

## CLINICAL SCIENCE

# The relation of atherosclerotic cardiovascular disease to retinopathy in people with diabetes in the Cardiovascular Health Study

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**Aims:** To describe the association of retinopathy with atherosclerosis and atherosclerotic risk factors in people with diabetes.

**Methods:** 296 of the 558 people classified as having diabetes by the American Diabetes Association criteria, from a population based cohort of adults (ranging in age from 69 to 102 years) living in four United States communities (Allegheny County, Pennsylvania; Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland) were studied from 1997 to 1998. Lesions typical of diabetic retinopathy were determined by grading a 45° colour fundus photograph of one eye of each participant, using a modification of the Airlie House classification system.

**Results:** Retinopathy was present in 20% of the diabetic cohort, with the lowest prevalence (16%), in those 80 years of age or older. Retinopathy was detected in 20.3% of the 296 people with diabetes; 2.7% of the 296 had signs of proliferative retinopathy and 2.1% had signs of macular oedema. The prevalence of diabetic retinopathy was higher in black people (35.4%) than white (16.0%). Controlling for age, sex, and blood glucose, retinopathy was more frequent in black people than white (odds ratio (OR) 2.26, 95% confidence interval (CI) 1.01, 5.05), in those with longer duration of diabetes (OR (per 5 years of diabetes) 1.42, 95% CI 1.18, 1.70), in those with subclinical cardiovascular disease (OR 1.49, 95% CI 0.51, 4.31), or coronary heart disease or stroke (OR 3.23, 95% CI 1.09, 9.56) than those without those diseases, in those with higher plasma low density lipoprotein (LDL) cholesterol (OR (per 10 mg/dl of LDL cholesterol) 1.12, 95% CI 1.02, 1.23), and in those with gross proteinuria (OR 4.76, 95% CI 1.53, 14.86).

**Conclusion:** Data from this population based study suggest a higher prevalence of retinopathy in black people than white people with diabetes and the association of cardiovascular disease, elevated plasma LDL cholesterol, and gross proteinuria with diabetic retinopathy. However, any conclusions or explanations regarding associations described here must be made with caution because only about one half of those with diabetes mellitus were evaluated.

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Diabetic retinopathy is an important cause of loss of vision in the United States.<sup>1,2</sup> Recent data from epidemiological studies and clinical trials have shown that hyperglycaemia is associated with increased incidence and progression of diabetic retinopathy in people with type 1 and 2 diabetes.<sup>3–6</sup> In a randomised controlled clinical trial in people with type 2 diabetes, the United Kingdom Diabetes Prospective Study, control of hypertension, independent of glycaemia, was shown to significantly reduce the progression of diabetic retinopathy and visual loss.<sup>7</sup> Dyslipidaemia, independent of glycaemia, has also been shown to be associated with an increased risk of developing retinopathy in some epidemiological studies, although the results have not been consistent.<sup>8–10</sup>

There are few data on whether diabetic people with signs of subclinical cardiovascular disease (for example, internal and common carotid intima media wall thickening (IMT) and plaque, echocardiogram abnormalities, decreased ankle-brachial blood pressure) or with coronary heart disease and stroke have a higher frequency of retinopathy than those without these signs.<sup>11</sup> The purpose of our study was to examine the associations of diabetic retinopathy with atherosclerotic cardiovascular disease in an older cohort of people with type 2 diabetes participating in the Cardiovascular Health Study (CHS).

## POPULATION

The CHS is a prospective, population based longitudinal study of coronary heart disease and stroke in adults aged 65 years and older.<sup>12</sup> Participants in the CHS were recruited from four counties, Allegheny County, Pennsylvania; Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland. Recruitment was from a random sample of Health Care Financing Administration Medicare Eligibility lists from these four counties. Potential participants were excluded if they were institutionalised, receiving hospice treatment, radiation therapy or chemotherapy for cancer, were wheelchair dependent, or expected to move from the area in the 3 years after recruitment. The study was approved by institutional review committees and subjects gave informed consent. Study design and methods have been published elsewhere.<sup>13</sup>

Recruitment of the original cohort of 5201 eligible people took place in 1989–90 in four field centres. A new cohort was recruited in 1992–3 and increased the study population to include an additional 687 eligible black people, 65 years and older. The new cohort participants were recruited from Forsyth County, Sacramento County, and Allegheny County. Differences between those recruited and those not recruited have been presented elsewhere.<sup>12</sup> At the study entry, there were 953 participants classified as having diabetes by the American Diabetes Association (ADA) criteria.

