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The Epidemiology of Retinal Reticular Drusen

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Abstract

Purpose—To describe the prevalence and 15-year cumulative incidence of and risk factors for reticular drusen.

Design—Population-based prospective study.

Setting: Beaver Dam, Wisconsin

Study population: 4,926 persons, 43–86 years of age in 1988–1990, of whom 3,684, 2,764, and 2,119 participated in 5-, 10-, and 15-year follow-up examinations, respectively.

Main outcome measures: Prevalence and 15-year incidence of reticular drusen determined by grading stereoscopic color fundus photographs.

Results—The prevalence at baseline and the 15-year cumulative incidence in either eye of reticular drusen was 0.7% and 3.0%, respectively. The 15-year incidence of reticular drusen varied with age from 0.4% in those 43–54 years of age to 6.6% in those 75 years or older at baseline ($P < 0.001$). In a multivariable model, while controlling for age, risk factors statistically significantly associated with increased risk of incident reticular drusen included (Odds ratio): being female (2.8), current smoking (vs never 1.9), less education (per category 1.7), B-vitamin complex use (vs none 2.5, single vitamin B (vs none 2.9), history of steroid eye drops use (5.9), glaucoma (2.8), and more severe drusen type (e.g., soft indistinct drusen) (1.4) while diabetes (0.1) at baseline was associated with decreased risk. Right eyes with reticular drusen at baseline had higher cumulative incidence of geographic atrophy (21% vs 9%) and exudative AMD (20% vs 10%) compared to eyes with soft indistinct drusen.

Conclusions—This population-based study documents the long-term cumulative incidence of reticular drusen, its risk factors, and shows its association with a high risk of incident late AMD.

Keywords

Reticular drusen; epidemiology; incidence; age-related macular degeneration

In the Wisconsin Age-Related Maculopathy (AMD) Grading System, “reticular drusen” was used to describe retinal drusen that “formed ill-defined networks of broad interlacing ribbons” (Figure 1).¹ Reticular drusen have also been described by others and have been shown to be associated with a high risk of progression to neovascular AMD.^{2–8} Most of the

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observations have been either from case reports, case series, or from clinical trials.²⁻⁸ These lesions have been found using scanning laser ophthalmoscopy to be hypoautofluorescent. Inflammation has been hypothesized to be involved in their etiology.^{3,6,8} Based on the histopathological study of one eye of a patient with this lesion, Arnold et al. reported no evidence of retinal drusen and speculated that the condition represented the loss of choroidal vessels accompanied by fibrous replacement of the choroidal stroma in a reticular pattern.³ Based on this finding, they labeled the lesion “reticular pseudodrusen”.

To our knowledge, there have been no published data from population-based epidemiologic studies describing the prevalence and incidence of reticular drusen and associated risk factors. The purposes of this report are to describe the prevalence, 15-year cumulative incidence, and associated risk factors of reticular drusen. In addition, we describe the incidence of late AMD, visual loss, and mortality associated with this lesion in the population-based Beaver Dam Eye study.

METHODS

Population

Methods used to identify the population and descriptions of the population have appeared in previous reports.⁹⁻¹³ A private census of the population of Beaver Dam, Wisconsin (99% white) was performed from fall 1987 to spring 1988.⁹ Of the 5,924 enumerated persons aged 43-84 years, 4,926 (83.2%) participated in the baseline examination in 1988 to 1990.¹⁰ Of these, 3,684 (81.1%) participated in the 5-year follow-up examination in 1993 to 1995.¹¹ Comparisons between participants and nonparticipants at baseline and the 5-year follow-up examination have appeared elsewhere.¹¹ Of the 3,334 surviving participants in the baseline and second examination, 2,764 (82.9%) participated in the 10-year follow-up examination between March 1, 1998, and June 9, 2000.¹² Comparisons between participants and nonparticipants at baseline and the 10-year examination have appeared elsewhere.¹² Of the 2,480 surviving participants who were examined at the baseline, 5-, and 10-year follow-up examinations, 2,119 (85.4%) participated in the 15-year follow-up examination between March 31, 2003 and April, 30, 2005.¹³ Comparisons between participants and nonparticipants at the 15-year follow-up have been presented elsewhere.¹³ In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed and higher systolic blood pressure than persons who participated. The mean and median times between the baseline and 15-year follow-up examination were 14.9 years (standard deviation was 0.5 years) and 14.8 years, respectively.

