



A Review: Association between Periodontal Disease and Airflow Limitation

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ABSTRACT:

Advances in science and technology over the last century have greatly expanded our knowledge of the pathogenesis of periodontal diseases. Periodontal disease is an infectious disease. However, environmental, physical, social and host stresses may affect and modify disease expression. It is clear that certain systemic conditions may affect the initiations and progression of gingivitis and periodontitis.

Evidence emerging in the last decade has shed light on the converse side of the relationship between systemic health and oral health. That is, the potential effect of periodontal disease on a wide range of organ systems. Recently, there has been a resurgence of interest in the interaction between periodontal disease and respiratory disease. Respiratory diseases are responsible for significant morbidity and mortality in human populations. Lower respiratory infections were the third commonest cause of mortality worldwide in 1990 (Causing 4.3 million death), and chronic obstructive pulmonary disease (COPD) was the sixth leading cause of mortality (2.2 million deaths). COPD was the fourth leading cause of death in the United States in 1996 claiming 100,000 lives, while pneumonia and influenza together caused almost 84,000 deaths. Oral periodontopathic bacteria can be aspirated into the lung to cause aspiration pneumonia. The teeth may also serve as a reservoir for respiratory pathogen colonization and subsequent nosocomial pneumonia. Typical respiratory pathogens have been shown to colonize the dental plaque of hospitalized intensive care and nursing home patients. This review article discusses the pathophysiology of association of periodontitis and respiratory diseases.

INTRODUCTION

Individuals with airflow limitation potentially demonstrate airway and systemic inflammation depending on the severity of lung disease, physical activity, and potential comorbidities (Rasmussen et al., 2009).¹ Besides smoking (Tamimi et al., 2012,) risk factors for lung function decline and airflow limitation include ageing and diseases usually associated with airflow limitation such as chronic obstructive pulmonary disease and infections (Guerra, 2009). Periodontal disease is one of the most prevalent human infections. The majority of adults suffer from some degree of periodontitis, with 15-20% of the adult population having severe periodontal disease (Holtfreter et al., 2009).² Periodontal disease is an oral bacterial infection, that results in gingival inflammation, breakdown of the supporting connective tissue, pocket formation between the gingiva and the tooth, destruction of alveolar bone, and eventually exfoliation of teeth (Kornman, 2008, Pihlstrom et al., 2005). This inflammatory response to the commensal oral flora is primarily provoked by colonization with anaerobic gram-negative microbes. While probing depth reflects current disease status, clinical attachment loss equals the reduction in the supporting connective tissue of the tooth and reflects cumulative disease experience.

BIOLOGICAL MECHANISMS LINKING PERIODONTITIS AND LUNG FUNCTION

Research on the relationship between periodontitis and systemic diseases has been given increasing attention over recent decades and established that

periodontal infection might be a possible risk factor for various systemic conditions including pulmonary impairment. A number of studies have found results favouring such an association (Scannapieco and Ho, 2001, Hyman and Reid, 2004, Sharma and Shamsuddin, 2011, Hamalainen et al., 2004, Mojon et al., 1997, Azarpazhooh and Leake, 2006).^{3,4,5}

Even though the mechanisms by which poor periodontal health may influence respiratory function still remains unclear and controversial, several potential mechanisms have been proposed to explain the biological plausibility for an association between periodontal disease and lung function (Travis et al., 1994, Scannapieco et al., 2003).⁶

LOW-GRADE SYSTEMIC INFLAMMATION

Elevated levels of cytokines and higher levels of circulating inflammatory parameters such as CRP, fibrinogen, and leukocyte counts have been observed in dentate subjects with periodontal disease (Yoshii et al., 2009, Slade et al., 2003, Takami et al., 2003, Joshipura et al., 2004) and in edentulous subjects (Russell et al., 1999). Takami et al. (Takami et al., 2003) reported that patients with periodontal disease had significantly higher levels of CRP compared to healthy individuals (for men: OR=1.74; 95% CI 1.34, 2.25; for women: OR=1.80; 95% CI=1.00, 3.23). In another study (Yoshii et al., 2009), a significant correlation was found between periodontal disease at baseline and CRP one year later for 10,376 Japanese men with low baseline CRP (OR=1.34;

