Retinopathy Predicts Cardiovascular Mortality in Type 2 Diabetic Men and Women

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OBJECTIVE — To investigate the association of retinopathy with the risk of all-cause, cardiovascular disease (CVD), and coronary heart disease (CHD) mortality in type 2 diabetic subjects in a population-based 18-year follow-up study with particular emphasis on sex differences.

RESEARCH DESIGN AND METHODS — Our study cohort comprised 425 Finnish type 2 diabetic men and 399 type 2 diabetic women who were free of CVD at baseline. The findings were classified based on standardized clinical ophthalmoscopy to categories of no retinopathy, background retinopathy, and proliferative retinopathy. The study end points were all-cause, CVD, and CHD mortality.

RESULTS — Adjusted Cox model hazard ratios (95% CIs) of all-cause, CVD, and CHD mortality in men were 1.34 (0.98–1.83), 1.30 (0.86–1.96), and 1.18 (0.74–1.89), respectively, for background retinopathy and 3.05 (1.70–5.45), 3.32 (1.61–6.78), and 2.54 (1.07–6.04), respectively, for proliferative retinopathy and in women 1.61 (1.17–2.22), 1.71 (1.17–2.51), and 1.79 (1.13–2.85), respectively, for background retinopathy and 2.92 (1.41–6.06), 3.17 (1.38–7.30), and 4.98 (2.06–12.06), respectively, for proliferative retinopathy.

CONCLUSIONS — Proliferative retinopathy in both sexes and background retinopathy in women predicted all-cause, CVD, and CHD death. These associations were independent of current smoking, hypertension, total cholesterol, HDL cholesterol, glycemic control of diabetes, duration of diabetes, and proteinuria. This suggests the presence of common background pathways for diabetic microvascular and macrovascular disease other than those included in the conventional risk assessment of CVD. The sex difference observed in the association of background retinopathy with macrovascular disease warrants closer examination.

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Hyperglycemia is the major determinant of the risk of microvascular complications of diabetes (1), whereas the evidence that hyperglycemia is a major risk factor for macrovascular complications of this disease is more limited (2,3). Population-based studies have shown that microvascular complications predict cardiovascular disease (CVD) mortality not only in type 1 (3,4) and type 2 (5–10) diabetic subjects but even in nondiabetic subjects (10) and in general population samples, controlling for the effect of glucose status (11–14). These observations suggest similar underlying pathogenic processes in microvascular complications and in atherosclerotic CVD in diabetes.

It has been suggested that microvascular processes might be especially important in the development of coronary heart disease (CHD) in women (11,13). However, epidemiological data are largely missing with respect to possible sex differences in the association of diabetic retinopathy with CVD. We have performed an 18-year follow-up study of 824 Finnish subjects with type 2 diabetes (425 men and 399 women) who were free of CVD at baseline to evaluate the predictive value of retinopathy for all-cause, CVD, and CHD mortality by sex.

RESEARCH DESIGN AND METHODS

— A detailed description of study participants has been published previously (15). Altogether, 1,059 subjects (581 men and 478 women) with type 2 diabetes, aged 45–64 years, were identified through a national drug reimbursement register. Subjects with type 1 diabetes were excluded based on the age of onset of diabetes, history of ketoacidosis, and, if needed, on glucagon-stimulated C-peptide measurement. Subjects with prior CVD (prior myocardial infarction, prior stroke, or prior lower-extremity amputation for vascular causes) were excluded. The diagnosis of previous myocardial infarction was based on the modified World Health Organization criteria for definite or possible myocardial infarction (16) and that of stroke on World Health Organization criteria for stroke (17). The final study population included 425 men and 399 women (n = 824) for whom the data of ophthalmoscopic examination at baseline were available.

Baseline study

The baseline examination, conducted in 1982–1984, has been described in detail previously (15). Subjects were classified as having hypertension if they were receiving drug treatment for hypertension or if systolic blood pressure was ≥160 mmHg or diastolic blood pressure was ≥95 mmHg in the sitting position after a 5-min rest.