Each year extensive physical and laboratory evaluations were performed on each participant. Data relevant to diabetic

**Table 1** Characteristics of those with and without gradable retinal photographs for retinopathy in people with diabetes in the Cardiovascular Health Study

Characteristics	Gradable photographs (296)		No gradable photograph (262)		p Value		
	No	%	No	%			
<b>Race</b>							
Non-black	231	78.0	184	70.2	0.04		
Black	65	22.0	78	29.8			
<b>Hypoglycaemic medications</b>					0.09		
None	74	25.0	57	22.5			
Oral only	171	57.8	133	52.6			
Insulin	51	17.2	63	24.9			
<b>Gross proteinuria (&gt;30 mg/dl)</b>					0.02		
Absent	257	91.1	158	84.0			
Present	25	8.9	30	16.0			
<b>Progestin use (females only)</b>					0.05		
Current	6	3.7	0	0			
Former	4	2.4	5	3.3			
Never	154	93.9	147	96.7			
<b>Emphysema</b>					0.01		
Never been told	293	99.3	233	96.3			
Told by doctor	2	0.7	9	3.7			
<b>Stroke</b>					<0.01		
Absent/questionable	274	92.6	223	85.1			
Present	22	7.4	39	14.9			
<b>Coronary heart disease</b>					0.02		
Absent/questionable	204	68.9	155	59.2			
Present	92	31.1	107	40.8			
<b>Cardiovascular disease</b>					0.02		
None	61	20.6	51	19.5			
Subclinical only	132	44.6	90	34.5			
CHD or stroke	103	34.8	120	46.0			
Characteristics	No	Mean	SD	No	Mean	SD	p Value
Age (years)	296	77.8	4.1	262	79.3	5.1	<0.01
Fasting plasma glucose (mg/dl)	284	155.5	46.0	185	169.0	55.5	<0.01
Haematocrit (%)	283	41.6	3.9	221	40.9	3.4	0.03
Serum fibrinogen (mg/dl)	287	326.2	57.7	221	340.2	74.5	0.02
Alcohol (drinks per week)	296	0.9	2.9	240	1.7	6.2	0.06
Time to walk 15 feet (seconds)	293	5.8	1.8	162	7.4	4.9	<0.01

SD = standard deviation; for progestin use based on 164 women with gradable fundus photographs and 152 for those with ungradable fundus photographs.

retinopathy status were first collected at the 1997–8 visit. Of the 4447 surviving participants, 4249 (95.5%) returned during the 1997–8 visit. Of these, 902 people did not have medication and glucose data, leaving 3347 people who were evaluated for diabetes. Of these, 558 people were classified as having diabetes mellitus according to the ADA criteria: treatment with either oral hypoglycaemic agents and/or insulin in the year before the examination ( $n = 418$ ); or having a fasting blood sugar of  $\geq 126$  mg/dl for those not using any hypoglycaemic agents in the past year ( $n = 140$ ).

Retinal photographs were taken of one eye.<sup>14</sup> The eye to be photographed was selected based on the subject's seven digit identification number, the right eye if even and the left eye if odd. If photography of the eye specified by this algorithm was not possible because of a missing eye, inability to dilate to at least 4 mm, inability to fixate adequately for proper photographic field definition, or opacities of the media preventing a reasonably clear view of the retina, the fellow eye was photographed. Of the 558 people classified as having diabetes who participated in the 1997–8 examination, photographs were not taken for 158 people and could not be evaluated in 104 because of poor quality, typically because of media opacities or small pupil size. Comparisons between those diabetic participants with ( $n = 296$ ) and those without ( $n = 262$ ) gradable fundus photographs appear in Table 1. Not having gradable fundus photographs was associated with older age, higher fasting blood sugar, lower haematocrit, more alcoholic drinks consumed per week, longer time to walk 15 feet, presence of gross proteinuria, and a history of emphysema, stroke,

and coronary heart disease. Sex, microalbuminuria, smoking status, duration of diabetes, plasma total cholesterol, plasma high density lipoprotein (HDL) cholesterol, plasma low density lipoprotein (LDL) cholesterol, plasma Lp(a), plasma triglycerides, systolic or diastolic blood pressure, body mass index, serum albumin levels, platelet count, ankle-brachial index, and internal or common carotid IMT were not associated with having gradable fundus photographs.