95% CI=1.12, 1.67).⁷ However, among those 4,997 Japanese men without periodontal disease, baseline CRP did not correlate with periodontal disease one year later (OR=1.16; 95% CI=0.89, 1.51) indicating that periodontitis increased the risk for high serum CRP levels in men after one year of follow-up and not the inverse.

Markers of systemic inflammation positively correlated with reduced spirometric lung volumes (Rasmussen et al., 2009, Glaser et al., 2011, Shaaban et al., 2006, Thyagarajan et al., 2006, Hancox et al., 2007, Dahl et al., 2001) suggesting that the chronic inflammatory burden of periodontal disease and the host response to this inflammation may lead to impaired lung function independently of the effects of smoking, obesity, cardiorespiratory fitness, or asthma. These studies indicated that different inflammatory markers may be similar in predicting changes in lung function. However, C-reactive protein (CRP) is the best studied and the most widely used clinically significant serum marker of systemic inflammation, endothelial cell damage, and infection. It is an acute-phase reactant primarily produced in the liver to the response of interleukin (IL)-6 (Loos et al., 2000, Gabay and Kushner, 1999). CRP levels can rise with age, obesity, diabetes mellitus, or smoking (Pearson et al., 2003). Epidemiological studies have reported a strong association between C-reactive protein and increased mortality independently of potential interfering factors such as age and smoking (Tice et al., 2003).

Findings of Rasmussen (Rasmussen et al., 2009)¹ showed a significant association between higher

levels of CRP at the age of 20 years and a greater reduction in spirometry values (FEV₁R, FVC) between the ages 20 and 29 years independently of sex, smoking, body mass index, cardiorespiratory fitness, and asthma.¹ Further, it has been suggested that inflammation leads to muscle wasting (Cesari et al., 2004, Fabbri et al., 2008), which is again associated with reduced lung function (Ito and Barnes, 2009, Janssens et al., 1999). Nevertheless, it is still debated whether inflammation leads to impaired lung function or the inverse (Fogarty et al., 2007, Olafsdottir et al., 2007).

It has been hypothesized that cytokines such as interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, and tumour necrosis factor (TNF)- α originating from inflamed periodontal tissues may modify the respiratory epithelium to promote adherence and colonization by respiratory pathogens to these mucosal surfaces (Wilson et al., 1996, Scannapieco et al., 2001, Reddi et al., 1996). Subsequently, the respiratory epithelium may release cytokines and attract neutrophils, which in turn infiltrate airway parenchyma and release proteolytic enzymes and toxic oxygen radicals that damage the epithelium (Birkedal-Hansen, 1993, Pesci et al., 1998). As a consequence, the resultant inflamed mucosal epithelium may be more prone to infection (Mojon, 2002, Hedges et al., 1995, Svanborg et al., 1996, Scannapieco, 1999). This mechanism has been observed for pathogens such as *Haemophilus influenzae* and *Streptococcus pneumoniae* that commonly cause respiratory tract infections (Hakansson et al., 1996, Khair et al., 1996). Thus, systemic inflammation might only be

of minor importance when considering the link between periodontal diseases and lung volume. Nevertheless, results are in agreement with others showing that hs-CRP and fibrinogen were associated with TLC (Rasmussen et al., 2009, Glaser et al., 2011, Shaaban et al., 2006, Thyagarajan et al., 2006, Hancox et al., 2007, Dahl et al., 2001).

