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ARTICLE

Retinopathy in old persons with and without diabetes mellitus: the Age, Gene/Environment Susceptibility—Reykjavik Study (AGES-R)

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Abstract
Aims/hypothesis We aimed to describe the prevalence of retinopathy in an aged cohort of Icelanders with and without diabetes mellitus.

Methods The study population consisted of 4,994 persons aged ≥67 years, who participated in the Age, Gene/Environment Susceptibility—Reykjavik Study (AGES-R). Type 2 diabetes mellitus was defined as HbA_{1c} ≥6.5% (>48 mmol/mol). Retinopathy was assessed by grading fundus photographs using the modified Airlie House adaptation of the Early Treatment Diabetic Retinopathy Study protocol. Associations between retinopathy and risk factors were estimated using odds ratios obtained from multivariate analyses.
Results The overall prevalence of retinopathy in AGES-R was 12.4%. Diabetes mellitus was present in 516 persons (10.3%), for 512 of whom gradable fundus photos were available, including 138 persons (27.0%, 95% CI 23.2, 31.0) with any retinopathy. Five persons (1.0%, 95% CI 0.3, 2.3) had proliferative retinopathy. Clinically significant macular oedema was present in five persons (1.0%, 95% CI 0.3, 2.3). Independent risk factors for retinopathy in diabetic patients in a multivariate model included HbA_{1c}, insulin use and use of oral hypoglycaemic agents, the last two being indicators of longer disease duration. In 4478 participants without diabetes mellitus, gradable fundus photos were available for 4,453 participants, with retinopathy present in 476 (10.7%, 95% CI 9.8, 11.6) and clinically significant macular oedema in three persons. Independent risk factors included increasing age and microalbuminuria.
Conclusions/interpretation Over three-quarters (78%) of retinopathy cases were found in persons without diabetes and a strong association between microalbuminuria and non-diabetic retinopathy was found. These results may have implications for patient management of the aged.

Keywords Diabetes mellitus · Microalbuminuria · Non-diabetic · Old age · Population sample · Random · Retinopathy

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Abbreviations

AGES-R	Age Gene/Environment Susceptibility—Reykjavik Study
CSMO	Clinically significant macular oedema
DR	Diabetic retinopathy
IHA	Icelandic Heart Association
MESA	Multi-Ethnic Study of Atherosclerosis
NHANES	National Health and Nutrition Examination Survey
NPDR	Non proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy

Introduction

The global burden of diabetes is increasing and trends in fasting plasma glucose have been on the rise since 1980 [1]. The number of people with diabetes in the world is expected to double between 2000 and 2030 [2]. According to the WHO, an estimated 5% of global blindness is due to diabetic retinopathy (DR) [3]. Retinopathy in persons without diabetes, sometimes mistakenly referred to as DR, is estimated to occur in up to 15% of the general population, this prevalence being attributed to older age and systemic hypertension [4–6].

The experience in Iceland parallels that observed globally. The prevalence of type 2 diabetes mellitus in middle-aged men in Iceland doubled from 1967 to 2002, coinciding with the increasing BMI in the population [7]. In a national diabetic eye screening programme, the prevalence of DR among Icelandic type 2 diabetic patients was reported in 1994 to be 41% [8]. Of those in this screening programme and without retinopathy at baseline, only 1% of patients with type 2 diabetes developed proliferative retinopathy over a 10 year observation period [9]. In a recent study, we reported that the overall prevalence of visual impairment in Icelanders aged 50 years and older was 1% according to WHO criteria (visual acuity <6/18 in the better eye) [10]. No participant had bilateral visual acuity less than 6/12 due to diabetic eye disease, and only one became visually impaired due to DR over a 5 year period [11].

Here, data from the Age, Gene/Environment Susceptibility—Reykjavik Study (AGES-R) [12] are used to provide population-based estimates of the prevalence and severity of retinopathy and associated factors among elderly Icelanders with and without diabetes mellitus.