Biochemical methods

All laboratory specimens were taken after a 12-h fast at 0800 h. The analyses were performed in duplicate except for glycated hemoglobin (A1). Serum total cholesterol and triglycerides were determined enzymatically (Boehringer).

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Baseline characteristics according to the grade of retinopathy*

	Men				Women			
	No retinopathy	Background retinopathy	Proliferative retinopathy	*P* value for linear trend	No retinopathy	Background retinopathy	Proliferative retinopathy	*P* value for linear trend
n	327	81	17	—	307	82	10	—
Age (years)	56.9 ± 5.2	57.2 ± 5.0	56.2 ± 5.2	0.911	58.7 ± 5.0	58.6 ± 4.8	59.4 ± 4.6	0.966
Area (% east)	40.4	35.8	52.9	0.851	51.5	57.3	30.0	0.972
Current smoking (%)	28.7	14.8	0.0	<0.001	8.5	3.7	10.0	0.302
Treatment of diabetes								
Diet only (%)	56.3	49.4	41.2	0.001	54.1	47.6	50.0	0.005
Oral drug treatment without insulin (%)	40.1	39.5	23.5		41.7	37.8	10.0	
Insulin treatment (%)	3.7	11.1	35.3	<0.001	4.2	14.6	40.0	<0.001
BMI (kg/m^2)	28.4 ± 4.8	27.2 ± 3.3	25.7 ± 3.4	0.002	30.8 ± 6.0	29.4 ± 5.5	31.3 ± 5.5	0.216
Systolic blood pressure (mmHg)	147 ± 20	151 ± 20	141 ± 18	0.748	157 ± 25	167 ± 26	150 ± 20	0.049
Diastolic blood pressure (mmHg)	87 ± 20	86 ± 12	83 ± 11	0.135	85 ± 11	87 ± 13	84 ± 11	0.162
Hypertension (%)	55.4	51.9	52.9	0.608	66.4	75.6	80.0	0.080
Total cholesterol (mmol/l)	6.3 ± 1.4	6.2 ± 1.5	6.5 ± 1.4	0.549	7.0 ± 2.0	6.8 ± 1.4	7.4 ± 1.5	0.883
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	0.026	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	0.167
Triglycerides (mmol/l)*	2.3 ± 2.3	1.8 ± 1.2	1.6 ± 1.2	0.001	2.8 ± 3.8	2.5 ± 1.7	2.9 ± 2.4	0.983
Urinary protein (g/l)*	0.24 ± 0.48	0.27 ± 0.47	0.31 ± 041	0.068	0.21 ± 0.43	0.54 ± 1.18	0.55 ± 1.20	<0.001
Fasting insulin (mU/l)*†	21.1 ± 15.2	17.5 ± 11.4	14.5 ± 6.8	0.012	23.0 ± 13.1	19.0 ± 11.5	13.2 ± 1.0	0.001
Glomerular filtration rate (ml/min)‡	107 ± 30	101 ± 21	93 ± 36	0.011	93 ± 27	92 ± 31	94 ± 25	0.969
Fasting glucose (mmol/l)	10.9 ± 3.6	11.6 ± 4.2	11.8 ± 1.1	0.119	11.9 ± 3.7	13.7 ± 3.8	13.8 ± 3.7	<0.001
A1C (%)	9.6 ± 2.4	9.8 ± 1.7	10.9 ± 2.2	0.036	10.1 ± 2.3	10.5 ± 1.9	10.9 ± 1.5	0.075
Duration of diabetes (years)	7.3 ± 3.6	9.6 ± 4.1	13.4 ± 5.5	<0.001	7.1 ± 3.4	10.3 ± 3.8	13.1 ± 4.4	<0.001

Data are means ± SD, unless otherwise indicated. *The significance of the group difference is tested with logarithmic transformation. †Patients with insulin treatment excluded. ‡From the Cockroft-Gault formula.