Procedures

A medical history questionnaire was administered and information regarding education, income, use of vitamins, medications, smoking, drinking and other factors were obtained at all examinations.

Deaths were confirmed with cause of death information obtained through matching to the Wisconsin Department of Health and Family Services or the National Death Index for all known deaths as well as persons with whom we had lost contact. We ascertained mortality between the baseline examination and December 31, 2002.

Similar examination procedures were used at baseline and follow-up and have been described in previous publications.^{1,10-19} Informed signed consent was obtained at the beginning of each examination as well as Institutional Review Board approval. Stereoscopic 30° color fundus film photographs centered on the disc (Diabetic Retinopathy Study [DRS] standard

field 1) and macula (DRS standard field 2) and a non-stereoscopic color fundus photograph temporal to but including the fovea of each eye were taken at each examination.

Details of the grading procedure have been described previously.^{1,18-20} In brief, a circular grid was placed on one photographic slide of the stereoscopic pair, which divided the macular area into nine subfields, consisting of a central circle (a single subfield), inner ring (comprised of the four inner subfields), and outer ring (comprised of four outer subfields). Reticular and other types of drusen were graded in each subfield, outside the grid in DRS field 2, and nasal to the disc in Field 1. Two gradings were performed for each eye at each examination.¹⁴⁻²⁰ First, a preliminary masked grading was done by one of two senior graders. Next, detailed gradings were performed by one of three other experienced graders. Each eye was graded independently of the fellow eye. The assessment consisted of a subfield-by-subfield, lesion-by-lesion, evaluation of each photograph set using the Wisconsin Age-Related Maculopathy Grading System.^{1,18} Next, a series of edits and reviews was performed. The presence of reticular and other types of drusen at the fourth examination, as determined by detailed grading, were compared to that of the preliminary grading. Standardized edit rules were used to adjudicate disagreements.^{14,15,19,20} Finally, the detailed graders were asked to make side-by-side comparisons between 10- and 15-year follow-up photographs for eyes which showed change for reticular and other types of soft drusen between these two examinations. These edits were masked as to whether the photographs were taken at 10- or 15-year follow-up. After the masked longitudinal review of 10- and 15-year visits was done, the senior grader (SMM) and principal investigator (RK) performed a final unmasked review of all four visits for progression and regression of reticular drusen. All eyes newly classified with reticular drusen were also confirmed at this time. Additional information on gradability at previous examinations can be found in the prevalence, 5-, and 10-year and 15-year incidence papers.^{14,15,19,20}

Definitions

Definitions of specific lesions and of the incidence, progression, regression, and disappearance of early and late AMD and their component lesions have been presented elsewhere.^{14,15}

Increasing order of severity of drusen were defined as follows: hard distinct, soft distinct, and soft indistinct. The incidence of a specific lesion, e.g., reticular drusen, geographic atrophy (GA), or exudative AMD, was defined by its presence at follow-up when it was not present at baseline. The incidence of late AMD was defined by the appearance of either exudative macular degeneration or pure GA at follow-up when neither lesion was present at baseline. The incidence of visual impairment was defined as the development of best-corrected visual acuity of 20/40 or worse in better eye with visual acuity of better than 20/40 at baseline in at least one eye.

Age was defined as the age at the time of the baseline examination. The mean systolic blood pressure was the average of the two systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the two diastolic blood pressures at baseline. Pulse pressure was defined as the mean systolic blood pressure minus the mean diastolic blood pressure. Hypertension was defined as a mean systolic blood pressure of ≥ 140 mmHg and/or a mean diastolic blood pressure of ≥ 90 mmHg and/or a history of hypertension using antihypertensive medication at the time of the baseline examination. Body mass index at baseline was defined as body weight (kg)/height (m^2). The ratio of serum total cholesterol to high density lipoprotein (HDL)-cholesterol was computed. A person was defined as having a positive history of cardiovascular disease if he/she responded affirmatively to the questions regarding history of angina, heart attack, or stroke. A person was defined as having diabetes if he/she had a previous history of diabetes mellitus and was treated with insulin, oral hypoglycemic agents, and/or diet or was newly discovered to have diabetes at baseline. The latter was defined as a casual blood sugar greater than 11.1 mmol/L and a glycosylated