## METHODS

Evaluations, including assessment of established risk factors for atherosclerotic vascular disease, were performed using common written protocols and were monitored for adherence to protocol. Ultrasound examination of the common and internal carotid arteries was used to determine the IMT and presence or absence of atherosclerotic plaque. The methods used to collect these data appear elsewhere.<sup>12</sup> The retinal photography performed at the eighth follow up clinic examination and the interpretation of the retinal photographs are described in detail elsewhere.<sup>14</sup> Briefly, a 45° retinal photograph was taken of one eye, centred on the region of the optic disc and the macula, using an autofocus camera. Pupillary dilatation was achieved after the participant spent 5 minutes in a dark room, without use of mydriatic drops. Photographic methods were standardised with written protocols and the photographer's performance was monitored with periodic feedback.

Photographs were evaluated at the Fundus Photograph Reading Center in Madison, Wisconsin, where they were

graded for quality of the images, and then viewed with an eight power lens by a grader who was masked to subject information and who graded the photograph for signs of retinopathy.

### Definitions of variables

To determine diabetic retinopathy status, all fundus photographs were graded in masked fashion using the modified Airlie House classification scheme.<sup>15 16</sup> Levels are assigned based on an algorithm combining information on presence and severity of the specific lesions. Level 10 represents no retinopathy, level 20 represents the presence of retinal microaneurysm only, levels 31–51 represent lesions of non-proliferative retinopathy ordered by severity, and levels 60–85 represent proliferative retinopathy also ordered by severity. In addition to grading the severity of diabetic retinopathy, the presence of clinically significant macular oedema was also determined.<sup>17</sup>

Current age was defined as the age at the time of the 1997–8 examination. Duration of diabetes was defined as the difference between the date participants were first told by a doctor they had diabetes and the date at the 1997–8 examination. For the 36 people with missing information about when they were first told by a doctor that they had diabetes, the duration of diabetes was defined by either the first time hypoglycaemic medications were used during the study period ( $n = 2$ ) or when the first study fasting blood sugar met the criteria as defined by the ADA ( $n = 35$ ); or when both occurred ( $n = 1$ ). Hypertension was defined by systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or the combination of self reported high blood pressure diagnosis and use of antihypertensive medications. A participant was classified as having treated controlled hypertension if the systolic blood pressure was  $< 140$  mm Hg and the diastolic blood pressure  $< 90$  mm Hg and they were taking antihypertensive medications, and as having uncontrolled hypertension if the systolic blood pressure was  $\geq 140$  mm Hg or the diastolic blood pressure was  $\geq 90$  mm Hg. Coronary heart disease was defined by a history of presence of myocardial infarction, angina, coronary artery bypass surgery, or coronary angioplasty. The common carotid IMT was determined to be the mean of the maximum wall thickness for near and far walls on both the left and right sides. The internal carotid IMT was obtained in the same way, but the mean value was obtained from measurements of both sides on three different scan planes.<sup>18</sup> Electrocardiography (presence of Minnesota Code 3–1, 3–3, and 4–1 to 4–3 or 5–1 to 5–3) and echocardiographic abnormalities (the residual of the left ventricular mass regressed on height and weight being above the sex specific 95th percentile) were used to define the presence of left ventricular hypertrophy.<sup>19</sup> Subclinical cardiovascular disease was

defined as major electrocardiogram abnormalities, echocardiogram wall motion abnormality or low ejection fraction, increased carotid or internal carotid artery wall thickness ( $> 80$ th percentile) or stenosis of  $> 25\%$ , a decreased ankle-brachial blood pressure ( $\leq 0.9$ ), and positive responses to the Rose questionnaire for angina or intermittent claudication.<sup>20</sup> Microalbuminuria was defined as having  $> 30$  mg of albumin per g of creatinine and gross proteinuria as 1+ (30 mg/dl of protein) in a randomly collected urine sample. Methods used to define other characteristics in the CHS are provided elsewhere.<sup>12</sup>

### Quality control

For quality control, assessment of photographs was repeated in a subset. Unweighted kappas (Cohen) for agreement on diabetic retinopathy severity level were 0.79 and 0.94 for 63 intragrader comparisons for the two graders. It was 0.89 for intergrader comparisons ( $n = 65$ ).