HDL cholesterol was determined enzymatically after precipitation of LDL and VLDL with dextran sulfate-$MgCl_2$. Plasma glucose was determined with the glucose oxidase method (Boehringer). A1C was determined by affinity chromatography (Isolab). Plasma insulin concentration was determined by a commercial radioimmunoassay method (antisera M8170 and 8309; Novo, Copenhagen, Denmark). Serum creatinine was determined by kinetic Jaffe method by using the Hitachi 705 analyzer (Tokyo, Japan). Total urinary protein concentration was measured from the morning spot urine specimen with the Coomassie brilliant blue method (Bio-Rad Laboratories, Hercules, CA) (18). Creatinine clearance was estimated by the Cockroft-Gault formula (19).

Ophthalmoscopic examination and classification of retinopathic changes

Ophthalmoscopic examination of fundi was performed after pharmacological dilatation of pupils at the baseline visit by two experienced diabetologists (M.L. and T.R.). For the purpose of this study, retinal findings were classified into three categories according to the status of the worse eye: no retinopathic changes, background retinopathy (microaneurysms, microinfarcts, hard exudates, or hemorrhages), and proliferative retinopathy (neovascularization or previous laser coagulation therapy). Because of poor visibility of fundi caused by cataract, 19 subjects were excluded from further analyses. Consistency of retinopathy findings between the two observers was ascertained by the examination of the fundi of 40 patients by both diabetologists. The κ-coefficient between the retinopathy categories determined by the two observers was 0.84.

Follow-up study

The follow-up period lasted until 1 January 2001. Copies of death certificates of deceased participants were obtained from the Cause-of-Death Register (Statistics Finland). In the final classification of causes of death, hospital and autopsy records were also used if available.

Definition of end points

The end points used in this study were all-cause mortality, CVD mortality (ICD-9 codes 390–459), and CHD mortality (ICD-9 codes 410–414).

Table 2—*Event rate per 1,000 person-years for all-cause, CVD, and CHD deaths in 425 men and 399 women with type 2 diabetes without prior CVD at baseline during 18 years of follow-up according to the grade of retinopathy*

	No retinopathy	Background retinopathy	Proliferative retinopathy	*P* value for linear trend
n	634	163	27	
All-cause mortality				
Men	51.3	57.1	93.7	0.066
Women	49.7	71.1	126.3	0.005
All	50.5	63.9	103.3	0.001
CVD mortality				
Men	32.1	32.2	64.4	0.341
Women	32.6	51.1	98.2	0.007
All	32.3	41.3	74.4	0.012
CHD mortality				
Men	24.5	23.9	41.0	0.841
Women	20.8	35.5	98.2	0.001
All	22.7	29.5	57.8	0.019

Approval of the ethics committees

The ethics committees of the Kuopio University Hospital and the Turku University Central Hospital approved the study. All study subjects had given informed consent.

Statistical methods

Data analyses were conducted with the SPSS 11.5.1 program (SPSS, Chicago, IL). The results for continuous variables were given as means ± SD and for categorical variables as percentages. The differences of continuous variables between the three categories of retinopathy were analyzed by test of linearity included in ANOVA. χ^2 test for trend (linear-by-linear association) was used to test the linear trend for cases compared with noncases by the three categories of retinopathy. Event-rates per 1,000 person-years were calculated. In all statistical analyses, logarithmic transformations were used for triglycerides, fasting insulin, and urinary protein to correct their skewed distribution. Cox models for overall versus no retinopathy, proliferative versus no retinopathy, and background versus no retinopathy were produced with two levels of adjustment. The limit for *P* value of statistical significance was considered 0.05, except for analyses of interaction ($P < 0.10$).

