

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.^{1,2} 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.^{3–6} 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.⁷ 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.^{8–10}

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.¹¹ 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.¹² 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.¹³

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.¹² 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 | % | | | |
| Race | | | | | | | |
| Non-black | 231 | 78.0 | 184 | 70.2 | 0.04 | | |
| Black | 65 | 22.0 | 78 | 29.8 | | | |
| Hypoglycaemic medications | | | | | 0.09 | | |
| None | 74 | 25.0 | 57 | 22.5 | | | |
| Oral only | 171 | 57.8 | 133 | 52.6 | | | |
| Insulin | 51 | 17.2 | 63 | 24.9 | | | |
| Gross proteinuria (>30 mg/dl) | | | | | 0.02 | | |
| Absent | 257 | 91.1 | 158 | 84.0 | | | |
| Present | 25 | 8.9 | 30 | 16.0 | | | |
| Progestin use (females only) | | | | | 0.05 | | |
| Current | 6 | 3.7 | 0 | 0 | | | |
| Former | 4 | 2.4 | 5 | 3.3 | | | |
| Never | 154 | 93.9 | 147 | 96.7 | | | |
| Emphysema | | | | | 0.01 | | |
| Never been told | 293 | 99.3 | 233 | 96.3 | | | |
| Told by doctor | 2 | 0.7 | 9 | 3.7 | | | |
| Stroke | | | | | <0.01 | | |
| Absent/questionable | 274 | 92.6 | 223 | 85.1 | | | |
| Present | 22 | 7.4 | 39 | 14.9 | | | |
| Coronary heart disease | | | | | 0.02 | | |
| Absent/questionable | 204 | 68.9 | 155 | 59.2 | | | |
| Present | 92 | 31.1 | 107 | 40.8 | | | |
| Cardiovascular disease | | | | | 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 ≥ 126 mg/dl for those not using any hypoglycaemic agents in the past year ($n = 140$).

Retinal photographs were taken of one eye.¹⁴ 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.¹² The retinal photography performed at the eighth follow up clinic examination and the interpretation of the retinal photographs are described in detail elsewhere.¹⁴ 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.^{15 16} 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.¹⁷

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 ≥ 140 mm Hg, diastolic blood pressure ≥ 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 ≥ 140 mm Hg or the diastolic blood pressure was ≥ 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.¹⁸ 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.¹⁹ 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 (≤ 0.9), and positive responses to the Rose questionnaire for angina or intermittent claudication.²⁰ 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.¹²

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 χ^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 (≤ 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 ≥ 126 mg/dl (24.2%) and least frequent in those who were classified as having diabetes based on fasting blood sugar ≥ 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.²¹ 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*¹¹ 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.²² 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.^{9,10} 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.²³ 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.^{24,25} The association of diabetic nephropathy with diabetic retinopathy has long been recognised.^{26,27} 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.²⁸

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.²⁹ 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.¹ 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 (≥ 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 ≥ 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.³⁰

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.³¹

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