### Statistical methods

Differences between those included in analyses and those excluded were examined using the two sample  $t$  test and  $\chi^2$  test, for continuous and categorical variables respectively. Then the relation of diabetic retinopathy to various demographic and physical characteristics was examined using univariate logistic regression. Multivariate relations were assessed by multivariate logistic regression adjusting for age, sex, and race. The full model was built using multivariate logistic regression and including age, sex, and race a priori. Groups of variables were considered sequentially and inclusion was determined by statistical significance ( $p < 0.10$ ). Measures of diabetic severity were considered first, followed by variables relating to atherosclerosis. Other variables identified as highly associative in univariate models and exploratory backward stepwise regression were also considered. Further modelling was not done because of concerns about the lack of power owing to the low event rate of retinopathy in the sample population. All statistical analyses were carried out using the SPSS software package.

### RESULTS

Retinopathy was detected in 60 (20.3%) of the 296 people with diabetes; 2.7% of the 296 had signs of proliferative retinopathy and 2.1% had signs of macular oedema (Table 2). Univariate analyses showed retinopathy to be associated with being black, longer duration of diabetes, user of insulin, higher fasting blood sugar, higher average systolic blood pressure, higher plasma total and LDL cholesterol, lower haematocrit, higher serum fibrinogen, the presence of microalbuminuria or gross proteinuria, longer timed walk, and the presence of cardiovascular disease (Table 3). Retinopathy was most frequent in

**Table 2** Retinopathy level and prevalence of macular oedema by diabetes classification\* and level of glycaemia in the Cardiovascular Health Study

	Diabetes classification							
	Glucose level only (n=74)		Hypoglycaemic medications only (n=65)		Glucose level and hypoglycaemic medications (n=157)		Total (n=296)	
	No	%	No	%	No	%	No	%
Retinopathy level								
None (level 10)	66	89.2	51	78.5	119	75.8	236	79.7
Minimal non-proliferative (levels 21–35)	3	4.1	4	6.2	15	9.6	22	7.4
Moderate to severe non-proliferative (levels 40–50)	5	6.8	7	10.8	18	11.5	30	10.1
Proliferative (levels 60+)	0	0	3	4.6	5	3.2	8	2.7
Macular oedema†	1	1.4	2	3.2	3	1.9	6	2.1

\*American Diabetes Association classification defines a person as having diabetes if s/he is currently using insulin or oral hypoglycaemic agents, or has a fasting blood sugar of 126 mg/dl or higher; †denominators for macular oedema for glucose only group is 74, hypoglycaemic medications only group is 62, glucose level and hypoglycaemic medications group is 155 and for total is 291.