RESULTS — Baseline characteristics according to the grade of retinopathy are given in Table 1. Men with retinopathy smoked less, received insulin treatment more frequently, were leaner, had higher HDL cholesterol, had lower triglycerides, had higher urinary protein, had lower estimated creatinine clearance, had lower plasma insulin, had higher A1C, and had longer duration of diabetes than men without retinopathy. Women with retinopathy received insulin treatment more frequently, had higher systolic blood pressure, had higher level of urinary protein, had lower plasma insulin, and had longer duration of diabetes than women without retinopathy.

During 18 years of follow-up, 287 (67.5%) men and 271 (67.9%) women died, and of those who died, 177 (61.7%) men and 183 (67.5%) women died of CVD and 133 (46.3%) men and 122 (45.0%) women died of CHD. The event-rates of all end points according to the grade of retinopathy are given in Table 2. In men there were 32.1, 32.2, and 64.4 deaths of CVD per 1,000 person-years in the presence of no retinopathy, background retinopathy, and proliferative retinopathy, respectively. Respective CVD death rates in women were 32.6, 51.1, and 98.2, respectively.

Figure 1 shows Kaplan-Meier curves for CVD mortality by the grade of retinopathy in men and women during the 18 years of follow-up. Background retinopathy had an impact on CVD mortality in women but not in men. The impact of proliferative retinopathy was similar in both sexes, but in women with proliferative retinopathy the risk of CVD death was already dramatically increased during the first half of the follow-up.

Table 3 shows Cox model hazard ratios with their 95% CIs and sex × retinopathy interaction of all-cause, CVD, and CHD mortality for overall, background, and proliferative retinopathy at two levels of adjustment. In model I, the adjustment is performed for age, sex (in the pooled analyses of men and women), and area of residence and in model II additionally for A1, current smoking, hypertension, total cholesterol, HDL cholesterol, duration of diabetes, and urinary protein (log). Background retinopathy predicted all-cause, CVD, and CHD mortality in women but not in men. Proliferative retinopathy predicted all-cause and CVD mortality in both sexes in both models and CHD mortality in both models in women but only in model II in men (Table 3).

Statistically significant sex × retinopathy interaction was observed for CVD death with respect to overall retinopathy and for all-cause, CVD, and CHD death with respect to background retinopathy. Proliferative retinopathy predicted mortality similarly in both sexes. Further adjustment for A1 did not influence the hazard ratios of CVD mortality for overall and background retinopathy in men or in women and decreased the hazard ratio of CVD mortality for proliferative retinopathy (by 13.4%) in women but not in men (data not shown). Also adding other risk factors into the adjustment (model II) increased the hazard ratios of overall retinopathy for all-cause, CVD, and CHD death by 21.1, 29.6, and 24.5%, respectively, in men but decreased these by 2.9, 5.8, and 10.5%, respectively, in women, compared with model I.

CONCLUSIONS — Our study showed that proliferative retinopathy predicted all-cause, CVD, and CHD death in both sexes of type 2 diabetic subjects who were free of CVD at baseline. Furthermore, overall and background retinopathy predicted all these categories of mortality in women, suggesting a sex difference in the effect of nonproliferative retinopathy on mortality. The association between retinopathy and mortality was independent not only of conventional CVD risk factors but also of glycemic control, duration of diabetes, and proteinuria. Thus, our results agree with the concept that similar underlying processes are responsible for micro- and macrovascular complications in diabetes.