hemoglobin value that was greater than two standard deviations above the mean for a given age-sex group (for those 43 to 54 years of age, men >9.5% and women >9.6%; for those 55 to 64 years of age, men >9.4% and women >10.0%; for those 65 to 74 years of age, men >9.6% and women >9.6%; and for those 75 years of age or older, men >9.5% and women >9.6%) with no reported medical history of diabetes mellitus nor use of hypoglycemic medications for diabetes mellitus. The definition of physical activity was based on the participant's response to the question, "On average, how many times a week do you engage in a regular activity like brisk walking, jogging, bicycling, etc. long enough to work up a sweat?". Persons reporting such activity less than 3 times/week were considered sedentary. Cigarette smoking status at the time of the baseline examination was determined as follows: a subject was classified as a non-smoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime; as an ex-smoker if he/she had smoked more than 100 cigarettes in his/her lifetime but had stopped smoking before the examination; and as a current smoker if he/she had not stopped smoking. Alcohol was recorded in terms of number of drinks per week. A drink was defined as any of the following: a 12 ounce beer, a 4 ounce glass of wine, or 1.5 ounces of liquor. A current heavy drinker was defined as a person consuming four or more servings of alcoholic beverages daily during the past year, a former heavy drinker had consumed four or more servings daily in the past but not in the previous year, and a non-heavy drinker had never consumed four or more servings daily on a regular basis. Vitamin use was defined in three levels of current use at baseline: no use, use of multivitamins, or use of other single or combination of vitamins (e.g., B-complex). Definitions of cataract and glaucoma appear elsewhere.²¹

Complement factor H (*CFH*) SNP was genotyped using the TaqMan assay in 1,947 family members of whom 1,846 had reticular drusen data available at baseline participating in the study (Thompson CL, et al. Invest Ophthalmol Vis Sci 2006; Submitted). Genomic DNA was subjected to PCR amplification in a volume of 25 μ L including 1x TaqMan Universal PCR Master Mix [PE Biosystems; 8% glycerol and 1x TaqMan buffer (100 mM Tris, pH 8.0, 500 mM KCl) with 7.5 mM MgCl₂, dNTPs (200 μ M dATP, 200 μ M dCTP, 200 μ M dGTP, 400 μ M dUTP), and 0.5 U of AmpliTaq Gold DNA polymerase]. Assays-on-Demand SNP Genotyping Assay Mix containing the two specific TaqMan MGB probes, forward and reverse primers, was also added. The 96-well or 384-well plate containing the reaction mixture was then run on the ABI 7900 Sequence Detection system. The overall genotyping error rate was estimated at less than 1% based on 609 replicates of all seven SNPs. No individual SNP showed error rates much higher than any other.

Statistical Methods

SAS version 9 was used for analyzing the data (SAS Institute Inc., Cary, NC). Age (defined at the time of the baseline examination) was treated categorically in the following groups: 43-54, 55-64, 65-74, and 75-86 years of age. The calculations of cumulative incidence of reticular drusen allow persons who were right censored not seen after the baseline, 5-, or 10-year examination due to death or non-participation to contribute information to the estimates. These estimates also account for the competing risk of death.²² A person only needed to have gradable photographs at the baseline and 5-year follow-up examination or die between baseline and the 5-year follow-up to contribute to the estimates. Included in the incidence analyses were 3,917 persons: 2,042 people examined with gradable photographs at all four visits, 629 examined with gradable photographs at baseline and at the 5- and 10-year follow-up only; 893 people examined with gradable photographs at baseline and at the 5-year follow-up only; and 353 people who died before the 5-year follow-up. The latter group contributes only mortality information for cumulative incidence estimates.

To investigate the relationship between age and reticular drusen, we present results in the worse eye but note that the relationships were similar in right and left eyes.

Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from discrete logistic hazard regression models for incidence and logistic regression for prevalence.²³ The test of trend between age and incidence rates were tested by treating age, categorized as previously described, as a continuous variable in the Cox proportional hazards model and computing the chi-square statistic for the parameter estimate. The same method was used to examine trend in other risk factors.²⁴ Multivariate models were developed by including all covariates significant ($p < 0.10$) in step-wise regression procedures. Only the final models are presented. Generalized estimating equations (GEE) were used when investigating eye specific risk factors (e.g., cataract) or to account for multiple siblings contributing to the *CFH* analysis.²⁵ Independent correlation structure was used to develop the working correlation matrix in the GEE models.