Methods

Study details The AGES-R study is an epidemiological, population-based study aimed at investigating genetic and environmental factors contributing to disease as well as to healthy ageing [12]. The study originates from the Reykjavik study, which was conducted by the Icelandic Heart Association (IHA) between 1967 and 1997 [12–14]. Participants of that study were men and women who were born between 1907 and 1935, and were randomly sampled and living in the Reykjavik area in 1967. At the time of recruitment into AGES-R, 11,549 persons participating in the original Reykjavik Study (38%) were still alive, and a random sample of 5,764 survivors was enrolled. The AGES-R examinations took place from February 2002 to February 2006 [12–14]. The comprehensive AGES-R examination protocol required each participant to complete three visits to the IHA Research Center over a period of 3 to 6 months. During the assessment at the IHA Research Center (see below), participants completed a detailed interview including questions about diabetes, eye health and cardiovascular history. Blood specimens were drawn and an extensive medical examination, including an eye examination, was performed as described below. Transport to the IHA Clinic was provided for those who asked for it. Participants were asked to bring all medications that they had used in the previous 2 weeks. The AGES-R study methods, examination protocol and characteristics of the cohort have been described in detail elsewhere [12–14]. Informed consent was obtained from all participants. The study was approved by the National Bioethics Committee in Iceland, which acts as the Institutional Review Board for the IHA (VSN-00-063), and by the National Institute on Aging Intramural Institutional Review Board.

Definition of diabetes mellitus and laboratory tests The criteria used for type 2 diabetes diagnosis were self-reported diabetes in the questionnaire, and/or use of diabetes medication or HbA_{1c} ≥6.5% (≥48 mmol/mol). The latter is a recently recommended approach and cut point for diagnosis of diabetes, and is intended to better avoid the problem of day-to-day variability of glucose values [15]. To be able to compare our results with results from earlier publications, we also, in a separate analysis, used fasting serum glucose of ≥7 mmol/l for undiagnosed diabetes mellitus, based on earlier WHO recommendations [16, 17]. These last results are briefly mentioned in the text. The criteria for type 1 diabetes included age ≤25 years at diagnosis and insulin dependence.

Blood samples were drawn after overnight fasting. Total cholesterol, HDL-cholesterol, triacylglycerol, high-sensitivity C-reactive protein, serum glucose and HbA_{1c} were analysed on an Hitachi 912 analyser (Mito, Japan) using reagents from Roche Diagnostics (Mannheim, Germany) and following the manufacturer's instructions. LDL-cholesterol was calculated using the Friedewald equation [18, 19]. The coefficient of variation (%) was: for serum

glucose 1.8, for total cholesterol 1.4, for HDL 2.3 and for urinary albumin 4.8.

Eye examination The visual acuity of each eye was measured using an auto-refractokeratometer (ARK-760A; Nidek, Tokyo, Japan) with a built-in Snellen chart. Pupils were then dilated with tropicamide eye drops 10 mg/ml and photographs of the retina taken. For each eye, two 45-degree digital retinal images, centred on the optic disc (field 1) and the macula (field 2), respectively, were taken using a CR6 non-mydriatic camera (Canon, Tokyo, Japan) with a Canon D60 camera back. Images were evaluated at the Ocular Epidemiology Reading Center, University of Wisconsin using the modified Airlie House Classification system [20]. EyeQ Lite image processing software was used [21]. All graders were masked to the health status of participants.

Definition of retinopathy and macular oedema If the grader was at least 90% certain that a retinopathy lesion was present, the lesion was marked as definite. The grader then assigned a retinopathy level according to the Modified Airlie House adaptation from the Early Treatment Diabetic Retinopathy Study protocol [20]. The following grading criteria were used: no DR (levels 10–13), mild non-proliferative DR (NPDR) (levels 14–20), moderate to severe NPDR (levels 41–51) or proliferative DR (PDR) (levels 60–80). Macular oedema was defined by hard exudates in the presence of microaneurysm and blot haemorrhage within 1 disc diameter from the foveal centre, or if focal or macular grid photocoagulation scars were present in the macula. Clinically significant macular oedema (CSMO) was considered present when oedema involved the fovea or was within 500 μm of the fovea, or if photocoagulation scars were present in the macula.

Assessment of factors associated with retinopathy The duration of diabetes was calculated as the difference between reported age of diabetes diagnosis from the interview and the year of the AGES-R examination. Use of medications was noted from medications brought to the clinic and from self-report questionnaire. Blood pressure was assigned using the mean value of two blood pressure measurements with a large-cuff mercury sphygmomanometer. Hypertension was defined by self-reported doctor's diagnosis of hypertension, use of hypertensive medication, or measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. BMI was calculated from measured height and weight (kg/m^2). Microalbuminuria was noted as present if the albumin/creatinine ratio in a random urine sample was >300 mg/g. GFR (ml min^{-1} 1.73 m^{-2}) was estimated using the Modification of Diet in Renal Disease (MDRD) formula [22].