In previous studies (20–22), hyperglycemia, duration of diabetes, elevated blood pressure, dyslipidemia, and obesity have been associated with the development and progression of diabetic retinopathy. Therefore, it could be expected that

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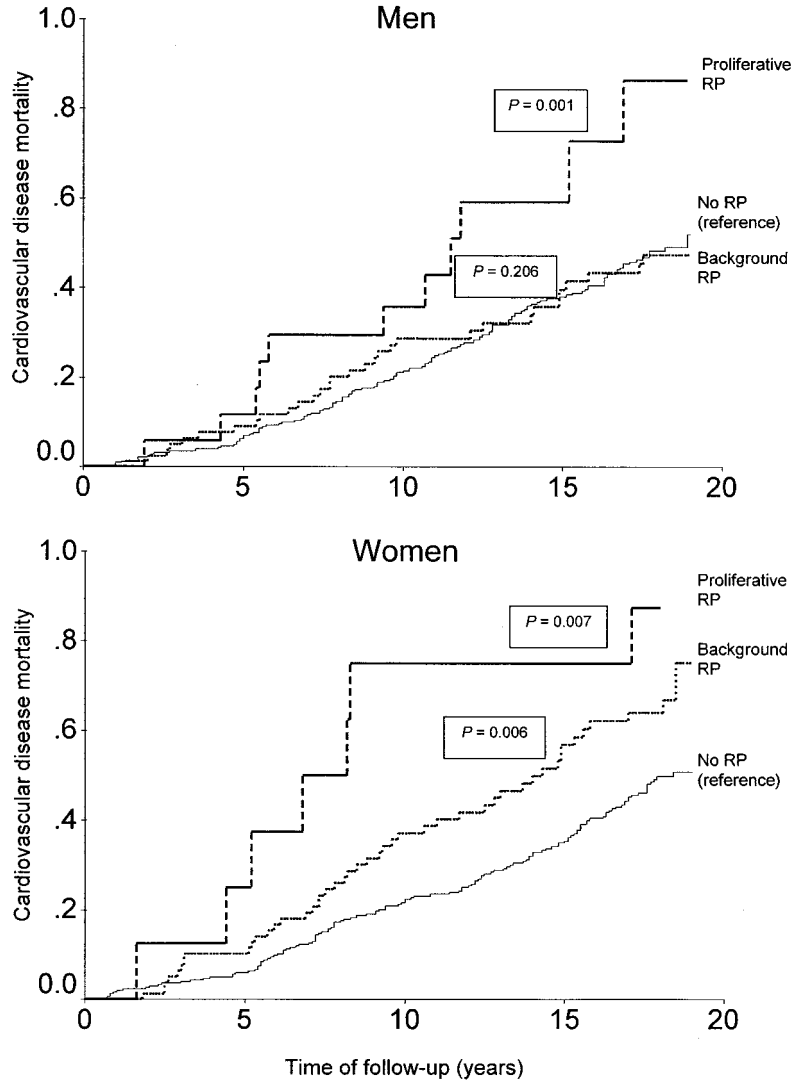

Figure 1— *Kaplan-Meier presentation for cardiovascular mortality in 425 men and 399 women with type 2 diabetes without prior CVD at baseline during 18 years of follow-up.* P *values denote significances Cox model hazard ratios of cardiovascular mortality for proliferative versus no retinopathy (RP) and background versus no retinopathy, after adjustment for age, area of residence, A1C, current smoking, hypertension, total cholesterol, HDL cholesterol, duration of diabetes, and urinary protein (log).*

these factors would be common underlying factors for retinopathy and atherosclerotic CVD. However, in our study, adjusting for these factors did not markedly influence the hazard ratios of mortality for retinopathy.

Several studies have been published on retinopathy as a predictor of CVD risk in type 2 diabetes (Table 4), but limited data exist with respect to the sex difference. A sex difference was observed in our study in the association of background retinopathy with all-cause, CVD, and CHD death, with a significant association in women but not in men. This accords with the findings of two large population-based cohort studies, one from the U.S. (13) and one from Australia (11). They have shown that retinal arteriolar narrowing is more strongly associated with risk of CHD in women than in men. In the World Health Organization Multinational Study on Vascular Disease in Diabetes, the presence of retinopathy indicated a relative risk of 1.4 (95% CI 1.1–2.0) in men and 2.3 (1.6–3.3) in women in the multivariate analysis during the 12-year follow-up, but interaction with sex was not separately analyzed (5). These epidemiological observations suggest that microvascular mechanisms are more important in the development of the macrovascular disease in women than in men. There is also some evidence from recent clinical studies that vasculopathy at microvascular level would be of greater importance in the pathogenesis of CHD in women than in men (23).

