

The role of the immune response in the development of pneumonia arising from oral periodontitis: a literature review



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ABSTRACT

A growing evidence links periodontitis, a chronic inflammatory disease of the oral cavity, to the development of systemic inflammation. One of the most commonly reported is pneumonia, arising from aspiration of the periodontal pathogens into the lung tissue. In high-risk individuals, the morbidity and mortality rate is high, raising the concern for prevention measures. Secondary systemic effects are proposed to arise from both direct periodontal pathogens spread and through leakage of bacterial byproducts and local inflammatory cytokines to the bloodstream. The association of periodontitis and systemic diseases is bi-directional, as systemic diseases may, in turn, increase the incidence and severity of periodontal diseases. Here, the conflicting roles of the immune system in both limiting pathogen growth and its potential catastrophic inflammatory activation is further discussed. In addition, possible approaches to prevent periodontitis from spreading into the respiratory organs are also proposed. Given the large number of the population affected by periodontitis, a comprehensive understanding of the pathomechanisms of the development of systemic diseases, notably pneumonia, as well as the discovery of prevention and therapeutic approaches, is urgently needed.

Keywords: Periodontitis, pneumonia, systemic disease, inflammation, immune response, oral health.

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INTRODUCTION

The oral cavity provides a complex environment where multiple microorganisms are encountered daily. Infections and inflammations occurring within the oral cavity has been linked to the development of systemic infection, including those of the respiratory tract, given the same port of entry. In particular, periodontitis, a chronic inflammatory disease of the supporting structures of the teeth, has been linked to the development of pneumonia, both in-hospital and in-community settings.¹⁻⁴ Periodontal diseases itself comprise a multitude of inflammatory conditions affecting the gingiva, alveolar bone, cementum structure, and periodontal ligament. The pathogenesis often involves dysbiosis of the commensal oral microbiota leading to alterations of biofilm, subsequent recruitment of immune cells, inflammatory responses, and loss of periodontal tissue.⁵ It affects the general population, and the prevalence increases with age. It is estimated that in 2011-2014, almost 40% of adults in the United States

suffered from periodontitis.⁶ The number further increases in immunocompromised individuals.⁷ With the high occurrence in the population, periodontitis is commonly overlooked, and management is mostly from regional, rather than systemic point of view.⁸

A cross-sectional study involving almost 14,000 adult subjects living in the United States found an association between periodontal attachment loss and chronic obstructive pulmonary disease (COPD), with a trend showing decreased lung function in subjects with more periodontal attachment loss.⁹ Patients with moderate to severe chronic periodontitis reportedly have a 4.4- and 2.9-fold higher risk of developing community-acquired and hospital-acquired pneumonia, respectively.^{2,10} Similarly, a prospective study on an elderly cohort revealed an increased risk of pneumonia-associated mortality when more periodontal pockets were discovered.¹¹

The association between periodontitis and the development of respiratory infections, notably pneumonia, has

been previously proposed to occur from direct and/or indirect routes. Periodontal pathogens can be directly aspirated into the respiratory system or cause local inflammation and leakage of inflammatory mediators to systemic circulation.¹² However, evidence on the involvement of the immune system is scarce, as the immune reaction has itself been described to lead to systemic inflammation. Still, at the same time, it is also supposed to restrict bacterial growth and dissemination. The detailed mechanism and pathogenesis are to be further discussed. In addition, the roles of the immune system are also within the scope of this review. Understanding the pathomechanism of pneumonia arising from oral periodontitis is expected to raise concern to the importance of public health efforts in maintaining oral health as a key prevention measure, as well as identifying potential therapy in the future.

IMMUNOPATHOGENESIS OF PERIODONTITIS

The oral cavity is one of the major entry portals for potential pathogens. The

unique environment is conducive for both transient and more permanent bacterial colonization within the oral mucosa, tongue and tooth surface, as well as the gingival sulcus. In fact, over 800 bacterial and fungal species have been identified within the oral cavity.^{13,14} Chronic periodontitis is associated with sub-gingival dysbiosis of the microbial communities and a dense immuno-inflammatory infiltrate in the periodontium. This may lead to the destruction of the periodontal ligament and loss of alveolar bone.¹⁵

Discussion on the anti-bacterial and inflammatory events within the oral cavity is incomplete without mentioning the complex oral microbiota known as commensal, which, not only provides essential nutrients for the host but also effectively defends against opportunistic pathogen.¹⁶ Around 18 species within the Streptococci group has been reported as the primary 'commensal' colonizers of the oral cavity¹⁷. The mitis/oralis group streptococci produced adhesins and metabolites, in addition to antagonizing other periodontal pathogens including *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* by secretion of hydrogen peroxide, various bacteriocins, and competitive binding.¹⁷⁻¹⁹ Moreover, studies have demonstrated the role of the commensal streptococci in regulating inflammation within the periodontal lesion as well as in the bronchial epithelial cells by inhibiting the proinflammatory nuclear factor kappa B (NF- κ B) pathway.^{20,21} The inhibition of NF- κ B transcription is further shown to be a downstream effect of nuclear factor erythroid 2-related factor 2 (Nfr2) signaling, which is activated by hydrogen peroxide secretion by *S. mitis* and *S. oralis*.²² Inhibition of the proinflammatory NF- κ B pathway ultimately leads to diminished inflammatory cytokines, including IL-8 and IL-6,^{20,21} and promotes homeostatic immune balance.

