included a total of 315 subjects. He concluded that individuals with periodontitis were three times more likely to present with nosocomial pneumonia (unadjusted odds ratio [OR unadjusted] = 3.06, 95% confidence interval [95% CI] 1.82 to 5.15) as compared to those without periodontal disease.

Oberoi et al. [65] in his study found that community periodontal index of treatment needs, treatment need 0 was found to be more among the controls whereas the treatment needs 1, 2, and 3 were more among the patients with respiratory disease. He concluded that respiratory diseases like pneumonia are associated with high severity of periodontal diseases.

Intervention Studies

Grap et al. [66] designed a study to describe the effect of an early post-intubation oral application of chlorhexidine gluconate on oral microbial flora and ventilator-associated pneumonia. The mean Clinical Pulmonary Infection Score (CPIS) for the control group increased to a level indicating pneumonia, whereas the CPIS for the treatment group increased only slightly. This suggests that proper oral hygiene prevents development of pneumonia in ventilated individuals. Koeman et al. [67] determined the effect of chlorhexidine (CHX) oral decontamination as compared to placebo in incidence of ventilator-associated pneumonia. He found that topical oral decontamination with CHX reduced incidence of ventilator-associated pneumonia (65% (hazard ratio [HR] = 0.352; 95% confidence interval [CI], 0.160, 0. 791; $P = 0.012$). Huang et al. [68] conducted a research to find out whether intensive periodontal treatment reduced risk of infection in hospitalized patients. He found that patients on intensive periodontal treatment had significantly lower risk of pneumonia (hazard ratio = 0.71. 95% CI—0.65–0.78).

Adachi et al. [69] evaluated the role of professional oral health care (POHC) by dental hygienists in reducing respiratory infections in elderly persons requiring nursing care. The relative risk of developing influenza while under POHC was 0.1 (95% CI 0.01–0.81, $P = 0.008$). These results suggest that POHC by dental hygienists is effective in preventing respiratory infections in elderly persons.

Bassim et al. [70•] investigated the association between oral health care and risk factors for mortality from pneumonia. The study concluded that the odds of dying from pneumonia in the group that did not receive oral care was more than three times than that of the group that did receive oral care (odds ratio = 3.57, $P = 0.03$). Sjogren et al. [71••] in a systematic review investigated the preventive effect of oral hygiene on pneumonia and respiratory tract infection, focusing on elderly people in hospitals and nursing homes. He concluded that mechanical oral hygiene has a preventive effect on mortality from pneumonia and non-fatal pneumonia in hospitalized elderly people and elderly nursing home residents.

Tada et al. in 2010 [72] reviewed the effect of oral care, including oral hygiene and improvement of oral function, on the prevention of AP among elderly people in hospitals and nursing homes. They found that oral hygiene, consisting of oral decontamination and mechanical cleaning by dental professionals, has resulted in significant clinical effects (decreased incidence of pneumonia and decreased mortality from respiratory diseases) in clinical randomized trials.

El Solh in 2011 [73•] stated that mechanical hygiene measures consistently seem to reduce the pneumonia incidence and the use of chemical agents alone yielded inconsistent improvement of the incidence of respiratory tract infections. van der Maarel-Wierink et al. [74] systematically reviewed the literature on oral health care interventions in frail older people and the effect on the incidence of aspiration pneumonia. According to the results of the current systematic literature, review oral health care, consisting of tooth brushing after each meal, cleaning dentures once a day, and professional oral health care once a week, seems the best intervention to reduce the incidence of aspiration pneumonia.

Shi et al. in 2013 [75] in a Cochrane systematic review assessed the effects of oral health care on incidence of ventilator-associated pneumonia in critically ill patients in intensive care units. He concluded that effective oral health care is associated with 40% reduction in odds for developing VAP. Ozcaka et al. in 2013 [76] evaluated effects of swabbing with 0.2% chlorhexidine on ventilator-associated pneumonia patients in intensive care units. Oral care with CHX swabbing reduced the risk of VAP development in mechanically ventilated patients. Vilela et al. [77] in a systematic review analyzed the control of oral biofilms and the incidence of nosocomial pneumonia. It was observed that the control of oral biofilm reduces the incidence of nosocomial pneumonia.

Conclusion

The available link suggests that there could be independent association between periodontitis and respiratory diseases. However, more structured studies are needed to establish the causal relationship between the two entities. The mechanism linking the oral and respiratory diseases is well established. The link between aspiration and ventilator-associated pneumonia is stronger as compared to chronic obstructive pulmonary diseases. It should also be understood that oral diseases are preventable and by control of oral diseases like

periodontitis, incidence and severity of respiratory diseases can be reduced.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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