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Prospective Study of Oral Health and Risk of Primary Open-Angle Glaucoma in Men

Data from the Health Professionals Follow-up Study

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Purpose: Tooth loss or periodontal disease is associated with systemic endothelial dysfunction, which has been implicated in primary open-angle glaucoma (POAG). The relationship between oral health and POAG has received limited attention. Thus, we evaluated the association between oral health history and risk of POAG and POAG subtypes.

Design: Prospective cohort study.

Participants: Health Professionals Follow-up Study participants (40 536 men) followed biennially from 1986 to 2012. At each 2-year risk period, eligible participants were aged 40+ years, were free of POAG, and reported eye examinations.

Methods: By using validated questions, we updated participants' status on number of natural teeth, teeth lost, periodontal disease with bone loss, and root canal treatments.

Main Outcome Measures: During follow-up, 485 incident cases of POAG were confirmed with medical records and classified into subtypes defined by intraocular pressure (IOP; $\geq$ or $<$22 mmHg) or visual field (VF) loss pattern at diagnosis (peripheral loss only or early paracentral loss). Multivariable relative risks (MVRRs) and 95% confidence intervals (CIs) were estimated.

Results: Number of natural teeth, periodontal disease, and root canal treatment were not associated with POAG. However, compared with no report of tooth loss, a report of losing teeth within the past 2 years was associated with a 1.45-fold increased risk of POAG (95% CI, 1.06−1.97); in particular, a report within the past 2 years of both losing teeth and having a prevalent diagnosis of periodontal disease was associated with a 1.85-fold increased risk of POAG (95% CI, 1.07−3.18). The associations with recent tooth loss were not significantly different for the POAG subtypes (P for heterogeneity $\geq$0.36), although associations were strongest in relation to the POAG subtypes with IOP $<$22 mmHg (MVRR, 1.93; 95% CI, 1.09−3.43) and early paracentral VF loss (MVRR, 2.27; 95% CI, 1.32−3.88).

Conclusions: Although the number of natural teeth was not associated with risk of POAG, recent tooth loss was associated with an increased risk of POAG. Because these findings may be due to chance, they need confirmation in larger studies. *Ophthalmology 2016;■:1−10 © 2016 by the American Academy of Ophthalmology.*

Oral infections, leading to tooth loss or periodontal disease, have been related to a multitude of systemic diseases, such as diabetes, cardiovascular disease, rheumatoid arthritis, certain cancers, and neurodegenerative diseases.[1−6] There are several mechanisms underlying the association with systemic illnesses, as have been previously reviewed and summarized.[1,2] Periodontitis, a common bacteria-induced oral inflammatory condition that destabilizes the tooth structural support apparatus, can produce transient bacteremia, which may lead to systemic endothelial dysfunction and chronic inflammatory responses in various extra-oral tissues.[7−9] Second, inflammatory markers generated from the affected periodontal tissue also can travel via the bloodstream to reach other tissue beds. For example, in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, there is growing evidence that peripheral inflammation exacerbates the development of neuronal cell loss.[3,4] The third mechanism is the immune response to the bacteria, which involves the generation of antibodies to bacteria and their toxins, which may have off-target effects in extra-oral tissues (e.g., cross-reactive antibodies that contribute to atherosclerosis).[10]

Primary open-angle glaucoma (POAG) is a leading cause of blindness worldwide and a chronic disease characterized by neurodegeneration of retinal ganglion cells and their axons. In a clinic-based, case-control study among African

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Americans,[11] compared with 45 controls, 58 glaucoma cases showed significantly higher oral bacterial loads and significantly fewer teeth, especially in older persons.[12] The same research group[11] found that when glaucoma animal models were administered low-dose bacterial toxins, glaucomatous neurodegeneration ensued and was accompanied by microglial activation, upregulation of the complement system, and toll-like receptor 4 signaling activity in the optic nerve. These results suggest that oral infections, particularly those that can lead to periodontal disease, may have systemic effects that can contribute to POAG.

We hypothesized that the vascular bed in the base of the tooth may be a conduit for inflammatory cytokines and microbes to access the systemic circulation and consequently the intricate optic nerve head microcirculatory system, leading to endothelial cell dysfunction that would compromise retinal ganglion cell axons. Periodontal disease is associated with impaired flow-mediated vasodilation, and treatment of periodontal disease has been shown to improve flow-mediated vasodilation.[7–9] Of note, POAG also has been associated with impaired flow-mediated vasodilation, and several studies have reported on genetic and environmental exposures related to endothelial cell function related to an early paracentral visual field (VF) loss subtype of POAG.[13–16]

To further test the possible link between oral infections and POAG at the population level, we prospectively evaluated a self-reported comprehensive analysis of oral health and risk of POAG and POAG subtypes using data from 40 536 men in the Health Professionals Follow-up Study (HPFS) followed for 25+ years.