RESULTS

Prevalence

Reticular drusen were present in 0.7% of the cohort at baseline and the frequency was similar in the right (0.7%) and left (0.5%) eyes. Of the 32 people at baseline with reticular drusen, 20 (63%) had it in both eyes. When present, they were found outside the macula defined by the grid 81% of the time (Figure 2a). When present in the macular area, they were most commonly found in the outer superior subfield 74% of the time, outer temporal subfield 70%, and never in the central subfield (Figure 2a). Rates for each location were not mutually exclusive. There was an increase in the frequency of reticular drusen with increasing age ($p \leq 0.001$, Table 1). The prevalence was higher in those homozygous (CC, 1.2%) or heterozygous (TC, 1.4%) for *CFH* gene variant Y402H (12775T to C) than in those without this variant (TT, 0.1%, age-adjusted $p=0.01$) from the GEE model.

While controlling for age, the presence of reticular drusen was associated with being female (OR 2.67, 95% CI 1.16, 6.17, $p=0.02$), lower income (OR per lower income group 1.75, 95% CI 1.16, 2.62, $p=0.007$), more pack years smoked (OR 35 or more pack years vs none 2.61, 95% CI 1.17, 5.85, $p=0.02$), body mass index (OR per 1 kg/m^2 1.08, 95% CI 1.02, 1.15, $p=0.006$), and use of vitamin E (OR single vitamin vs no use of 3.33, 95% CI 1.11, 9.95, $p=0.03$), with no other associations of systemic, environmental, or ocular factors (data not shown). When included in the same model, all associations remained statistically significant (Table 2).

15-year Cumulative Incidence

The overall 15-year cumulative incidence of reticular drusen was 3.0% and it rose with age (Table 1). While controlling for age, women had a higher 15-year cumulative incidence of reticular drusen than men (OR 2.59, 95% CI 1.56, 4.32, $p < 0.001$). There were no differences in incidence between right (2.4%) and left eyes (2.5%). In 88 persons free of reticular drusen at baseline that developed reticular drusen, 51 (58%) developed it in both eyes. Incident drusen were found outside the grid in 77% of eyes, in the outer superior subfield of the macula 92% of the time, outer temporal subfield 42%, and never in the central subfield (Figure 2b).

While controlling for age, incident reticular drusen were associated with less education, lower income, a history of being a current smoker, a history of sedentary lifestyle, use of steroid eye drops, history of anti-depressant use, use of B-vitamins, and a history of ever using birth control pills in women at baseline and were inversely associated with history of amount of wine or liquor drank, diabetes, increased amount of sunlight at work, and use of UV protection (Table 3). While controlling for age, soft indistinct drusen (OR present vs absent 2.92, 95% CI 1.87, 4.55, $p < 0.001$), increasing drusen area (OR 4th vs 1st quartile 1.78, 95% CI 1.06, 2.98, $p=0.03$), and nuclear cataract (OR present vs absent 1.89, 95% CI 1.14, 3.13, $p=0.01$) were related to

incident reticular drusen. While controlling for age, history of pack-years smoked, current beer and heavy alcohol consumption, hair color, history of gout, arthritis, emphysema, x-ray radiation exposure to the head, cumulative UV-exposure, systolic and diastolic blood pressure, pulse pressure, hypertension status, height, weight, body mass, serum total and HDL cholesterol, hematocrit, white blood cell count, platelet count, cardiovascular disease history, use of blood pressure lowering medications, use hormone replacement therapy in women, use of oral steroids, thyroid medications, and anti-anxiety medications, glycosylated hemoglobin level, serum albumin, serum uric acid, iris color, refractive error, intraocular pressure, cataract surgery, glaucoma, retinal pigmentary abnormalities, and retinal vessel diameters at baseline were not related to the 15-year cumulative incidence of reticular drusen (data not shown). In a multivariable model, incident reticular drusen were associated with age, sex, education, smoking status, diabetes history, and use of B vitamins and there was a borderline association with amount of wine drunk (Table 4). While adjusting for these factors in another multivariable model, drusen type (OR per more severe drusen type 1.37, 95% CI 1.07, 1.75, $p=0.01$), glaucoma (OR 2.82, 95% CI 1.11, 7.19, $p=0.03$), and steroid eye drops (OR 5.85 95% CI 1.46, 23.47, $p=0.01$) at baseline were related to the 15-year incidence of reticular drusen. In a separate model, excluding drusen type in the model, drusen area was not associated with incident reticular drusen (data not shown). When the analyses were restricted to those free of cataract surgery at baseline, the relationship of history of use of steroid eye drops to incident reticular drusen remained statistically significant (OR 5.40 95% CI 1.40, 20.9, $p=0.01$). There was a borderline association with nuclear cataract (OR 1.62, 95% CI 0.98, 2.69, $p=0.06$) but not cataract surgery (OR 1.85, 95% CI 0.88, 3.93, $p=0.11$). While controlling for these systemic and ocular factors in another multivariable model in women only, there was no relation of hormone replacement use, birth control use, menopause history, age at menarche, and number of pregnancies at baseline to the 15-year cumulative incidence of reticular drusen (data not shown).