HbA_{1c} was imputed for 7% of the participants with missing data by applying the expectation-maximisation (EM) algorithm in the statistical program PROC MI (SAS/STAT Institute, Cary, NC, USA). The imputation was performed separately for participants without and those with diabetes, depending on medication use, and using age, fasting serum glucose and duration of diabetes as the predictors for HbA_{1c}. Neither diabetes status nor retinopathy status was associated with missing HbA_{1c}. HbA_{1c} was imputed for five persons with undiagnosed diabetes mellitus. However, their fasting serum glucose was 8.9 mmol/l or higher.

Data handling and statistical analysis For statistical analysis we used SAS Enterprise Guide software, version 9.1 (SAS Institute, Cary, NC, USA). Analysis of eyes was based on the participant's eye with the most severe retinopathy lesion (worse eye). If images from an eye were ungradable or if fundus photographs were unavailable, scores from the contralateral gradable eye were used. The overall prevalence of retinopathy was calculated using the entire sample with information on retinopathy in at least one eye.

Differences between groups were tested using χ^2 test for categorical variables and t test for continuous variables. Confidence intervals for ratios were calculated using binominal distribution. Logistic regression models adjusting for age and sex were run for each risk factor. In the multivariate models, we included age, sex, systolic blood pressure, hypertension as a categorical variable, HbA_{1c} and microalbuminuria; and, for participants with diabetes, duration of diabetes and use of glucose-lowering medication.

Results

Study cohort Of the 5,764 AGES-R participants, 4,994 completed an eye examination. Of these, 4,965 had gradable photographs for at least one eye, as well as clinical examination findings, along with blood and urine test results. A comparison of participants and non-participants is reported elsewhere [12]. Of the 4,994 participants, 516 (10.3%) fulfilled the criteria for diagnosis of diabetes mellitus. Two persons (both women) were younger than 25 years at diabetes diagnosis and insulin-dependent. These two were therefore classified as having type 1 diabetes mellitus, but were included in the analysis. If we had classified by onset of diabetes mellitus <35 years and insulin dependence, three more persons would also have been classified as having type 1 diabetes mellitus.

Characteristics of participants by diabetes status are presented in Table 1. Men were significantly more likely

