

Periodontal Diseases and Age-Related Macular Degeneration: Is There a Link? A Review

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ABSTRACT

Background: Age-related macular degeneration (AMD) induces irreversible loss of vision in older people. The exact pathophysiology remains unclear, but numerous studies highlight the role of inflammation and multiple risk factors. Recent data show an altered periodontal condition subject to AMD. Periodontal diseases lead to the destruction of tooth-supporting tissues, mainly caused by the periodontal infection inducing a chronic inflammation. Periodontal diseases are known to be associated with several extraoral diseases such as diabetes, polyarthritis (rheumatoid arthritis), cardiovascular disease, and preeclampsia.

Objectives: To assess emerging evidence suggesting an association between periodontitis and AMD.

Methods: To support this review, we performed a literature search using PubMed, Cochrane, and Google Scholar databases, completed by manual searches in periodontology journals. We included only the original studies published before July 2017 reporting data on periodontal diseases and AMD. No restrictions were made on the language.

Results: Persons with AMD showed more periodontal diseases, fewer teeth, and more alveolar bone loss than those without AMD. Also, a significant association was observed between periodontal diseases and AMD, but only in the youngest individuals studied.

Conclusion: According to the studies included in this review, periodontal disease may be a plausible risk factor for AMD and may have a potential role in the earlier stages of this eye disease. Further studies should be encouraged for better understanding of this potential new relationship.

INTRODUCTION

Periodontal diseases (PDs) are oral pathology that lead to the destruction of tooth-supporting tissues.¹ They result from an inappropriate response by the host to a pathogenic bacterial challenge (bacterial biofilm) associated with genetic and environmental risk factors (genetic polymorphisms, tobacco, diabetes, stress, etc).² Clinically, PDs are characterized by the presence of gingival bleeding (spontaneous or brushing), clinical gingival inflammation, gingival recessions, dental mobility, and loss of clinical attachment (presence of periodontal pockets and alveolar bone resorption).³ In the US, the prevalence of PDs (moderate to severe form) varies from 60% to 70% in adults older than age 65 years.⁴ In France, more than 50% of the adult population has mild, moderate, or severe periodontitis.⁵

In age-related macular degeneration (AMD), lesions of the macula at the center of the retina occur on a previously normal eye, inducing irreversible vision loss in older people.⁶ In industrialized countries, AMD is considered to be the leading cause of

visual impairment in older adults.⁷ The disease is asymptomatic and evolves silently before the appearance of a scotoma (blind spot) in the center of the visual field during advanced AMD. This macular degeneration is subdivided into 2 types: 1) dry or atrophic AMD and 2) wet or exudative AMD.⁸ The dry type of AMD represents the majority (up to 90%) of cases.⁹

Presently, the etiology of AMD is not exactly known, and there is no curative treatment available for this disease. However, the management of AMD relies on palliative treatments (laser, dynamic phototherapy, surgery, antivascular endothelial growth factor therapy) and on identification of risk factors.¹⁰ In addition to the risk factors already known in its pathogenesis (older age, tobacco use, obesity, polymorphism of the complement factor, diet), recent studies have highlighted the role of systemic inflammatory biomarkers in the pathogenesis of AMD.^{9,11} Hong et al's¹² meta-analysis revealed that persons with C-reactive protein levels higher than 3 mg/L have a double risk of advanced AMD developing compared with persons having C-reactive protein levels lower than 1 mg/L. Similar observations have been reported by other studies.^{13,14} Moreover, pro-inflammatory cytokines interleukin (IL)-1 β , IL-6, and tumor necrosis factor can promote pathologic changes in the retinal pigment epithelium.⁹

PDs induce a chronic inflammation and bacteremia in susceptible individuals and have also been associated with elevated systemic biomarkers such as tumor necrosis factor- α , C-reactive protein, IL-1 β , and IL-6.^{15,16} Thus, PDs have been associated with several extraoral diseases such as polyarthritis (rheumatoid arthritis), diabetes, and cardiovascular disease, as well as preterm birth, low birth weight, and preeclampsia.¹⁷⁻²⁰

This article aimed to assess, through a literature review, the emerging potential relationship between PD and AMD.

