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Mortality in Older Persons with Retinopathy and Concomitant Health Conditions

The Age, Gene/Environment Susceptibility-Reykjavik Study

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Purpose: To assess the impact of retinopathy on mortality in older persons with concomitant health conditions.

Design: Population-based prospective cohort study.

Participants: A total of 4966 individuals aged 67 to 96 years (43.2% were male) from the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS).

Methods: Retinopathy was evaluated from digital fundus images (2002−2006) using the modified Airlie House adaptation of the Early Treatment Diabetic Retinopathy Study protocol. Mortality was assessed through September 2013 (cause of death assigned through 2009). Cox proportional hazards regression models, with age as the time scale, estimated the association between retinopathy and death while controlling for risk factors and the presence of concomitant health conditions.

Main Outcome Measures: Mortality from all causes and cardiovascular disease (CVD).

Results: Among the 4966 participants, 503 (10.1%) had diabetes and 614 (12.4%) had retinopathy at baseline. A subset of these (136 [2.7%]) had both diabetes and retinopathy. After a median follow-up of 8.6 years, 1763 persons died, 276 (45.0%) with retinopathy and 1487 (34.2%) without retinopathy, of whom 76 and 162 persons, respectively, also had diabetes. There were 366 deaths from CVD through 2009, 72 (11.7%) in persons with retinopathy and 294 (6.8%) in those without retinopathy. In multivariable analyses, retinopathy was significantly associated with all-cause mortality (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.10−1.43; $P < 0.01$) and CVD-related mortality (HR, 1.57; 95% CI, 1.20−2.06; $P < 0.01$). Findings were more striking in men: all-cause HR, 1.33 (95% CI, 1.11−1.60) and CVD HR, 1.81 (95% CI, 1.25−2.63). Risk of mortality was further increased among those with retinopathy concomitant with microalbuminuria (all-cause HR, 1.70; 95% CI, 1.03−2.23, and CVD HR, 2.04; 95% CI, 1.27−3.28) and those with retinopathy, microalbuminuria, and diabetes (all-cause HR, 2.01; 95% CI, 1.22−3.31, and CVD HR, 5.24; 95% CI, 1.91−14.42). History of clinical stroke increased the risk of CVD-related mortality among persons with retinopathy (HR, 3.30; 95% CI, 2.05−5.32), particularly those with retinopathy and diabetes (HR, 5.38; 95% CI, 1.80−16.06).

Conclusions: Even minimal retinopathy was a significant predictor of increased mortality in older persons, particularly men, irrespective of diabetes status. Persons with retinopathy may warrant closer clinical management of general health. *Ophthalmology 2016;■:1−11 © 2016 Published by Elsevier on behalf of the American Academy of Ophthalmology.*

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Retinopathy, a common condition, has been independently associated with several adverse health conditions, including diabetes, hypertension, coronary heart disease, and chronic kidney disease.[1−8] In the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-RS), retinopathy was present in 1 or both eyes in 27% of participants with diabetes mellitus and 10.7% of those without diabetes; among the latter group, microalbuminuria was the only statistically significant factor associated cross-sectionally with increased risk of retinopathy.[9] Another analysis from the same cohort showed that retinopathy was associated with multiple cerebral microbleeds, particularly in participants with diabetes.[10] Results from the Lipid Research Clinic's Coronary Primary Prevention Trial suggested that retinopathy predicts coronary heart disease in high-risk men, independently of other risk factors,[5] and more recently, the Chronic Renal Insufficiency Cohort Study demonstrated, after adjustment for a wide array of risk factors, a strong cross-sectional association between severity of retinopathy and chronic kidney disease.[3]

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Retinopathy also has been associated with an increased risk of mortality, specifically, cardiovascular disease (CVD)−related mortality, in older adults.[11−17] The Beijing Eye Study[11] followed 3224 Chinese participants with a mean age of 56 years (range, 40−101 years) over 5 years and found the mortality rate among the 8.8% of persons who had retinopathy at baseline was twice that of those without retinopathy. Likewise, the Blue Mountains Eye Study[12] followed 2967 participants aged 49+ years over 12 years and reported retinopathy to be a significant predictor of coronary heart disease deaths in the 28.6% of persons with retinopathy and diabetes and the 9.7% of persons with retinopathy without diabetes. In the Ibaraki Prefectural Health Study in Japan,[13] 87 890 participants aged 40 to 79 years were followed for 15 years, and retinopathy was a significant risk factor for death due to cardiovascular causes independent of other cardiovascular risk factors, including hypertension.