Disappearance of Reticular Drusen

There were no eyes where reticular drusen disappeared without the appearance of lesions such as retinal pigment epithelial depigmentation or signs of late AMD.

Risk of Progression to Late AMD, Visual Loss, and Survival

Reticular drusen were associated with high 15-year cumulative incidence of signs of late AMD and visual impairment (Table 5). Eyes with reticular drusen were more likely than eyes with other types of soft drusen to progress to late AMD and visual impairment (Table 4). While controlling for age and sex, persons with reticular drusen at baseline were more likely to have poorer survival (HR [hazard ratio], 95% CI: 1.54 (1.03, 2.31) $p=0.04$). Controlling further for smoking status, cardiovascular disease history, systolic blood pressure, cancer, body mass, education level, diabetes status, history of vitamin use, and history of wine drinking did not change the relation of reticular drusen at baseline to poorer survival (HR 1.58, 95% CI 1.04, 2.39 $p=0.03$). The hazard ratios for mortality were similar between men and women with no interaction (data not shown).

DISCUSSION

Using standardized detailed procedures for obtaining stereoscopic color fundus photographs of the macula and an objective system for grading those photographs for AMD, we found a prevalence of reticular drusen of 0.7% and a 15-year cumulative incidence, accounting for the competing risk of death, of 3.0% in the Beaver Dam population aged 43-86 years of age at baseline. In addition, we report a high 15-year cumulative incidence of late AMD (43% and 46% in right and left eyes, respectively), visual impairment (58% and 75% in right and left eyes, respectively), and a 54% poorer survival in those with reticular drusen at baseline.

To our knowledge, there are no other published population-based data available to compare the prevalence and incidence of reticular drusen with. In a retrospective review of 121 patients enrolled in a multicentered, randomized controlled trial of patients with neovascular AMD in one eye and 10 or more drusen in the other eye, reticular drusen were found in 3% of non-AMD fellow eyes.⁷ In a case series of patients with AMD who presented at a retinal specialty clinic, 13% were found to have reticular drusen.³ In a retrospective study of 166 eyes of 83 patients with bilateral soft drusen with or without geographic atrophy and 55 fellow eyes of patients with unilateral neovascular AMD, 30 (13%) had signs of reticular drusen.⁸ None of these studies provided estimates of incidence of reticular drusen to compare with.

While controlling for age and other factors, we found an approximately 2 ½ fold increase in the prevalence and incidence of reticular drusen in women compared to men. This was similar to Arnold et al.'s finding that 87% of those with this lesion were women.³ In our study, this finding was not explained by hormonal exposures. Saito et al. reported a case of preeclampsia of pregnancy in a 36 year old woman who had a similar appearing reticular pattern attributed to choroidal ischemia due to transient spasm or occlusion of the choroidal artery.²⁶ We do not have history of preeclampsia in Beaver Dam and, at present, the reasons for the higher frequency in women remain unknown.

Prevalent and incident reticular drusen were more likely to be found in outer superior and temporal location of the macula. This is similar to findings of others as to where prevalent and incident soft drusen are likely to appear.^{3,6,8,27,28} The reasons may reflect differences in choroidal blood flow (more interconnection of choriocapillaris nasally) and possibly how light affects different areas of the macula, although we found little evidence to suggest light or UV exposure to be associated with the incidence of reticular drusen.^{29,30}

Inflammation and ischemia of the choroidal circulation have been hypothesized as possible explanations for appearance of reticular drusen.^{3,31} The finding of an association of the *CFH* CC variant, smoking, and the history of use of steroid eye drops with incident reticular drusen are supportive of the inflammatory hypothesis while the lack of a relation with white blood cell count or diseases associated with inflammation (e.g., gout, emphysema) is not. The lack of a relationship of atherosclerotic cardiovascular disease and most of its risk factors with reticular drusen does not support the hypothesis that vascular disease is a pathogenetic mechanism for this lesion.