Anatomically, the gingival tissue and gingival crevicular fluid present within the gingival sulcus are rich of immune components derived from the serum, in addition to the resident inflammatory cells.²³ Early clinical pathogenesis describes periodontitis based on its histopathologic characteristics as: initial

stage, in which neutrophil is the major infiltrate; early stage, in which macrophage and T cells are more commonly seen; and established lesion stage, where B and plasma cells predominate.²⁴ This clearly reflects the process of immune response to infection, which impose the innate to the adaptive responses. Acting as the first line of defense to infection, the innate immunity indiscriminately eliminates the target pathogen and prevents overt inoculation and subsequent infection. This stage is marked by infiltration of polymorphonuclear leukocytes within the gingival crevicular fluid into the periodontal space.²⁵ When this response is inadequate, further cellular and humoral response of the adaptive arm is activated and is usually followed by progressive tissue destruction. The orchestrated immune response is also characterized by notable secretion of inflammatory mediators and cytokines, among which have been reported include prostaglandin E2, interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, IL-10, transforming growth factor (TGF)- β , and tumor necrosis factor (TNF)- α .²⁵⁻²⁷

MECHANISM OF ORAL MICROBIOTA PATHOGENICITY FOR THE DEVELOPMENT OF PNEUMONIA

One of the most plausible routes of systemic dissemination of periodontal pathogens is through a direct route, in which the pathogen enters systemic circulation through ulceration in the periodontal pocket lining.^{28,29} The same could happen during invasive dental procedures or surgery, which cause breaks in the periodontal pocket and migrating pathogens into the bloodstream.³⁰ It is therefore confirmed that most systemic involvement cases arising from periodontitis are reported from the cardiovascular system,³¹⁻³³ including coronary heart disease,³⁴ atherosclerotic disease,^{29,35} and infective endocarditis,³⁶ where a significant blood flow is returning to the heart through the vessels.

Rather than through systemic circulation, the direct route leading to bacteremia within the lung could be an aspiration of oral bacteria capable of

inducing pneumonia or the formation of dental plaque containing respiratory pathogens, which may later aspirate back into the lungs.³⁷ The latter was possible due to the alteration of the mucus surface in periodontitis, which may increase the adhesion and colonization capability of respiratory pathogens.³⁸ In fact, several oral bacteria have been implicated in causing pneumonia and lung abscesses, with some overlapping with pathogens causing periodontal disease, including *P. gingivalis*.³⁹ Evidence has also reported identical pathogen identification from dental plaque and bronchoalveolar fluid aspirate.⁴⁰ The possibility of this direct bacterial aspiration is inevitably increased in patients with swallowing difficulty, a decreased level of consciousness, or in critically ill patients requiring mechanical ventilation.¹²

Periodontal pathogens have also been reported to alter the barrier function of the bronchial and alveolar epithelium, as noted by increased expression of matrix metalloproteinase (MMP)-12, which is involved in the disintegration of alveolar walls, and lower gene expression of claudin 1 and junctional adhesion molecule A (JAM-A), both involved in epithelial construction.⁴¹ Additionally, aspirated oral pathogen also promoted overproduction of mucin within the respiratory lumen, subsequently leading to impaired respiratory function.⁴² Altogether, these alterations will further lead to increased susceptibility to respiratory infection.

IMMUNE INVOLVEMENT IN LIMITING BACTERIAL GROWTH AND INITIATING INDIRECT INFLAMMATORY ACTIVATION IN DISTANT ORGANS

Most periodontal pathogens are obligate anaerobes, which are unlikely to grow within the aerobic respiratory organs. Therefore, it is hypothesized that a mere contact of pathogens onto the respiratory epithelial cells is capable to induce immune response and cytokine secretion.⁴² Previous evidence revealed increased secretion of pro-inflammatory cytokines, including IL-6 and IL-8 from bronchial, alveolar, and pharyngeal epithelial cells upon stimulation with *P. gingivalis* and

F. nucleatum.^{43,44} In fact, these studies utilized inactivated bacteria, proving the capability of immune activation upon introduction to pathogen component, without any established infection. In addition, an increase of both IL-6 and IL-8 isoform secretion from the lungs and bronchi, along with a high circulating concentration of these cytokines, were also observed upon intra-tracheal instillation of periodontal pathogens in mice model.⁴⁵ *P. gingivalis* is recognized by Toll-like receptor (TLR) 2 in the human bronchial and epithelial cell membranes and further activates its downstream pathways, although NF- κ B signaling was not obviously observed.⁴⁴

As previously described, dysbiosis within the periodontal cavity attracts a cascade of immune responses from the rapid innate to the coordinated adaptive immunity. While attempting to eliminate local pathogens, secreted cytokines resulting from local inflammatory reactions within the periodontal cavity may affect the respiratory epithelium and facilitate infection within the epithelium.³⁸ Therefore, a coordinated mechanism to limit inflammatory reactions is the crucial point to minimize excessive tissue damage and prevent further distant inflammatory activation.