Table 1 Comparison of characteristics of participants in AGES-R

Characteristic	Total group (n=4,994)			Diabetes mellitus by diagnosis time (n=516)			Diabetes mellitus by treatment (n=516)			
	No diabetes	Diabetes	p value	Undiagnosed	Previously known	p value	Insulin ± oral[a]	Only oral[a]	Diet or no treatment	p value[b]
n (%)	4,478 (89.7)	516 (10.3)	–	83 (16.1)	433 (83.9)	–	37 (6.2)	273 (52.9)	206 (40.0)	–
Male sex, n (%)	1,880 (42.0)	272 (52.7)	<0.001	36 (43.4)	236 (54.5)	0.06	21 (56.8)	164 (60.1)	87 (42.2)	0.61
Age (years)	76.4±5.5	76.4±5.3	0.97	76.6±5.3	76.5±5.4	0.89	75.7±4.6	76.3±5.2	76.9±5.6	0.35
Age at T2DM diagnosis (years)	–	64.9±12.6	–	76.3±5.4	63.7±12.6	<0.001	53.1±13.5	64.7±10.2	67.7±13.7	<0.001
DM duration (years)	–	10.3 (11.2)	–	0	12.4 (11.2)	<0.001	24.9 (13.7)	11.1 (9.7)	6.8 (10.4)	<0.001
Hypertension, n (%)	3,579 (79.9)	466 (90.3)	<0.001	72 (86.8)	394 (91.0)	0.23	33 (89.2)	250 (91.6)	184 (89.3)	0.81
Systolic BP (mmHg)	141.9±20.2	146.0±20.4	<0.001	141.6±21.9	146.0±20.4	0.10	145.6±19.8	145.2±20.6	145.4±21.0	0.93
BMI (kg/m^2)	26.8±4.3	28.9±4.7	<0.001	27.8±4.4	28.6±4.6	0.14	28.5±5.8	28.6±4.4	28.2±4.5	0.94
Measured HbA_{1c} (%)	5.6±0.3	6.5±0.9	<0.001	7.0±0.9	6.5±0.9	<0.001	7.4±0.9	6.6±0.9	6.5±1.0	<0.001
Imputed HbA_{1c} (%)	5.9±0.3	6.5±0.9	<0.001	7.0±0.8	6.5±0.9	0.007	7.3±0.9	6.6±0.9	6.5±1.0	<0.001
Measured HbA_{1c} (mmol/mol)	37.6±3.5	48.8±10.4	<0.001	53.1±9.5	48.0±10.3	<0.001	56.9±9.5	48.6±9.7	47.6±10.8	<0.001
Imputed HbA_{1c} (mmol/mol)	37.6±3.4	48.7±10.1	<0.001	53.0±9.3	47.8±10.1	0.007	56.5±9.4	48.6±9.4	47.3±10.6	<0.001
Fasting glucose (mmol/l)	5.5±0.6	7.8±2.1	<0.001	7.6±2.6	7.8±2.4	0.50	9.2±3.8	8.1±2.1	7.1±2.3	<0.001
Total cholesterol (mmol/l)	5.7±1.1	5.2±1.1	<0.001	5.4±1.2	5.1±1.1	0.007	4.6±1.1	5.0±1.1	5.4±1.1	0.008
GFR <60 ml min^{-1} 1.73^{-2}, n (%)	1,336 (29.8)	206 (39.9)	<0.001	34 (41.0)	172 (39.7)	0.83	17 (45.9)	105 (38.5)	84 (40.8)	0.33
Current smoker, n (%)	546 (12.2)	60 (11.6)	0.71	10 (12.0)	50 (11.6)	0.90	5 (13.5)	34 (12.5)	21 (10.2)	0.71
Ever smoker, n (%)	2,550 (56.9)	305 (59.1)	0.34	47 (56.6)	258 (59.7)	0.25	25 (67.6)	161 (59.0)	119 (57.8)	0.28
Previous CVD, n (%)	921 (20.6)	160 (31.0)	<0.001	21 (25.3)	139 (22.3)	0.20	14 (37.8)	95 (34.8)	51 (24.8)	0.30
Microalbuminuria, n (%)	434 (7.4)	101 (19.6)	<0.001	10 (12.0)	91 (21.3)	0.06	11 (29.7)	66 (24.2)	24 (11.7)	0.12

Values are mean±SD unless otherwise indicated

CVD, cardiovascular disease according to hospital records; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus

[a] Oral hypoglycaemic agents

[b] For insulin users compared with the two other treatment groups combined

than women to have diabetes mellitus. Persons with diabetes were more likely than those without to have hypertension, larger BMI, higher fasting serum glucose, lower total cholesterol, GFR <60 ml min^{-1} 1.73 m^{-2}, a positive history of cardiovascular disease, higher levels of HbA_{1c} and microalbuminuria. The 83 participants with undiagnosed diabetes mellitus had a mean age of 76.3 years.

Prevalence and factors associated with retinopathy in participants with diabetes mellitus Gradable fundus photographs from at least one eye were available from 512 of the 516 persons with diabetes mellitus. Any DR was present in one or both eyes in 138 persons (27.0%). Table 2 shows the prevalence of DR and macular oedema by age, sex, categories of diabetes duration and diabetes treatment. Among those with diabetes mellitus, there were no

Table 2 Prevalence and severity of retinopathy and macular oedema in persons with diabetes mellitus