**Table 3** Prevalence of retinopathy by characteristics of the Cardiovascular Health Study, 1996–7

	Exam year measured	Number at risk	Retinopathy prevalence % (No)	Odds ratio (95% confidence interval)	p Value for trend
Sex	Baseline				0.10
Male		132	15.9 (21)		
Female		164	23.8 (39)	1.65 (0.92 to 2.97)	
Race	Baseline				0.001
Non-black		231	16.0 (37)		
Black		65	35.4 (23)	2.87 (1.55 to 5.33)	
Age (years)	1997–8				0.825
69–74		61	16.4 (10)		
75–79		154	24.0 (37)	1.61 (0.75 to 3.49)	
80–102		81	16.0 (13)	0.98 (0.40 to 2.40)	
Duration of diabetes (years)	1997–8				<0.001
0–1		55	5.5 (3)		
2–7		91	13.2 (12)	2.63 (0.71 to 9.77)	
8–12		71	21.1 (15)	4.64 (1.27 to 16.94)	
13–50		79	38.0 (30)	10.60 (3.04 to 36.96)	
Hypoglycaemic medications	1997–8				0.002
None		74	10.8 (8)		
OHGA only		171	19.3 (33)	1.97 (0.86 to 4.51)	
OHGA or insulin		51	37.3 (19)	4.90 (1.94 to 12.39)	
Fasting plasma glucose (mg/dl)	1996–7				0.03
67–128		70	14.3 (10)		
129–145		71	12.7 (9)	0.87 (0.33 to 2.29)	
146–174		72	19.4 (14)	1.45 (0.60 to 3.52)	
175–355		71	28.2 (20)	2.35 (1.01 to 5.48)	
Total plasma cholesterol (mg/dl)	1992–1993				0.03
105–177		72	15.3 (11)		
178–200		70	18.6 (13)	1.26 (0.52 to 3.05)	
201–230		75	20.0 (15)	1.39 (0.59 to 3.26)	
231–369		72	29.2 (21)	2.28 (1.01 to 5.18)	
Plasma LDL cholesterol (mg/dl)	1992–3				0.002
26–94		69	13.0 (9)		
95–117		70	14.3 (10)	1.11 (0.42 to 2.93)	
118–140		70	21.4 (15)	1.82 (0.74 to 4.49)	
141–255		70	32.9 (23)	3.26 (1.38 to 7.71)	
Systolic blood pressure (mm Hg) (study average)	NA				0.01
102–125		73	15.1 (11)		
126–134		67	19.4 (13)	1.36 (0.56 to 3.28)	
135–145		78	16.7 (13)	1.13 (0.47 to 2.70)	
146–184		78	29.5 (23)	2.36 (1.05 to 5.27)	
Microalbuminuria	1996–7				<0.001
Absent		175	12.6 (22)		
Present		98	31.6 (31)	3.22 (1.74 to 5.97)	
Gross proteinuria	1996–7				0.01
Absent		257	17.5 (45)		
Present		25	40.0 (10)	3.14 (1.33 to 7.44)	
Haematocrit (%)	1992–3				0.05
27.1–39.2		72	29.2 (21)		
39.3–41.7		72	26.4 (19)	0.87 (0.42 to 1.81)	
41.8–43.8		74	10.8 (8)	0.29 (0.12 to 0.72)	
43.9–54.2		65	15.4 (10)	0.44 (0.19 to 1.03)	
Serum fibrinogen (mg/dl)	1992–3				0.05
178–283		70	21.4 (15)		
284–323		73	15.1 (11)	0.65 (0.28 to 1.54)	
324–366		72	20.8 (15)	0.97 (0.43 to 2.16)	
367–528		72	25.0 (18)	1.22 (0.56 to 2.67)	
Time to walk 15 ft (seconds)	1997–8				0.003
3–5		157	15.9 (25)		
6–8		113	23.0 (26)	1.58 (0.86 to 2.91)	
9–15		23	34.8 (8)	2.82 (1.08 to 7.34)	
Ankle-arm index	1992–3				0.08
<0.9		27	33.3 (9)	2.15 (0.91 to 5.07)	
≥0.9 (normal)		254	18.9 (48)		
Subclinical disease	1992–3				0.07
No	1994–5	77	13.0 (10)		
Yes	1996–7	219	22.8 (50)	1.98 (0.95 to 4.13)	
Internal carotid IMT (mm)	1992–3				0.93
0.66–1.04		72	12.5 (9)		
1.05–1.39		72	22.2 (16)	2.00 (0.82 to 4.88)	
1.40–1.77		72	30.6 (22)	3.08 (1.30 to 7.28)	
1.78–3.95		72	18.1 (13)	1.54 (0.61 to 3.87)	
Coronary heart disease	1996–7				0.05
Absent/questionable		204	17.2 (35)		
Present		92	27.2 (25)	1.80 (1.00 to 3.24)	
Cardiovascular disease					0.03
None	1992–3	61	11.5 (7)		
Subclinical only	1994–5	132	18.2 (24)	1.71 (0.70 to 4.23)	
CHD, stroke, or subclinical	1996–7	103	28.3 (29)	3.02 (1.23 to 7.41)	

CHD = cardiovascular heart disease, IMT = intima media wall thickening, OHGA = oral hypoglycaemic agents.

**Table 4** Multivariate logistic regressions\* on diabetic retinopathy in Cardiovascular Health Study

Model	Characteristic	Odds ratio (95% confidence interval)	pValue
1	Cardiovascular disease		
	Subclinical only v none	1.57 (0.99 to 4.17)	0.03
	Coronary heart disease or stroke v none	3.27 (1.21 to 8.84)	
2	Plasma LDL cholesterol per 10 mg/dl	1.01 (1.00 to 1.02)	0.01
3	Gross proteinuria	4.22 (1.50 to 11.86)	0.01

\*All models include age, sex, fasting blood glucose, and duration of diabetes and the characteristic specified.

**Table 5** Full model from logistic regression on diabetic retinopathy (age, sex, race, and duration forced into the model and all continuous measures are modeled continuously)

Variables in the model	Odds ratio (95% confidence interval)	p Value
Age (per year)	0.96 (0.87 to 1.06)	0.41
Sex (men v women)	0.42 (0.19 to 0.95)	0.04
Race (black v non-black)	2.26 (1.01 to 5.05)	0.05
Plasma glucose*	1.98 (0.55 to 7.70)	0.29
Gross proteinuria (present v absent)	4.76 (1.53 to 14.86)	<0.01
Plasma LDL cholesterol (per 10 mg/dl)	1.12 (1.02 to 1.23)	0.02
Duration of diabetes (per 5 years)	1.42 (1.18 to 1.70)	<0.001
Cardiovascular disease†		
Subclinical only	1.49 (0.51 to 4.31)	0.463
Prevalent coronary heart disease or stroke	3.23 (1.09 to 9.56)	0.034