Among individuals with diabetes, a Finnish cohort study of persons aged 45 to 64 years suggested that retinopathy predicted all-cause, cardiovascular, and coronary disease−related mortality in men and women,[14] whereas a meta-analysis of 20 studies involving retinopathy determined that the presence of retinopathy was associated with an increased risk of all-cause mortality and cardiovascular events in diabetic patients.[15] Data from the Third National Health and Nutrition Survey reported a synergistically increased all-cause mortality risk among adults with both retinopathy and chronic kidney disease.[16]

It is unclear why retinopathy, particularly mild signs that are the most common, would be associated with mortality. We speculate that the influence of common concomitant age-related health conditions, particularly diabetes and CVD, may affect associations between retinopathy and mortality, but there are few published reports on the topic. The current study extends previous work on retinopathy in the well-phenotyped AGES-RS cohort of Icelandic elders by investigating the relationship between retinopathy and mortality in the context of concomitant health conditions.

Methods

Study Population

The AGES-RS is a population-based prospective cohort study designed to investigate the contribution of interacting genetic and environmental factors on common age-related conditions and has been described in detail by Harris et al.[18] Participants were recruited between 2002 and 2006 from randomly selected surviving men and women born between 1907 and 1935 (n = 11 549) from the Reykjavik Study, which was initiated by the Icelandic Heart Association (IHA) in 1967. Of the 5764 individuals (aged ≥67 years) examined as part of the AGES-RS, retinal images were collected from 4994 (86.6%). Ungradable or incomplete images from both eyes excluded 28 participants from retinopathy assessment, resulting in an analytic sample of 4966 persons for the current study.

In adherence with the Tenets of the Declaration of Helsinki, the AGES Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Icelandic Data Protection Authority, Iceland, and the Institutional Review Board for the National Institute of Aging, National Institutes of Health. Written informed consent was obtained from all participants.

Retinal Examination

After pharmacologic dilation of the pupils, a Canon CR6 nonmydriatic camera (US Canon Inc, Lake Success, NY) with a Canon D60 camera back was used to capture two 45-degree images of each retina, 1 centered on the optic disc (field 1) and 1 centered on the fovea (field 2), from both eyes using a standardized protocol. Procedures have been described in detail.[19] Graders, masked to health status, at the Ocular Epidemiology Reading Center at the University of Wisconsin evaluated retinal images using EyeQ Lite image processing software (Digital Healthcare Inc, Cambridge, UK) and the modified Airlie House Classification adaption of the Early Treatment Diabetic Retinopathy Study protocol,[20] the same retinopathy grading method used for the Multi-Ethnic Study of Atherosclerosis.[21]

Retinopathy lesions were classified as definite if the grader was at least 90% certain that a retinal lesion was present, and once classified as definite, a retinopathy level was assigned to the lesion on the basis of the presence of hard exudates, dot or blot hemorrhages (HEMs), microaneurysms (MAs), cotton wool spots (CWS), intraretinal microvascular abnormalities (IRMAs), venous beading (VB), and new vessels.[21] Grading levels were categorized as no retinopathy (levels 10−13, findings of no or questionable retinopathy), mild nonproliferative retinopathy (levels 14−31, findings indicative of HE, IRMA, CWS, or VB without MA or HEM; MA only; HEM only), moderate to severe nonproliferative retinopathy (levels 41−51, findings of MA and at least 1 other of these lesions: CWS, IRMA, VB, or HEM; multiple MA), or proliferative retinopathy (levels 60−80, findings indicative of fibrous proliferation; panretinal photocoagulation laser scars; vitreous hemorrhage). Unless otherwise stated, retinopathy was dichotomized as no retinopathy or any retinopathy (levels 14−80) for the participant's worse eye (i.e., the eye with the most severe retinopathy lesion). If fundus images were unavailable or ungradable for 1 eye, the retinopathy level from the other eye was used. Because retinopathy signs in the presence of diabetes and hypertension share many similarities,[22] care was taken not to attribute an underlying cause of the retinopathy but rather to consider concomitant conditions that co-occurred with it.

Mortality Outcome

Records for AGES-RS participants were linked, with the permission of the Icelandic Data Protection Authority, to the complete adjudicated registry of deaths of all Icelanders, dying in country and abroad, whose names appear in the Icelandic National Roster maintained by Statistics Iceland (http://www.statice.is/Statistics/Population/Births-and-deaths), from which IHA ascertained mortality events. All-cause mortality was assessed through September 27, 2013, but cause of death was available only for deaths recorded through December 31, 2009, when Icelandic funding for such classification ceased. The IHA determined cause of death due to CVD using guidelines from the SCORE project[23] and the International Classification of Diseases, 9th Revision, in which deaths with the International Classification of Diseases codes 401 to 414, 426 to 443, and 798.1 and 798.2, with the exception of the codes for definitely nonatherosclerotic causes of death 426.7, 429.0, 430.0, 432.1, 437.3, 437.4, and 437.5, were due to CVD.

Assessment of Participant Characteristics

A wide array of information was assessed through detailed in-person interviews and clinical examinations. Education was