METHODS

An electronic search was performed of PubMed, Cochrane, and Google Scholar databases by the combination of the following keywords: *Periodontal disease, periodontitis, periodontal, gingival inflammation, eye disease, ocular disease, retinal disease,*

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Keywords: age-related macular degeneration, periodontitis, periodontal disease, periodontal medicine, risk factors, systemic inflammation

age-related macular degeneration, macular degeneration, and risk factors (Figure 1). A complementary search was made from the bibliographic references of the selected articles.

No restrictions were made on the languages. The last search was conducted for all databases on July 2017. Initially, 8 articles were identified. After a thorough analysis of titles and abstracts, 2 articles were removed because they were letters to an editor, and another article was removed because it was out of our study context. Thus, 5 articles were selected for a full-text examination. Later, 1 more article was removed after a thorough reading because it was out of our study context.

RESULTS

From 8 articles identified, 4 articles were selected for the analysis.

The studies were conducted in Poland, Finland, the US, and Korea. Some characteristics of these studies are presented chronologically (Table 1).

In 2012, Brzozowska and Puchalska-Niedbał²¹ were the first to report about periodontal status and AMD. In their study, 56 patients with AMD between ages 45 and 90 years were recruited. Dental and periodontal checkups found many lesions in their oral cavities, which were mainly located in the periodontal tissues.²¹

In 2013, Karesvuo et al²² analyzed the relationship between AMD and oral status using 1751 individuals aged 30 years

and older. The AMD diagnosis was obtained with a self-report using questionnaires before dental and periodontal examination. In this population, the prevalence of AMD was 3.1% (54 individuals). The authors reported that persons with AMD had fewer teeth ($p < 0.001$) and more alveolar bone loss ($p = 0.004$) compared with participants who did not have AMD.²² Also, they observed a significant association between alveolar bone loss and AMD in men ($p = 0.013$).²²

In 2015, Wagley et al²³ published their study results that focused on AMD and PD. They used data of 5887 participants aged 40 years or older from the US Third National Health and Nutrition Examination Survey (NHANES III) data (1988–1994). An AMD diagnosis was obtained using ocular fundus photographs according to international protocol.⁸ In this study, PD was defined according to loss of clinical attachment level ($> 10\%$ of sites with > 3 mm of loss of attachment).²³ The participants were stratified into 2 groups: The “youngest group” (40–60 years) and the “oldest group” (> 60 years). After a logistic regression model controlled for AMD confounders and risk factors and was stratified by age, the authors observed that PD was independently associated with AMD only in the youngest group (odds ratio = 1.96, 95% confidence interval = 1.22–3.14, $p = 0.006$).²³

In 2017, Shin et al²⁴ published the results of their investigation concerning the same topic. From the Korean NHANES (2008–2010 and 2012), they enrolled 13,072 adults at least age 40 years. The AMD diagnosis and periodontal status were