\*Natural log transformation used in modelling due to skewed distribution; †odds ratio for comparison against no cardiovascular disease. Subclinical disease defined as major electrocardiogram abnormalities, echocardiogram wall motion abnormality or low ejection fraction, increased carotid or internal carotid artery wall thickness (>80th percentile) or stenosis of >25%, a decreased ankle-brachial blood pressure ( $\leq 0.9$  mm Hg) and positive responses to the Rose questionnaire for angina or intermittent claudication.

those taking medications to lower blood sugar whose fasting blood sugar was  $\geq 126$  mg/dl (24.2%) and least frequent in those who were classified as having diabetes based on fasting blood sugar  $\geq 126$  mg/dl only (10.8% (Table 2)). Retinopathy was not associated with internal carotid or common carotid wall IMT or plaque, left ventricular hypertrophy status, plasma HDL cholesterol, Lp(a), and triglycerides, diastolic or mean blood pressure, body mass index, use of angiotensin converting enzyme (ACE) inhibitors or oestrogens, number of cigarettes smoked, alcoholic beverages consumed per week, white blood cell or platelet count, or serum albumin (data not shown).

To evaluate the relative influence of several variables on the prevalence of retinopathy, we developed models based on logistic regression. These models are used to test the significance of variables in predicting the presence of retinopathy when the effects of other variables are being considered. Separate models were run first, always controlling for age, sex, race, fasting blood sugar, and duration of diabetes (Table 4). Significant associations (in separate models) were found between diabetic retinopathy and the presence of cardiovascular disease as manifest by coronary heart disease or stroke, higher plasma LDL cholesterol, and the presence of gross proteinuria. Next, a model controlling for age, sex, race, fasting blood glucose, and duration of diabetes was run, adding each of the variables found in the separate models in Table 4, step by step. While controlling for age, sex, and fasting blood glucose, diabetic retinopathy was associated with longer duration of diabetes, black race, presence of cardiovascular disease, higher plasma LDL cholesterol, and presence of gross proteinuria (Table 5). When microalbuminuria was added to the model, plasma LDL cholesterol was no longer associated with diabetic retinopathy (data not shown).

Retinal hard exudate was present in six (2.1%) of the cohort. In univariate analyses, both mean plasma total cholesterol and LDL cholesterol were higher in people with retinal hard exudate than in people without (data not shown).

## CONCLUSIONS

Our data are compatible with the hypothesis that atherosclerosis, as manifest by coronary heart disease and stroke, may be associated with retinopathy in people with diabetes. This finding is independent of blood sugar, duration of diabetes, and gross proteinuria or microalbuminuria. This is consistent with previous reports of an association of proliferative retinopathy with coronary heart disease in people with type 2 diabetes.<sup>21</sup> However, in our study, we did not find an association of retinopathy with internal carotid artery wall IMT or other signs of subclinical atherosclerosis. This is inconsistent with data from a case-control study by Visonia *et al*<sup>11</sup> that showed a higher frequency of increased IMT in the common carotid artery and atherosclerotic lesions of the carotid bifurcation, as measured by high resolution echo Doppler scan in people with type 2 diabetes and diabetic retinopathy compared with those without retinopathy. The association was not explained by differences in carotid IMT or in frequency of subclinical atherosclerosis in those with gradable fundus photographs compared with those without. The association of atherosclerosis with retinopathy may, in fact, be even stronger than we report because retinopathy and atherosclerosis are both associated with increased risk of death and morbidity in people with diabetes.<sup>22</sup> Because atherosclerosis may be present before the onset of diabetes, further assessment of a possible association of atherosclerosis with retinopathy in people with type 2 diabetes may be better evaluated if done in long term cohort studies beginning before the onset of diabetes.