A retrospective clinic-based study had suggested that reticular drusen were associated with a high risk of developing only exudative AMD attributed to progressive choroidal ischemia.³ However, this has not been found in our study in which eyes with reticular drusen at baseline had a similar 15-year cumulative incidence of both pure GA and exudative AMD. Data from the Age-Related Eye Disease Study showed that eyes with reticular drusen were at similar risk for the 5-year incidence of both GA (36%) and of exudative AMD (29%) (Armstrong JR, et al. IOVS 2005; 46: ARVO E-Abstract 220). The relation of poorer survival in persons with reticular drusen, independent of systemic risk factors, suggests that this lesion, unlike other types of soft drusen which are not related to survival, may be markers of pathophysiologic processes associated with death that were not measured in the study.

While there are many strengths of our study, conclusions regarding estimates of prevalence and incidence of reticular drusen and associations described herein must be made with caution. Misclassification may have resulted from not identifying subtle signs of reticular drusen that might have been detected by measurement of hypoautofluorescence using a scanning laser ophthalmoscope. We estimate that this may have resulted in about a 12% higher incidence than reported herein.⁸ It is also possible that other pathological processes, e.g., choroidal reticulum cell sarcoma or metastatic cancer, may have been misclassified as reticular drusen, although

the rarity of both conditions would unlikely have a significant affect on the estimates.³² Chance, unadjusted confounding, and bias must be considered when interpreting our findings regarding associations of reticular drusen with risk factors reported herein. We have examined a large number of possible risk factors and conducted multiple tests of significance. Therefore, some of our findings that are statistically significant may be the result of chance alone.

While Arnold et al. labeled the lesion pseudodrusen based on their finding of choroidal stromal replacement of atrophied mid-size choroidal blood vessels, it is not as yet certain whether this characterizes this condition or if these lesions are a type of drusen (i.e., represents material deposited in inner Bruch's membrane) that belongs in the drusen family (e.g., hard distinct, soft distinct, and soft indistinct).³ While epidemiologic data show an association of increasing risk of developing reticular drusen in eyes with soft distinct and indistinct drusen, similar locations of appearance, and similar environment and genetic risk factors, there are differences between reticular and other types of soft drusen. About 20% of soft distinct and indistinct drusen regress in the absence of progression while reticular drusen do not regress. Reticular drusen are also associated with greater risk of progression to late stages of AMD and visual impairment than other types of soft drusen and, unlike soft drusen, reticular drusen are associated with decreased survival.^{20,33} Reticular drusen may represent a different phenotype of AMD than eyes with soft drusen without reticular drusen. Understanding of the pathogenesis of these lesions requires further histological and epidemiological study. Based on these observations, until more information is available, we have opted to continue to label them as a specific type of drusen rather than call them pseudodrusen.

In summary, the Beaver Dam Eye Study data provides new population-based estimates documenting the relatively high long-term cumulative incidence of reticular drusen, especially in older women. Understanding the risk factors and natural history of reticular drusen are of importance because of increased risk for incidence of late AMD and visual impairment.

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B. FINANCIAL DISCLOSURES

None (RK, SM, MK, SI, MK, BK)

C. CONTRIBUTIONS OF AUTHORS

Design and conduct of the study, data collection and management, obtained funding and provided resources, and manuscript preparation (RK, BK); analysis and interpretation of data (RK, SM, MK, SI, SK, BK); critical revision and final approval of manuscript (RK, SM, MK, SI, SK, BK); statistical expertise (MK); literature search (RK).

D. CONFORMITY WITH AUTHOR INFORMATION

Written informed consent for the use and disclosure of protected health information was obtained from all subjects before being enrolled in the study and Institutional Review Board approval was granted by the Health Sciences Institutional Review Board at the University of Wisconsin, Madison.

Biography

Dr. Ronald Klein is a Professor of Ophthalmology and Visual Sciences at the University of Wisconsin School of Medicine and Public Health interested in ocular epidemiology of age-related eye disease and hypertensive and diabetic retinopathy.

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Figure 1.
Reticular drusen in retina of left eye.