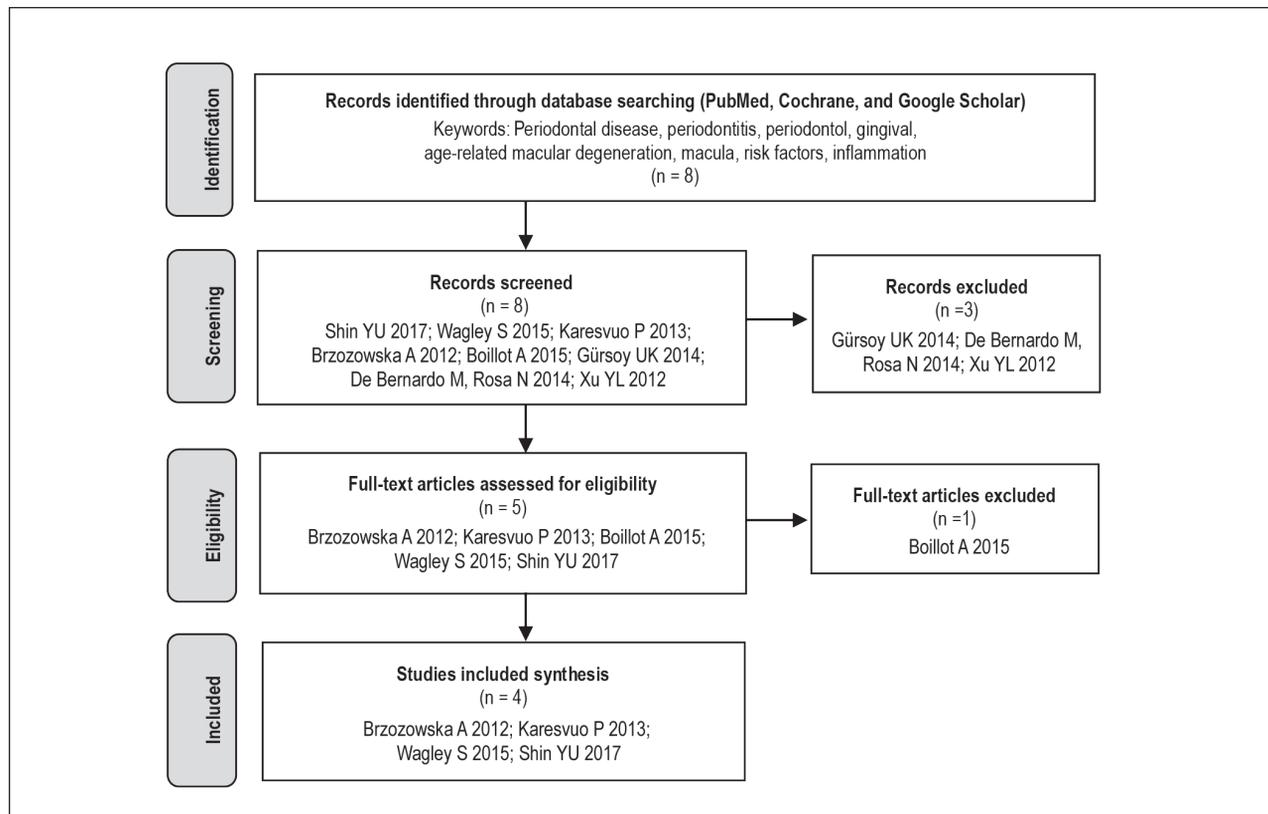


Figure 1. Flowchart diagram.

obtained. The AMD diagnosis was also determined using ocular fundus photographs, but PD was defined as the presence of periodontal pockets using the Community Periodontal Index score, in which mild PD was a score of 3 (periodontal pocket depth = 4-5mm) and severe PD was a score of 4 (periodontal pocket depth \geq 6 mm). The prevalence of PD and AMD in the study was around 37.4% and 5.6%, respectively. All participants were divided into 2 groups: The youngest (\leq 62 years) and the oldest ($>$ 62 years). The authors reported that individuals with AMD had more PD than participants without AMD in the youngest group ($p = 0.031$). Also, a multivariate logistic regression model after adjusting for all AMD confounding factors was performed. Shin and coworkers²⁴ observed a significant link between severe PD and AMD only in the youngest group (odds ratio = 1.61, 95% confidence interval = 1.02-2.54). No significant association was observed between PD and AMD in the oldest age group and between mild PD and AMD in both age groups.

DISCUSSION

A potential association between PDs and AMD is a recent focus in periodontal medicine as assessed by 4 cross-sectional studies. According to these epidemiologic data, individuals with AMD showed more PDs than those without AMD ($p = 0.031$), and persons with AMD had fewer teeth ($p < 0.001$) and more

alveolar bone loss ($p = 0.004$) than did individuals without AMD.²² This finding was observed in whites ($p = 0.031$) and in a heterogeneous population of whites and nonwhites.²⁴ Also, a significant association was observed between PDs and AMD only in the youngest individuals.²² These observations can be explained by several reasons. Possibly, PDs could have a potential role in the earlier stages of AMD, or covariates increasing with age might dilute the effect of PDs on ages older than 60 years. These findings may be caused by a methodology bias because there were more subjects between ages 40 and 60 years than subjects older than age 60 years in both the US study (4432 vs 3876) and the Korean sample (8616 vs 4456). According to the literature, there could be a selection bias because AMD may start beyond age 60 years. Nevertheless, advanced age is the main risk factor for AMD.¹⁰ Multiple studies have shown that AMD is rare before age 55 years and is very common after age 75 years.^{7,25} Similarly, the prevalence and severity of PDs increase considerably with age.²⁶

In addition to age, PD and AMD have other common risk factors. Scientific findings have suggested diabetes as a risk factor for advanced AMD.²⁷ However, PD and diabetes have a bidirectional relationship.^{28,29} Indeed, the number of patients with diabetes increased in the presence of 2 or 3 risk factors of PD. In contrast, PD increases the susceptibility toward development of diabetes.³⁰ Through diabetes, PD could have an