Our data also suggest that plasma LDL cholesterol may be associated with retinopathy and is consistent with earlier observations in the Early Treatment Diabetic Retinopathy Study.<sup>9,10</sup> In the latter study, higher levels of serum lipids (triglycerides, LDL cholesterol, and VLDL cholesterol) were associated with an increased risk of developing hard exudates in the macula and visual loss in people with diabetes. In the CHS, the association may be due, in part, to factors associated with mild to moderate renal impairment as the relation of plasma LDL cholesterol with diabetic retinopathy was no longer statistically significant in the presence of microalbuminuria.<sup>23</sup> Nevertheless, elevations in plasma LDL cholesterol may contribute to the deposition of hard exudate in the retina in people with diabetes, as found in the CHS cohort. Randomised controlled clinical trials are currently in progress to examine whether lipid lowering agents will reduce the risk of incidence and progression of diabetic retinopathy.

Our data suggest that both gross proteinuria and microalbuminuria may be associated with diabetic retinopathy. This is consistent with data from other studies that demonstrated an association of gross proteinuria with an increased risk of progression of retinopathy.<sup>24,25</sup> The association of diabetic nephropathy with diabetic retinopathy has long been recognised.<sup>26,27</sup> Retinal ischaemia and exudation that characterise diabetic retinopathy might be due, in part, to elevations in lipoprotein (elevated total cholesterol and LDL cholesterol), haemostatic (platelet hyperactivity and changes in fibrinolytic activity with higher levels of plasminogen activator inhibitor of type 1) and blood pressure abnormalities, and endothelial dysfunction (high levels of von Willebrand factor and prosta-cyclins) associated with diabetic nephropathy.<sup>28</sup>

Any conclusions or explanations regarding associations described here must be made with caution because only about one half of those with diabetes mellitus were evaluated and those were the healthier half. We cannot evaluate how the strengths of these relations might have varied with complete ascertainment nor can we speculate about how this influenced the relation of subclinical cardiovascular disease, hyperglycaemia, or hypertension to retinopathy. In addition, we may have missed some important relations because of both the smaller sample size and the non-representative nature of the survivors.

Black people had a higher prevalence of diabetic retinopathy than white people in the CHS. Similarly, in the NHANES III, black people had a 46% higher prevalence than white people.<sup>29</sup> However, in that study, after adjustment for duration of diabetes, glycosylated haemoglobin levels, and treatment with insulin and oral agents, black people were not at a higher risk of retinopathy than white people. None of the characteristics of the population studied in the CHS explained the racial differences found in our study.

The prevalence of retinopathy in the cohort was 20%. Age and duration specific rates in the CHS are lower than those found in a population based cohort studied in Wisconsin.<sup>1</sup> The lower rates of retinopathy in the CHS compared with Wisconsin cohort was not a result of different definitions of diabetes between the cohorts. The CHS cohort used the new ADA criteria for classification of diabetes ( $\geq 126$  mg/dl), while the Wisconsin study defined a person as having diabetes by the older classification system which included having a fasting blood sugar of  $\geq 140$  mg/dl on two separate occasions. Retinopathy level using a fasting blood sugar of 140 mg/dl to define diabetes did not change the distribution of the frequency of severity of retinopathy in the CHS (Klein R, unpublished data). Another reason for lower rates of retinopathy in the CHS compared with the Wisconsin cohort is that in the CHS, a 45° photograph of one field (centred on the fovea) of one eye was graded, whereas in the Wisconsin study, retinopathy was detected by grading of seven stereoscopic fundus photographs of both eyes. The lack of stereopsis and the limited magnification of photographs taken with the non-mydiatic camera

may also explain the lower rates of retinopathy and macular oedema (retinal thickening) in the CHS than in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.<sup>30</sup>

In summary, these data show an association of coronary heart disease or stroke and LDL cholesterol with retinopathy in a cohort of older people with type 2 diabetes. Further understanding of the relation of atherosclerosis with retinopathy will require long term cohort studies begun at or before the onset of diabetes. Regardless of the benefits of lowering LDL cholesterol to reduce retinopathy risk, clinical trials have demonstrated the efficacy of such lowering in people with diabetes.<sup>31</sup>