ORAL BACTERIA AND RESPIRATORY PATHOGENS

Oral bacteria play an essential role in the pathogenesis of pulmonary impairment. Because of its humidity and temperature, the oral cavity provides an optimal environment for bacterial colonization hosting a wide variety of different species of bacteria with varying degrees of virulence (Sachdeo et al., 2008).⁸ 1mm³ of plaque, for instance, contains more than 10⁶ bacteria with 300 different anaerobic and facultative anaerobic species (Slots et al., 1988). Poor oral hygiene results in high supragingival plaque accumulation and higher concentrations of oral pathogens on both teeth and oral mucosa as well as in the saliva, being jointly responsible for periodontitis with pocketing (Aas et al., 2005, Russell et al., 1999, Scannapieco et al., 1992, Mojon and Bourbeau, 2003).

Under specific conditions, dental plaque can harbour respiratory pathogens and promote their growth (Mojon, 2002, Scannapieco and Mylotte, 1996).⁹ Hence, the oral cavity may be a potential reservoir for respiratory pathogens leading to aspiration pneumonia (Rajasuo et al., 1996, Yoneyama et al., 1999, Scannapieco et al., 1998,

Sumi et al., 2007, Fourrier et al., 1998). The presence of the following predisposing factors can foster such an occurrence: cigarette smoking, antibiotic treatment, diabetes mellitus, congestive heart failure, congenital defects in host defence, presence of underlying disease (e.g., chronic obstructive pulmonary disease (COPD)), immunosuppression, depressed consciousness, mechanical ventilation, enteral tube feeding, gastroesophageal reflux, and prolonged hospitalization (Scannapieco et al., 2003, Limeback, 1998, Russell et al., 1999, Scannapieco and Mylotte, 1996, Paju and Scannapieco, 2007, Fourrier et al., 1998).

Oropharyngeal colonization by gram-negative bacteria is common in elderly nursing home residents (Scannapieco et al., 1992) and debilitated hospitalized patients, in particular intensive care unit (ICU) patients (DeRiso et al., 1996, Yoneyama et al., 1999, Fourrier et al., 2000). These patients have more dental plaque accumulation than their community-dwelling counterparts, which can cause colonization of the oral flora by bacteria such as respiratory pathogens (Scannapieco et al., 1992, Pietrokovski et al., 1995, Abe et al., 2001). Several trials demonstrated that better oral hygiene, either by the use of mechanical cleansing or oral antiseptic rinses (e.g., betadine, chlorhexidine gluconate), significantly reduces the rate of lower respiratory tract infection in institutionalized subjects (Russell et al., 1999, Scannapieco, 1999, Mojon, 2002, Fourrier et al., 1998, Yoneyama et al., 2002, DeRiso et al., 1996). Diminished salivation and lower salivary pH are side effects of the intake of

various medications (e.g., non-steroidal anti-inflammatory drugs, diuretics) and may promote colonization by pathogens (Scannapieco, 1999). Mojon and Bourbeau (Mojon and Bourbeau, 2003) reported that oral infections can cause upper respiratory tract infections even in young adults. The resident oral bacteria are likely aspirated along with respiratory pathogens and may facilitate the adhesion and colonization of respiratory pathogens to mucosal surfaces by altering the environment of the upper airways (Scannapieco and Mylotte, 1996), spread of infection from contiguous sites (Toews, 1986), inhalation of infectious aerosols, or haematogenous spread from extrapulmonary sources of infection (e.g., translocation from the gastrointestinal tract, inevitable adverse effect of some dental treatments) (Mandell and Wunderink, 2008) may also be possible pathways for microorganisms to contaminate the lower respiratory tract (Azarpazhooh and Leake, 2006, Scannapieco, 1999). Oral bacteria stimulate the inflamed periodontal tissues to release cytokines via the sulcus fluid into the saliva, which promotes the adhesion and colonization of respiratory pathogens to oropharyngeal surfaces (Scannapieco, 1999) (see Figure 13). In subjects with periodontal disease salivary biomarker load is increased (Saygun et al., 2011, Ramseier et al., 2009). Subsequently, respiratory epithelial cells may release cytokines, which can cause a recruitment of inflammatory cells and increase its susceptibility to infection (Mojon, 2002, Svanborg et al., 1996, Hedges et al., 1995, Scannapieco, 1999).⁹