Group		Any retinopathy	Retinopathy			Macular oedema	
			NPDR			Any	CSMO
			Mild	Moderate	PDR		
Persons with DM (*n*=512)	*n*	138	120	13	5	9	5
	%	27.0	23.4	2.5	1.0	18	1.0
	95% CI	23.2, 31.0	19.8, 27.4	1.4, 4.3	0.3, 2.3	0.8, 3.3	0.3, 2.3
Age group (years)							
67–74 (*n*=190)	*n*	52	45	4	3	3	2
	%	27.7	23.7	2.1	1.6	1.6	1.1
	95% CI	21.2, 34.3	17.8, 30.4	0.6, 5.3	0.3, 4.5	0.3, 4.5	0.1, 3.7
≥75 (*n*=322)	*n*	86	75	9	2	6	3
	%	26.7	23.3	2.8	0.6	1.9	0.9
	95% CI	22.0, 31.9	18.8, 28.3	1.3, 5.2	0.1, 2.2	0.7, 4.0	0.2, 2.7
Sex							
Male (*n*=272)	*n*	78	74	8	1	4	1
	%	28.7	26.4	2.9	0.4	1.5	0.4
	95% CI	23.4, 34.4	20.3, 31.0	1.3, 5.7	0.0, 2.0	0.4, 3.7	0.0, 2.0
Female (*n*=240)	*n*	60	51	5	4	5	4
	%	25.0	21.3	2.1	1.7	2.1	1.7
	95% CI	19.8, 31.0	16.3, 27.0	0.7, 4.8	0.5, 4.2	0.7, 4.8	0.5, 4.2
DM							
Undiagnosed (*n*=82)	*n*	9	8	1	0	0	0
	%	11.0	9.8	1.2	0	0	0
	95% CI	5.1, 19.8	4.3, 18.3	0.0, 6.6	0.0, 4.4	0.0, 4.4	0.0, 4.4
Previously known (*n*=430)	*n*	129	112	12	5	9	5
	%	30.0	26.1	2.8	1.2	2.1	1.2
	95% CI	25.7, 34.6	22.0, 30.5	1.5, 4.8	0.4, 2.7	1.0, 3.9	0.4, 2.7
Treatment							
Insulin ± oral[a] (*n*=37)	*n*	24	14	7	3	4	2
	%	64.9	37.8	18.9	8.1	10.8	5.4
	95% CI	47.5, 79.8	22.5, 55.2	8.5, 35.2	1.7, 21.9	3.0, 25.4	0.7, 18.2
Only oral[a] (*n*=270)	*n*	82	76	4	2	4	3
	%	30.4	28.1	1.5	0.7	1.5	1.1
	95% CI	24.9, 36.2	22.9, 33.9	0.4, 3.8	0.1, 2.7	0.4, 3.7	0.2, 3.2
Diet or no treatment (*n*=205)	*n*	32	30	2	0	1	0
	%	15.6	14.6	1.0	0	0.5	0
	95% CI	10.9, 21.3	10.1, 20.2	0.1, 3.5	0.0, 1.8	0.0, 2.7	0.0, 1.8

DM, diabetes mellitus

[a] Oral hypoglycaemic agents

statistically significant age- or sex-specific differences in the prevalence of any DR measure. Of the 83 persons with undiagnosed type 2 diabetes mellitus, one did not have readable fundus photographs and nine (11.0%) had any retinopathy (eight mild, one moderate NPDR). The prevalence of any DR and CSMO was higher in those who were being treated with insulin than in persons receiving other forms of treatment. Their mean duration of diabetes was 24.9 (SD 13.7) years, compared with 11.1 (SD 9.7) years for participants receiving oral treatment only and 6.8 (SD 10.4) years for participants without medical treatment.

Persons with any DR were younger at the time of diabetes mellitus diagnosis (mean age 61.1 [SD 14.4] vs 66.3 [SD 11.6] years) and had longer duration of diabetes mellitus, i.e. mean 13.7 (SD 12.6) vs mean 9.1 (SD 10.5)years.

In the multivariate analysis of participants with diabetes mellitus (Table 3), we found HbA_{1c}, insulin use and use of oral hypoglycaemic agents to be associated with increased risk of any retinopathy. Systolic blood pressure was associated with increased risk of retinopathy in the multivariate model. However, the categorical variable for hypertension was not associated with increased risk of retinopathy. As shown above, duration of diabetes mellitus was highly confounded with type of treatment; in other words, the use of insulin or oral hypoglycaemic agents was an indicator of longer duration of diabetes mellitus. The duration variable was therefore included in the multivariate model, even though the p value (p=0.0645) did not reach statistical significance. When the multivariate analysis was limited to persons with diabetes of duration more than 10 years, however, the association with the use of insulin or oral hypoglycaemic agents was of similar magnitude and statistically significant. We found HbA_{1c} to be significantly associated with retinopathy if fasting glucose was left out of the model. Additionally, the fasting glucose level was found to be significantly associated with retinopathy when selected before HbA_{1c}, but after adjustment for diabetes duration and medication use. Both variables could not be retained in the model due to co-linearity; the correlation between fasting glucose and HbA_{1c} in participants with diabetes was 0.73. The final variables in the multivariate model were: age, sex, duration of diabetes mellitus, insulin use, oral hypoglycaemic agent use, systolic blood pressure and HbA_{1c}.