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## REFERENCES

- 1 Klein R, Klein BEK. Vision disorders in diabetes. In: *Diabetes in America*. 2nd ed. Harris MWH, et al, eds. NIH-NIDDK Publication No 95-1468. Chapter XIV. Bethesda, MD: US Public Health Service, 1995:293-338.
- 2 Klein R, Klein BEK. Diabetic eye disease. *Lancet* 1997;**350**:197-204.
- 3 Klein R, Klein BEK, Moss SE, et al. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 1988;**260**:2964-71.
- 4 The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977-86.
- 5 Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;**28**:103-17.
- 6 UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes. UKPDS 33. *Lancet* 1998;**352**:837-53.
- 7 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in Type 2 diabetes. UKPDS 38. *BMJ* 1998;**317**:703-13.
- 8 Klein BEK, Moss SE, Klein R, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XIII. Relationship of serum cholesterol to retinopathy and hard exudate. *Ophthalmology* 1991;**98**:1261-5.
- 9 Chew EY, Klein ML, Ferris FL 3rd, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Arch Ophthalmol* 1996;**114**:1079-84.
- 10 Ferris FL 3rd, Chew EY, Hoogwerf BJ. Serum lipids and diabetic retinopathy. Early Treatment Diabetic Retinopathy Study Research Group. *Diabetes Care* 1996;**19**:1291-3.
- 11 Visona A, Lusiani L, Bonanome A, et al. Wall thickening of common carotid arteries in patients affected by noninsulin-dependent diabetes mellitus: relationship to microvascular complications. *Angiology* 1995;**46**:793-9.
- 12 Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;**1**:263-76.
- 13 Tell GS, Fried LP, Hermanson B, et al. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol* 1993;**3**:358-66.

- 14 **Atherosclerosis Risk in Communities (ARIC) Study Research Group.** ARIC retinal photography protocol, Manual 14A, and ARIC Reading Center protocol, Manual 14B. Available from the ARIC Coordinating Center, Department of Biostatistics (CSCC), University of North Carolina, CB#8030, Suite 203, Nationsbank Plaza, 137 E Franklin Street, Chapel Hill, NC 27514.
- 15 **Early Treatment Diabetic Retinopathy Study Research Group.** Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS Report No 10. *Ophthalmology* 1991;**98**:786–806.
- 16 **Early Treatment Diabetic Retinopathy Study Research Group.** Risk factors for progression of diabetic retinopathy. ETDRS Report No 12. *Ophthalmology* 1991;**98**:823–33.
- 17 **Early Treatment Diabetic Retinopathy Study Research Group.** Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;**103**:1796–806.
- 18 **O’Leary DH, Polak JF, Wolfson Jr SK, et al.** Use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. *Stroke* 1991;**22**:1155–63.
- 19 **Furberg CD, Manolio TA, Psaty BM, et al.** Major electrocardiographic abnormalities in persons aged 65 years and older (the Cardiovascular Health Study). Cardiovascular Health Study Collaborative Research Group. *Am J Cardiol* 1992;**69**:1329–35.
- 20 **Kuller L, Borhani N, Furberg C, et al.** Prevalence of subclinical atherosclerosis and cardiovascular disease and association with risk factors in the Cardiovascular Health Study. *Am J Epidemiol* 1994;**139**:1164–79.
- 21 **Klein R, Klein BEK, Moss SE.** The epidemiology of proliferative diabetic retinopathy. *Diabetes Care* 1992;**15**:1875–91.
- 22 **Klein R, Klein BEK, Moss SE, et al.** Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol* 1999;**117**:1487–95.
- 23 **Ehtinger WH, Wahl PW, Kuller LH, et al.** Lipoprotein lipids in older people. Results from the Cardiovascular Health Study. *Circulation* 1992;**86**:858–69.
- 24 **Klein R, Moss SE, Klein BEK.** Is gross proteinuria a risk factor for the incidence of proliferative diabetic retinopathy? *Ophthalmology* 1993;**100**:1140–6.
- 25 **Jensen T, Deckert T.** Diabetic retinopathy, nephropathy and neuropathy. Generalized vascular damage in insulin-dependent diabetic patients. *Hormone Metab Res (Suppl)* 1992;**26**:68–70.
- 26 **Lunbaek K.** Diabetic angiopathy. A specific vascular disease. *Lancet* 1954;**1**:377–9.
- 27 **West KM.** *Epidemiology of diabetes mellitus and its vascular lesions.* New York: Elsevier, 1978.
- 28 **Jensen T.** Albuminuria—a marker of renal and generalized vascular disease in insulin-dependent diabetes mellitus. *Danish Med Bull* 1991;**38**:134–44.
- 29 **Harris MI, Klein R, Cowie CC, et al.** Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A US population study. *Diabetes Care* 1998;**21**:1230–5.
- 30 **Klein R, Klein BEK, Neider MW, et al.** Diabetic retinopathy as detected using ophthalmoscopy, a nonmydriatic camera and a standard fundus camera. *Ophthalmology* 1985;**92**:485–91.
- 31 **Pyorala K, Pedersen TR, Kjekshus J, et al.** Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival. *Diabetes Care* 1997;**20**:614–20.

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