ASPIRATION OF SALIVARY SECRETIONS

The most common route by which the oral cavity may influence pulmonary function is aspiration of oropharyngeal contents including oral pathogens. Aspiration of small amounts of saliva during sleep is quite common, even in healthy subjects (Sinclair and Evans, 1994). However, individuals with altered consciousness (e.g., alcoholics, drug abusers, epileptics, stroke patients, patients with Parkinson's disease) (Huxley et al., 1978), mechanically ventilated patients (Kollef, 1999), or those who are fed by others (Elpern et al., 1994, Russell et al., 1999) aspirate secretions of oropharyngeal flora more frequently and in larger amounts yielding greater incidences of bacterial pneumonia. Subjects who have gastroesophageal reflux may even aspirate gastric contents. In all these neurological conditions the coordinated breathing and swallowing mechanism is often disordered.

There is evidence in the literature indicating that oral bacteria, poor oral hygiene, and periodontal disease may influence respiratory pathogen colonization and subsequently cause aspiration pneumonia, especially in high-risk subjects (Scannapieco and Mylotte, 1996, Scannapieco, 1999).¹⁰ The majority of pulmonary infections and emphysema cases are the result of aerobic bacteria found in the oral cavity including various *Streptococcus* species, various gram-negative bacilli (e.g., *Enterobacteriaceae* such as *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia species*, and *Enterobacter species*), *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Scannapieco, 1999). Several studies (Bartlett and

Gorbach, 1975, Bartlett and Finegold, 1974) indicated that periodontal organisms such as *Porphyromonas gingivalis*, *Staphylococcus aureus*, *Aggregatibacter actinomycetemomitans* are involved in aspiration pneumonia, independent of the presence or absence of teeth (Terpenning, 2001). Nevertheless, the quantity of aspirated bacteria seems to be more important than the type (Inglis et al., 1993).

FAILURE OF HOST DEFENCE

MECHANISMS

The lung is able to protect itself from aspirated material and infection by various defence mechanisms (DeRiso et al., 1996, Yoneyama et al., 1999, Fourrier et al., 2000). Intact cough reflexes that depend on the diaphragm and the stiffness or compliance of the pleura, the action of tracheobronchial secretions, mucociliary transport of inhaled microorganisms, particulate material from the lower airways to the oropharynx along with humoral and cellular immune mechanisms maintain the sterility of the lower respiratory tract (Thurlbeck, 1990, Burrows et al., 1988, Burrows, 1990). Furthermore, the airways of the lung, even the smallest ones, have the ability to spring back helping to clear the lung (Burrows, 1990, Burrows et al., 1988). However, these instruments have to be neurologically intact and not suppressed by medication or other noxious agents. Factors like smoking, COPD, diabetes, malnutrition, corticosteroid use, and endotracheal or nasogastric intubation can affect the efficiency of these different defence mechanisms (Donowitz and Mandell, 2000, Mandell and Wunderink, 2008,

Marik, 2001). The failure of the host defence mechanisms to eliminate pathogens from the mucosal surface results in proliferation of these pathogens, which are subsequently aspirated into the lung causing infection and tissue destruction (American Thoracic Society, 1996, Azarpazhooch and Leake, 2006).¹¹

MODIFICATION OF RESPIRATORY MUCOSAL SURFACES BY SALIVARY ENZYMES

Periodontitis associated enzymes in the saliva (e.g., mannosidase, fucosidase, hexosaminidase, sialidase) may modify the oral and respiratory epithelium leading to enhanced adhesion and colonization of respiratory pathogens. A possible further cause could be destruction of macromolecules on the mucosal surface, exposing receptors that permit the adhesion and colonization of respiratory pathogens and release of cytokines (Estes and Meduri, 1995, Scannapieco, 1999, Fagon and Chastre, 1996).¹²