MEASURES FOR PREVENTING PNEUMONIA ARISING FROM ORAL PERIODONTITIS

A substantial amount of evidence has pointed out the importance of improving oral hygiene in preventing the incidence of systemic disease,⁴⁶⁻⁴⁸ especially in elderly populations, hospitalized patients, as well as those living in nursing homes and long-term care facilities. A meta-analysis revealed that improvement of oral hygiene reduced the incidence of nosocomial pneumonia by an average of 40%.³⁹ The reported oral care measures include frequent tooth brushing, regular professional dental cleaning,⁴⁸ application of 0.2% chlorhexidine gel,⁴⁷ regular cleaning of removable prostheses,⁴⁹ and periodontal treatments.^{50,51}

Tobacco use induces immune dysfunction and poor vascularization,⁵² and is a shared risk factor for both

periodontal disease and respiratory infection. Smoking also alters the subgingival microbial community and facilitates the colonization of periodontal pathogens, leading to the initiation, extent, and severity of periodontal disease.⁵²⁻⁵⁴ Therefore, smoking cessation is one of the pivotal approaches in the preventive area.

The treatment of periodontitis generally uses anti-microbial prescription to directly eliminate the causative pathogen. Recently, studies have addressed the extended properties of several antibiotics to also limit inflammation. Several studies pointed out the immunomodulatory properties of moxifloxacin in the treatment of periodontitis and revealed decreased level of IL-1 β , IL-6, IL-8 and TNF- α .⁵⁵⁻⁵⁸ Another study reported the potential use of macrolide antibiotics, notably erythromycin, in regulating inflammation and protecting against lethal pulmonary and periodontal bone loss in mouse models. The authors reported that erythromycin upregulates developmental endothelial locus (DEL)-1 by reversing the inhibitory effect of IL-17 to further activates JAK2-MAPK p38-CCAAT/enhancer binding protein- β (C/EBP β) signaling pathways, finally resulted in diminished neutrophilic inflammation within the lungs and periodontal tissue.⁵⁹

RECOMMENDATIONS AND DIRECTION OF FUTURE STUDIES

Preventing the development of pneumonia stemming from oral periodontitis indeed includes a proactive approach centered around robust oral hygiene practices and regular dental check-ups. The significance of maintaining excellent oral hygiene cannot be overstated, as it curtails the buildup of harmful bacteria that can migrate from the oral cavity to the respiratory tract, potentially causing pneumonia. Studies on the use of antibiotics for both treatment and prophylaxis attempts are intriguing. However, further clarification and larger-scale human cohort study should be of priority, and antibiotics medication should be cautiously implemented according to the epidemiology-specific sensitivity within each area to prevent further development of anti-microbial resistance.

Future studies which scrutinize

the intricate relationship between periodontitis and pneumonia could involve elucidating the specific mechanisms through which oral pathogens may contribute to respiratory infections and pneumonia, potentially uncovering novel pathways for intervention. Moreover, investigating innovative strategies such as targeted antimicrobial agents, immune modulation, or probiotics that could mitigate the impact of periodontitis on pneumonia development should also be a topic of interest. As technology advances, incorporating omics technologies like metagenomics and proteomics may offer a comprehensive understanding of the microbial landscape in both oral and respiratory ecosystems, paving the way for precision medicine approaches tailored to individual patient needs.

CONCLUSION

Periodontitis is characterized by chronic inflammation within the periodontal tissues. It has been associated with the incidence of systemic involvement, to note, respiratory infection and pneumonia. Pneumonia arising from direct aspiration of the potentially pathogenic bacteria has been widely reported. From the perspective of immunity, dysbiosis within the oral microbiota niche leads to the activation of the immune system to eliminate the pathogen, however, in the same time, the excessive inflammatory response also leads to the destruction of periodontal tissues and may further trigger the alteration of respiratory epithelia, leading to increased susceptibility of respiratory infections.

Given the high prevalence of the population affected by periodontitis, immediate attempts to comprehensively manage oral health are needed. Multidisciplinary cooperation involving both medical and dental healthcare practitioners, as well as public health managers and authorities, are expected to collaborate in emphasizing prevention measures and exhaustive management of oral disease to prevent unnecessary systemic complications. This will, in fact, benefit in preventing the development of drug-resistant bacteria, lowering the medical cost, and reducing mortality rate, especially in elderly patients and susceptible individuals.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ETHICAL CLEARANCE

The manuscript did not involve human or animal study requiring ethical clearance approval.

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