Table 1. Characteristics of studies included in review

Source	Country	No. of participants/ age/race	Methods	Main results
Brzozowska & Puchalska-Niedbal, ²¹ 2012	Poland	56 patients/ 45-90 y/white	Cross-sectional study Dental and periodontal checkups + radiography	Patients with AMD had several inflammatory lesions in their oral cavity, which were mainly located in the periodontium (53.17%)
Karesvuo, ²² 2013	Finland	1751 patients/ \geq 30 y/white	Cross-sectional study; national population-based Health 2000 survey Dental and periodontal checkups + radiography + laboratory analyses Self-report on AMD with questionnaire + interview	Persons with AMD had fewer teeth ($p < 0.001$) and more alveolar bone loss ($p = 0.004$) compared with participants without AMD. Also, a significant independent association was found between alveolar bone loss and AMD in men ($p = 0.013$)
Wagley, ²³ 2015	US	5887 patients/ $>$ 40 y/white and nonwhite	Cross-sectional study; US NHANES III, 1988-1994 2 groups: \leq 60 y, $>$ 60 y Diagnosis of AMD: Ocular fundus photographs Diagnosis of PD: $>$ 10% of sites with $>$ 3 mm of CAL Multivariate regression analysis stratified with AMD confounders and risk factors	PD is independently associated with AMD in those aged 40-60 y (odds ratio = 1.96, $p = 0.006$) but not for subjects $>$ 60 y ($p = 0.120$)
Shin, ²⁴ 2017	Korea	13,072 patients/ $>$ 40 y/Asian	Cross-sectional study; Korean NHANES, 2008-2010 and 2012 2 groups: \leq 62 y; $>$ 62 y Diagnosis of AMD: Ocular fundus photographs Diagnosis of PD: CP Index score 3 and 4 Mild PD: Score 3 (PPD = 4-5 mm) Severe PD: Score 4 (PPD \geq 6 mm) Multivariate regression analysis stratified with AMD confounders and risk factors	Persons with AMD in \leq 62 y age group had more PD than participants without AMD ($p = 0.031$) Severe PD is independently associated with AMD in individuals 40-62 y No association between PD (both mild and severe) and AMD in participants $>$ 62 y old

AMD = age-related macular degeneration; CAL = clinical attachment level; CP = community periodontal; NHANES = National Health and Nutrition Examination Survey; PD = periodontal disease; PPD = periodontal pocket depth; + = plus.

indirect effect on AMD. Also, smokers have a higher risk of having PD.³¹ Several studies have demonstrated an association between smoking and both the wet and dry forms of AMD.^{30,32,33}

In addition, PD and AMD occur in susceptible persons. Alteration of the complement pathway or its polymorphism is considered to play an important role in the pathogenesis of periodontitis and AMD.^{34,35} This dysfunction could be the common pathway for both diseases. In addition to genetic susceptibility, inflammatory deregulation/upregulation should be a potential key between a PD and AMD relationship. However, high levels of systemic inflammatory biomarkers have been associated with AMD and were significantly increased in patients with chronic PD.^{15,36}

CONCLUSION

Recent epidemiologic data suggest that PDs are plausible additional risk factors for AMD. The link between the diseases remains unclear for the moment, but PD and AMD share similar risk factors such as inflammation disorders, advanced age, smoking habits, gene polymorphism, and diabetes. Other studies are necessary for better understanding of a potential PD and AMD relationship. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Author Contributions

Zocko Ange Désiré Pockpa, DDS, MSc, developed the idea and experimental design, performed research, and wrote the manuscript. Xavier Struillou, PhD, contributed substantially to the discussion. Assem Soueidan, PhD, contributed substantially to the discussion and proofread the manuscript. Zahi Badran, PhD, developed the idea and experimental design and contributed substantially to the discussion. Dramane Kone, DDS, performed critical proofreading and contributed to the discussion. Gnaba Samson Mobio, DDS, performed critical proofreading and contributed to the discussion. All authors have given final approval and take full responsibility for the integrity and accuracy of this article.

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A New Way of Living

Going blind, especially later in life, presents one with a huge, potentially overwhelming challenge: to find a new way of living, of ordering one's world, when the old way has been destroyed

— Oliver Sacks, CBE, FRCP, 1933-2015, British neurologist, naturalist, historian of science and author