Methods

Study Population

The HPFS[17] is an ongoing cohort study initiated in 1986 when 51 529 U.S. male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, or podiatrists) aged 40 to 75 years responded to a mailed health questionnaire. In the HPFS, participants are followed every 2 years with questionnaires that ask about newly diagnosed diseases such as periodontitis and glaucoma, as well as other health and lifestyle factors. The follow-up rate for the HPFS cohort is greater than 85%. This work was Health Insurance Portability and Accountability Act compliant, and the described research adhered to the tenets of the Declaration of Helsinki. The Human Research Committees of Massachusetts Eye and Ear Infirmary and the Harvard School of Public Health ceded the oversight for this work to the Brigham & Women's Hospital Institutional Review Board, which approved the study. The Brigham & Women's Hospital Institutional Review Board regarded participants' return of completed questionnaires as implied informed consent.

Ascertainment of Primary Open-Angle Glaucoma Cases and Subtype Classification

We included 485 confirmed incident cases of POAG. Glaucoma case ascertainment occurred every 2 years; in questionnaires, participants were asked about eye exams and physician diagnoses of glaucoma. For participants who reported a diagnosis of glaucoma, we sought permission to contact their eye care providers. Eye care providers were asked to send all VF tests and medical records that established the diagnosis or a completed glaucoma questionnaire that asked about maximal intraocular pressure (IOP), status of the filtration apparatus, optic nerve structural information, ophthalmic surgery, and VF loss. Finally, records were reviewed by a glaucoma specialist (LRP), masked to participants' oral health history, to confirm POAG cases using standardized criteria.

For the majority of POAG cases (>70% of cases), the following criteria were met: (1) gonioscopy showed that the filtration angle was not occludable in either eye; (2) slit-lamp biomicroscopy showed no evidence in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma, or rubeosis; and (3) at least 2 reliable tests demonstrated reproducible VF defects consistent with POAG. For the remaining POAG cases, the slit-lamp examination and VF criteria were met, but documentation of pupil dilation without subsequent adverse events or of the angle appearing open based on slit-lamp biomicroscopy was considered as evidence for nonoccludable angles. For VF defects, we did not require a specific type of perimetry; however, full static threshold testing was documented in 95% and kinetic VFs in <1%. For static threshold or suprathreshold tests, we used the following reliability definitions: fixation loss ≤33%, false-positive rate ≤20%, and false-negative rate ≤20%. For kinetic VFs, a VF test was considered reliable unless the examiner noted test circumstances to the contrary.

New glaucoma diagnoses were self-reported by 4239 HPFS participants. These were confirmed as various types of glaucoma or glaucoma suspect in 52%: potential POAG with VF loss (25%), only elevated IOP or optic disc cupping (15%), and other types of glaucoma/glaucoma suspect (12%). The remaining (48%) were unconfirmed, because participants (16%) or eye care providers (6%) were unreachable, participants denied permission for record review (9%), participants indicated the report was erroneous (15%), or eye care providers refuted the glaucoma diagnosis (2%). Among those classified as potential POAG with VF loss, we included only the POAG cases that met our case definition (485 cases); other confirmed and unconfirmed self-reports were censored in the analyses as of the diagnosis date.

For secondary analyses, we classified cases into subtypes by IOP and by VF loss pattern at diagnosis. We defined subtypes of "high-tension" (n = 341) and "normal-tension" POAG (n = 144) as those with maximum untreated IOP > or ≤21 mmHg, respectively. We defined subtypes by VF loss pattern: those with peripheral VF loss only (n = 260) or early paracentral VF loss (n = 147) or undetermined VF loss (n = 78) with a method previously described.[18] For POAG with peripheral VF loss only, any combination of nasal step, temporal wedge, or Bjerrum area defects were present without any paracentral loss. For POAG with early paracentral loss, there was (1) paracentral loss only or (2) paracentral loss with VF loss in the Bjerrum area and/or nasal step zone in the same hemifield, but without any temporal wedge loss. We included the latter paracentral group because cases with only paracentral loss were uncommon (~21%) and cases with clear paracentral loss frequently also showed peripheral loss. Cases (n = 78) with undetermined VF loss (i.e., VF loss in the paracentral and any temporal wedge region in the same eye or paracentral in 1 hemifield with peripheral loss only in the other hemifield) were censored in the analyses as of the diagnosis date.

Ascertainment of Oral Health

For determining the number of teeth and number of teeth lost, in 1986, we asked about the number of natural teeth, and in the follow-up questionnaires, we asked about any tooth loss during the previous 2 years. In a validation study of a general population sample, self-reported number of teeth was highly correlated with the actual number of teeth on clinical assessment ($r = 0.97$).[19]