Prevalence and factors associated with retinopathy in non-diabetic participants Of the 4,478 non-diabetic persons in the sample, 4,453 had gradable fundus photographs. Of

Table 3 Univariate and multivariate logistic regression results on risk factors for any retinopathy in persons with and without diabetes mellitus

Logistic regression	n	With diabetes mellitus[a]		Without diabetes mellitus[b]		
		OR (95% CI)	p value		OR (95% CI)	p value
Multivariate						
Age, per 10 years		0.86 (0.57, 1.31)	0.4687		1.30 (1.09, 1.55)	0.0036
Sex, male vs female		0.96 (0.62, 1.51)	0.871		0.97 (0.79, 1.18)	0.7245
Systolic BP, per 10 mmHg		1.16 (1.04, 1.29)	0.0095		1.05 (1.00, 1.10)	0.0699
Duration per 10 years		1.21 (0.99, 1.48)	0.0645			
Insulin use, yes vs no		3.51 (1.59, 7.77)	0.002			
Oral hypoglycaemic, yes vs no		1.93 (1.21, 3.07)	0.0056			
HbA_{1c} per percentage point		1.35 (1.08, 1.68)	0.0078		0.93 (0.68, 1.27)	0.6431
Hypertension		1.23 (0.53, 2.86)	0.6235		1.01 (0.76, 1.33)	0.9665
Microalbuminuria, yes vs no		1.48 (0.88, 2.48)	0.1356		1.77 (1.30, 2.40)	0.0003
Univariate, adjusted for age and sex						
Age, per 10 years	512	0.89 (0.61, 1.28)	0.5175	4,453	1.38 (1.16, 1.63)	0.0002
Sex, male vs female	512	1.21 (0.81, 1.79)	0.3498	4,453	1.01 (0.83, 1.22)	0.9216
Systolic BP, per 10 mmHg	512	1.18 (1.07, 1.29)	0.001	4,452	1.06 (1.01, 1.11)	0.0128
Duration per 10 years	498	1.41 (1.20, 1.66)	<0.0001			
Insulin use, yes vs no	512	5.79 (2.85, 11.76)	<0.0001			
Oral hypoglycaemic, yes vs no	512	2.15 (1.40, 3.29)	0.0004			
HbA_{1c} per percentage point	512	1.42 (1.19, 1.68)	0.0005	4,453	0.94 (0.69, 1.27)	0.6699
Hypertension	512	1.52 (0.74, 3.14)	0.2592	4,453	1.12 (0.87, 1.43)	0.3923
Microalbuminuria, yes vs no	506	1.97 (1.22, 3.17)	0.0056	4,403	1.82 (1.34, 2.47)	0.0001

[a] n=496 for multivariant analysis, n=512 for univariant analysis

[b] n=4,402 for multivariant analysis, n=4,453 for univariant analysis

these, retinopathy was found in 476 persons (10.7%), as shown in Table 4. Macular oedema was present in five persons (0.1%), all of whom had branch retinal vein occlusion. There was no sex-specific difference in the prevalence of retinopathy among non-diabetic persons. Factors associated with any retinopathy in a multivariate model were older age and microalbuminuria (p=0.0003) (Table 3). Higher systolic blood pressure was significantly associated with retinopathy in the age- and sex-adjusted model, but its significance was only marginal in the multivariate model.