Indeed, it is well known that this salivary enzymatic activity is increased in subjects with periodontal disease and in subjects with poor oral hygiene (Gomes-Filho et al., 2010, Scannapieco, 1999, Estes and Meduri, 1995, Gibbons et al., 1990). In addition, the presence of *Streptococcus gordonii*, a key bacterium in dental plaque formation, facilitates adhesion of pathogens such as *Haemophilus influenzae* to respiratory mucosal surfaces via specific adhesion-receptor interactions (Loesche and Lopatin, 1998, Scannapieco et al., 2001, Scannapieco and Rethman, 2003).¹³ The infection of the respiratory

epithelium is initiated through a transmitted signal to the epithelial cell, either direct via the adhesion receptor (Svanborg et al., 1996) or through the release of biologically active molecules such as lipopolysaccharides (Scannapieco et al., 2001)¹⁴.

CONCLUSIONS

To conclude, periodontal disease is significantly associated with reduced lung volumes, hyperinflation, and airflow limitation in a general adult population independently of potential confounders. Systemic inflammation did not provide a mechanism linking both diseases. However, large cohort studies with long observation periods evaluating comprehensive lung function parameters are needed to validate the observed associations and to assess causality more closely. Further to this, it needs to be investigated, with the help of randomized clinical trials, whether prevention or treatment of periodontitis might have a beneficial impact on lung function.

REFERENCES

1. Rasmussen, F., Mikkelsen, D., Hancox, R. J., Lambrechtsen, J., Nybo, M., Hansen, H. S. & Siersted, H. C. (2009) High-sensitive C-reactive protein is associated with reduced lung function in young adults. *Eur Respir J* 33, 382-388.
2. Holtfreter, B., Schwahn, C., Biffar, R. & Kocher, T. (2009) Epidemiology of periodontal diseases in the Study of Health in Pomerania. *J Clin Periodontol* 36, 114-123.
3. Scannapieco, F. A. (1999) Role of oral bacteria in respiratory infection. *J Periodontol* 70, 793-802
4. Hyman, J. J. & Reid, B. C. (2004) Cigarette smoking, periodontal disease: and chronic obstructive pulmonary disease. *J Periodontol* 75, 9-15.
5. Azarpazhooh, A. & Leake, J. L. (2006) Systematic review of the association between respiratory diseases and oral health. *J Periodontol* 77, 1465-1482.
6. Travis, J., Pike, R., Imamura, T. & Potempa, J. (1994) The role of proteolytic enzymes in the development of pulmonary emphysema and periodontal disease. *Am J Respir Crit Care Med* 150, S143-146.
7. Yoshii, S., Tsuboi, S., Morita, I., Takami, Y., Adachi, K., Inukai, J., Inagaki, K., Mizuno, K. & Nakagaki, H. (2009) Temporal association of elevated C-reactive protein and periodontal disease in men. *J Periodontol* 80, 734-739.
8. Sachdeo, A., Haffajee, A. D. & Socransky, S. S. (2008) Biofilms in the edentulous oral cavity. *J Prosthodont* 17, 348-356.
9. Mojon, P. (2002) Oral health and respiratory infection. *J Can Dent Assoc* 68, 340-345.
10. Scannapieco, F. A. (1999) Role of oral bacteria in respiratory infection. *J Periodontol* 70, 793-802.
11. American Thoracic Society (1996) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive

strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med* 153, 1711-1725.

12. Estes, R. J. & Meduri, G. U. (1995) The pathogenesis of ventilator-associated pneumonia: I. Mechanisms of bacterial transcolonization and airway inoculation. *Intensive Care Med* 21, 365-383
13. Loesche, W. J. & Lopatin, D. E. (1998) Interactions between periodontal disease, medical diseases and immunity in the older individual. *Periodontol 2000* 16, 80-105
14. Scannapieco, F. A. & Ho, A. W. (2001) Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III. *J Periodontol* 72, 50-56.