Figure 2a.
Location of prevalent (n=54 eyes) reticular drusen in retina of left eye.

Figure 2b. Incident (n=154 eyes) reticular drusen in and outside of macular area in the Beaver Dam Eye Study (1988-1990). Rates for each location are not mutually exclusive.

Table 1

15-Year Cumulative Incidence and Prevalence of Reticular Drusen by Age and Sex

Prevalence Incidence

Age (years)	Women			Men			Both			Women			Men			Both		
	N at Risk	%		N at Risk	%		N at Risk	%		N at Risk	%		N at Risk	%		N at Risk	%	
43-54	788	0.3		712	0.0		1500	0.1		652	0.6		577	0.2		1229	0.4	
55-64	683	0.6		612	0.0		1295	0.3		543	3.7		494	0.4		1037	2.2	
65-74	719	1.1		523	0.6		1242	0.9		540	8.4		407	4.7		947	6.7	
75-86	452	2.9		266	1.5		718	2.4		238	11.2		176	0.6		414	6.6	
P-trend	<0.001			<0.001			<0.001			<0.001			<0.001			<0.001		
Total	2642	1.0*		2113	0.3*		4755	0.7		1973	4.5 [†]		1654	1.3 [†]		3627	3.0	

* Age-adjusted difference between sex: p=0.02

[†] Age-adjusted difference between sex: p<0.001

Table 2

Multivariable Model of Relationships of Characteristics to Prevalent Reticular Drusen* in the Beaver Dam Eye Study 1988-1990

Risk Factor	OR	95% CI	P
Age			
75-86 vs 43-54 years	9.6	(1.9, 48.2)	0.006
65-74 vs 43-54 years	3.2	(0.6, 15.6)	0.16
55-64 vs 43-54 years	1.3	(0.2, 7.5)	0.75
Female Sex	5.2	(1.8, 14.8)	0.002
Pack Years			
>35 vs 0 pack years	5.1	(2.0, 13.0)	<0.001
15-34 vs 0 pack years	1.6	(0.4, 6.1)	0.46
1-14 vs 0 pack years	2.5	(0.8, 7.2)	0.10
Vitamin E single vs none	3.9	(1.2, 12.3)	0.02
Increasing income	0.6	(0.4, 0.96)	0.03
Body mass index / per 1 kg/m ²	1.07	(1.02, 1.13)	0.01

Abbreviations: OR=odds ratio; CI=confidence interval

* Controlling for multivitamin use

Table 3
Age-Adjusted Associations of Characteristics to 15-Year Cumulative Incidence of Reticular Drusen in The Beaver Dam Eye Study

Characteristics	No. at Risk	Age-Adjusted Incidence of Reticular Drusen			P-value
		Incident Event No.	OR	95% CI	
Gender					
Male	1458	19	1.00	- -	<0.001
Female	1826	73	2.59	(1.56, 4.32)	
Education					
<High school	744	47	1.00	- -	0.001
High school	1510	31	0.46	(0.28, 0.74)	
Some college	513	11	0.50	(0.26, 0.99)	0.047
College +	515	3	0.14	(0.04, 0.46)	0.001
Trend			0.58	(0.44, 0.76)	<0.001
Income (\$)					
<10K	361	27	1.00	- -	0.048
10K-19K	809	33	0.59	(0.34, 0.99)	
20K-29K	697	18	0.50	(0.27, 0.94)	0.030
30K-44K	733	6	0.23	(0.09, 0.58)	0.002
45K+	571	4	0.22	(0.07, 0.66)	0.007
Trend			0.67	(0.54, 0.83)	<0.001
Smoking history					
Never	1472	44	1.00	- -	0.93
Past	1172	32	1.02	(0.64, 1.62)	
Current	640	16	1.90	(1.04, 3.46)	0.04
History of current wine drank					
None	2877	87	1.00	- -	0.23
1 per week	178	3	0.49	(0.15, 1.56)	
2+ per week	227	2	0.27	(0.07, 1.12)	0.07
Trend			0.51	(0.28, 0.95)	0.03
History of current liquor drank					
None	2151	69	1.00	- -	0.76
1 per week	321	10	1.11	(0.56, 2.19)	
2-3 per week	353	8	0.76	(0.36, 1.59)	0.46
4+ per week	455	5	0.34	(0.14, 0.85)	0.02
Trend			0.77	(0.61, 0.96)	0.02
History of sunlight at work					
<25%	2153	71	1.00	- -	0.09
25%	476	8	0.53	(0.25, 1.10)	
>25%	655	13	0.59	(0.32, 1.07)	0.08
Trend			0.73	(0.54, 0.99)	0.04
History of UV protection					
None	757	28	1.00	- -	0.90
Little	931	36	1.03	(0.62, 1.71)	
Moderate	560	11	0.62	(0.30, 1.25)	0.18
High	1033	17	0.60	(0.33, 1.12)	0.11
Trend			0.82	(0.68, 1.00)	0.05
Diabetes					
No	3038	90	1.00	- -	0.04
Yes	232	1	0.13	(0.02, 0.94)	
History of average distance walk/day					
None	1431	46	1.00	- -	0.71
1-4 blocks	683	24	1.10	(0.66, 1.82)	
5-12 blocks	718	16	0.59	(0.33, 1.05)	0.08
13+ blocks	463	6	0.36	(0.15, 0.85)	0.02
Trend			0.75	(0.61, 0.92)	0.006
History of sedentary lifestyle					
No	856	16	1.00	- -	0.04
Yes	2428	76	1.79	(1.04, 3.10)	
History of anti-depressants use					
No	3155	83	1.00	- -	0.03
Yes	113	8	2.36	(1.11, 5.01)	