Discussion

This large population-based study of old persons reports an overall prevalence of retinopathy of 12.4%. The prevalence of DR was 27.0% and the prevalence of retinopathy in non-diabetic participants was 10.7%. We used the recently recommended and presumably more accurate HbA_{1c} ≥6.5% (≥48 mmol/mol) for diagnosis of diabetes. This classification is expected to be better at capturing chronic hyperglycaemia than the older classification using fasting glucose ≥7 mmol/l [15]. Persons with diabetes mellitus are 2.5 times more likely to have retinopathy than non-diabetic participants of comparable age, but over 75% of retinopathy cases in our study occurred in persons without diabetes. HbA_{1c}, duration of diabetes mellitus, use of insulin and use of oral hypoglycaemic agents were associated with increased risk of retinopathy in persons with diabetes in a multivariate model. Use of insulin and hypoglycaemic agents was also associated with longer duration of diabetes in a multivariate model. In persons without diabetes, increased risk of retinopathy was associated with advancing age and microalbuminuria. Microalbuminuria data show a sort of dose–response, with a prevalence of 7.4% in those with no diabetes mellitus, 12.0% in those undiagnosed and 21.3% in those with previously diagnosed diabetes mellitus and mean disease duration of 12.4 years. These results support the hypothesis that microalbuminuria may be a marker of microvascular dysfunction. Studies of DR have until recently used fasting blood glucose (7 mmol/l) to diagnose diabetes mellitus. To facilitate comparison with previous work, we additionally did uni- and multivariate analysis using this definition, which is based on a one-time event, in contrast to our present classification of type 2 diabetes mellitus (HbA_{1c}), which is expected to capture cases with chronic hyperglycaemia. Using the new classification, the group of participants with undiagnosed type 2 diabetes mellitus included only 50% of the number of persons classified, based on fasting serum glucose. In general, results were similar using the two classifications.

Table 4 Prevalence and severity of retinopathy and macular oedema in persons without diabetes mellitus

Group		Any retinopathy	Retinopathy			Macular oedema	
			NPDR			Any	CSMO
			Mild	Moderate	PDR		
Persons without DM (n=4,453)	n	476	472	4	0	5	3
	%	10.7	10.6	0.1	0	0.1	0.1
	95% CI	9.8, 11.6	9.7, 11.5	0.0, 0.2	0.0, 0.1	0.0, 0.3	0.0, 0.2
Age group (years)							
67–74 (n=1,828)	n	169	167	2	0	3	2
	%	9.2	9.1	0.1	0	0.2	0.1
	95% CI	8.0, 10.7	7.9, 10.6	0.0, 0.4	0.0, 0.2	0.1, 0.5	0.0, 0.4
≥75 (n=2,625)	n	307	305	2	0	2	1
	%	11.7	11.6	0.1	0	0.1	0.0
	95% CI	10.5, 13.0	10.4, 12.9	0.0, 0.3	0.0, 0.1	0.0, 0.3	0.0, 0.2
Sex							
Male (n=272)	n	201	199	2	0	2	0
	%	10.7	10.6	0.1	0	0.1	0
	95% CI	9.4, 12.2	9.3, 12.1	0.0, 0.4	0.0, 0.2	0.0, 0.4	0.0, 0.2
Female (n=240)	n	275	273	2	0	3	3
	%	10.7	10.6	0.1	0	0.1	0.1
	95% CI	9.5, 11.9	9.4, 11.8	0.0, 0.3	0.0, 0.1	0.0, 0.3	0.0, 0.3

DM, diabetes mellitus

Retinopathy in patients with diabetes mellitus The overall prevalence of retinopathy using HbA_{1c} ≥6.5% for diagnosis was 27.0% (95% CI 23.0, 31.0). The prevalence of DR in the present study is lower than the 41% for any retinopathy and 7% for PDR reported in 1994 in a previous study on DR in Iceland [8]. This would also hold true if we used the older classification of type 2 diabetes mellitus, which includes fasting glucose ≥7 mml/l and would give an overall prevalence of 25.3% in the present study, whereby sex distribution in both studies is similar. However, the previous study was based on clinical referrals and is therefore likely to reflect selection bias. We attribute the lower cholesterol to the use of lipid-lowering agents among the group with type 2 diabetes.

The 25.3% overall prevalence of DR in AGES-R using the older diagnostic criteria is similar to recent reports of: (1) 24.8% in the Multi-Ethnic Study of Atherosclerosis (MESA) in a white population with mean age of 64 years [23]; and (2) the age- and sex-adjusted rate of 26.4% in whites aged 40 years and older in the National Health and Nutrition Examination Survey (NHANES) 2005–2008 [24], the latter diagnosed using the HbA_{1c} criteria.

The overall DR prevalence in the Beaver Dam Study in the USA and the Blue Mountains Study in Australia was 36.8% and 32.4%, respectively [25, 26]. These older studies, however, used different definitions of type 2 diabetes mellitus, including higher fasting serum glucose values than our additional analysis, and therefore may have included cases with more advanced disease than in the present study. Differences in photographic techniques may also complicate a direct comparison of the studies because the AGES-R and MESA studies used digital non-stereoscopic 45° photographs of two fields, while the Beaver Dam and the Blue Mountains Eye studies used 30° stereoscopic photographs of up to seven fields and might therefore have detected more peripheral retinopathy lesions.

We confirmed findings from previous studies [23–30], including a significant correlation between any DR in persons with diabetes mellitus and insulin use, oral hypoglycaemic medications, HbA_{1c} ≥6.5% (≥48 mmol/mol) and longer duration of diabetes mellitus. In agreement with NHANES 2005–2008 [24], we found that higher systolic blood pressure was associated with any DR in a multivariate model. In a multivariate model, we found no correlation between DR and BMI, hypertension or diastolic blood pressure; this is in agreement with results from other studies [23, 24, 26, 28]. Due to the extremely low prevalence of PDR (1.0%; n=5) and CSMO (1.0%; n=5), statistical analysis of associated factors was not attempted.

Retinopathy in non-diabetic persons We found a 10.7% (n=476) prevalence of retinopathy in non-diabetic persons, which is comparable to the 11.9% prevalence of retinopathy reported in white non-diabetic persons in the MESA Study [5]. In fact, although the prevalence of retinopathy in diabetic patients is higher than in those without diabetes, the actual number of individuals with retinopathy was threefold higher in the non-diabetic group in our sample. Retinopathy lesions among non-diabetic participants have been associated in other studies with older age and hypertension [4, 6]. Non-diabetic participants with signs of retinopathy in our study were not more likely to be hypertensive, nor did they have higher values of fasting serum glucose or HbA_{1c} than those without retinopathy. We did, however, find a strong association between microalbuminuria and non-diabetic retinopathy. While microalbuminuria has been confirmed to be a reliable marker of retinopathy in diabetic patients [31], we are not aware of previous data to confirm this relationship in non-diabetic persons. Several studies [32, 33] have suggested that since microvascular damage manifests outside the eye in other organ systems, retinopathy and nephropathy may share a common pathogenesis and be signs of systemic microvascular dysfunction.

Patients who have been diagnosed with retinopathy in eye clinics or screening programmes may want to know how this affects management of their condition. Should these elderly persons be referred for a diabetic work-up, which commonly happens, or for a cardiovascular work-up, or for both or neither? Interestingly, the Blue Mountains Eye Study [5] describes most retinopathy lesions as being transient, with only 3.5% of persons developing diabetes over 5 years. We will need longitudinal data to further understand the pathophysiology underlying retinopathy in non-diabetic patients and to provide an evidence basis for clinical management.

Study strengths and weaknesses A strength of the AGES-R study is that the sample was drawn from a large, randomly selected, population-based cohort. We also used a recently recommended diagnosis criterion for diabetes mellitus, namely HbA_{1c} ≥6.5% (≥48 mmol/mol), thus avoiding day-to-day variability of glucose values. HbA_{1c} may be better at predicting the development of retinopathy [34], although this classification also has limitations [35]. This is a multidisciplinary study, providing detailed information on various physiological systems, including metabolic regulation and ophthalmic health. The diabetes cases in our sample included 83 individuals, i.e. 16.1% of the diabetes mellitus sample, who were first diagnosed at the baseline examination. All participants are survivors from the Reykjavik study, which took place in several stages over a 30 year period from 1967 to 1997, with testing for diabetes occurring at each examination, using the same fasting serum glucose cut-off (≥7 mmol/l) as was used in our additional analysis. Another strength of our study includes the use of digital photographic documentation of each

fundus through dilated pupils, as well as the masked grading of retinopathy using standardised methods. Limitations of this study include the relatively few cases of diabetes mellitus and DR, resulting in reduced power to detect factors associated with increased risk of retinopathy.

Summary This Icelandic population-based study reports that more than one in seven elderly persons has retinopathy. Although the prevalence of retinopathy among diabetic patients is 2.5 times higher than among non-diabetic persons, the actual number of individuals with retinopathy is more than threefold higher in the non-diabetic group. Retinopathy occurs in persons with HbA_{1c} <6.5% (≥48 mmol/mol) and also in persons with normal levels of fasting serum glucose, and in these were significantly associated with microalbuminuria in the present study. Further study of the association between retinopathy and microalbuminuria is needed to provide insight into underlying systemic disease processes, which could help in the management of elderly patients to preserve vision and health, and to maintain quality of life in old age.

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