Abbreviations: OR=odds ratio; CI=confidence interval; UV=ultraviolet

Table 4

Multivariable Model of Relationships of Characteristics to Incident Reticular Drusen in The Beaver Dam Eye Study.*

Risk Factor	OR	95% CI	P-value
Age			
75-86 vs 43-54 years	47.3 (15.5, 144.3)		<0.001
65-74 vs 43-54 years	22.9 (8.1, 65.3)		<0.001
55-64 vs 43-54 years	5.8 (1.9, 17.3)		0.002
Female sex	2.8 (1.6, 4.9)		<0.001
Increasing education	0.6 (0.4, 0.8)		<0.001
Smoking			
Current vs never smoker	1.9 (1.03, 3.6)		0.04
Past vs never smoker	1.4 (0.9, 2.3)		0.18
Increased wine drinking	0.6 (0.3, 1.1)		0.08
Diabetes history	0.1 (0.02, 0.8)		0.03
B vitamin use			
B-complex vs none	2.5 (1.1, 5.7)		0.04
Single B vs none	2.9 (1.1, 7.5)		0.03

Abbreviations: OR=odds ratio; CI=confidence interval

* Controlling for vitamin use

Table 5

Multivariable Analyses of Relationships of Reticular Drusen at Baseline to the 15-Year Cumulative Incidence of Late Age-Related Macular Degeneration (AMD), Pure Geographic Atrophy (GA) Exudative AMD, and Visual Impairment in the Beaver Dam Eye Study

IncidentOutcome	Most Severe Drusen Type at Baseline	Right Eyes		Left Eyes		Age-Adjusted GEE		
		No at Risk	Incidence	No at Risk	Incidence	OR	95% CI*	P
Late AMD	Soft distinct drusen	263	3.9%	326	6.3%	28.29	(9.48, 84.44)	<0.001
	Soft indistinct drusen	280	18.2%	305	16.5%	6.34	(2.28, 17.63)	<0.001
	Reticular drusen	20	43.0%	13	46.2%			
Pure GA	Soft distinct drusen	274	0.9%	335	2.9%	41.78	(9.43, 185.14)	<0.001
	Soft indistinct drusen	277	9.0%	300	11.1%	6.23	(1.70, 22.73)	0.006
	Reticular drusen	18	21.1%	11	36.4%			
Exudative AMD	Soft distinct drusen	263	3.0%	327	3.5%	9.89	(2.16, 45.23)	0.003
	Soft indistinct drusen	289	10.0%	311	8.3%	2.82	(0.66, 12.01)	0.16
	Reticular drusen	22	19.5%	15	13.3%			
Visual impairment	Soft distinct drusen	251	30.3%	305	23.1%	3.72	(1.53, 9.01)	0.004
	Soft indistinct drusen	260	34.5%	270	29.7%	3.05	(1.26, 7.40)	0.01
	Reticular drusen	16	57.5%	12	75.0%			

Abbreviations: GEE=generalized estimating equation; OR=odds ratio; CI=confidence interval

* Odds ratios compare reticular drusen versus the given drusen type