Diabetic retinopathy and atherosclerosis include pathophysiological similarities. Both processes include components of endothelial dysfunction, inflammation, neovascularization, apoptosis, and the hypercoagulable state (24). The neovascularization of the vessel wall has been found to be a consistent feature of the development of atherosclerotic plaque (25), and vasa vasorum neovascularization precedes endothelial dysfunction (26). Endothelial dysfunction could be a feature linking retinopathy and large-vessel disease. However, in the Hoorn Study applying the method of flow-mediated vasodilatation, endothelial dysfunction–related mechanisms were not clearly associated with retinopathy (27). In the development of retinopathy, vascular endothelial growth factor acts as a primary regulator, and retinal hypoxia and hyperglycemia interact as promoting factors, with possible roles of IGF, transforming growth factor, tumor necrosis factor-α, and epidermal growth factor (28), as well as cyclooxygenase-2 and nitric oxide (29). Inflammation may be important in the pathogenesis of both macrovascular (30–34) and microvascular disease (35–37).

Elegant studies of Brownlee et al. (38) have shown that a single unifying process of diabetes complications is hyperglycemia-induced overproduction of superoxide by the mitochondrial electron transport chain. Mitochondrial overproduction of superoxide activates four damaging pathways: polyol pathway, hexosamine pathway, protein kinase C pathway, and advanced glycation end products formation. There is no doubt that these pathways lead to microvascular complications. However, in addition to hyperglycemia, other risk factors are operative in the development of macrovascular complications, among them "conventional risk factors" and insulin resistance. Insulin resistance is a characteristic finding in type 2 diabetes, but long-lasting hyperglycemia also induces insulin resistance in type 1 diabetes. High circulating free fatty acid levels induce mitochondrial overproduction of reactive oxygen species and activate protein kinase C pathway, which leads to the formation of advanced glycation end products.

The major limitation of our study is

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Table 3—*Cox model for all-cause, CVD, and CHD mortality in 425 type 2 diabetic men and 399 type 2 diabetic women without prior CVD at baseline with overall, background, and proliferative retinopathy compared with subjects with no retinopathy*

	Overall versus no retinopathy		Background versus no retinopathy		Proliferative versus no retinopathy		*P* value for interaction sex × retinopathy		
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Overall	Background	Proliferative
All-cause mortality									
Model I									
Men	1.23 (0.94–1.61)	0.127	1.09 (0.81–1.47)	0.573	2.24 (1.33–3.78)	0.002			
Women	1.71 (1.31–2.25)	<0.001	1.63 (1.23–2.17)	0.001	2.74 (1.40–5.38)	0.003			
All	1.44 (1.19–1.74)	<0.001	1.32 (1.08–1.62)	0.007	2.52 (1.67–3.79)	<0.001	**0.085**	**0.052**	0.581
Model II									
Men	1.49 (1.11–1.99)	0.007	1.34 (0.98–1.83)	0.063	3.05 (1.70–5.45)	<0.001			
Women	1.66 (1.22–2.26)	0.001	1.61 (1.17–2.22)	0.003	2.92 (1.41–6.06)	0.004			
All	1.58 (1.28–1.95)	<0.001	1.48 (1.19–1.84)	<0.001	3.06 (1.96–4.78)	<0.001			
CVD mortality									
Model I									
Men	1.15 (0.81–1.62)	0.443	0.97 (0.65–1.43)	0.871	2.42 (1.28–4.54)	0.006			
Women	1.91 (1.38–2.63)	<0.001	1.80 (1.28–2.52)	0.001	3.22 (1.50–6.93)	0.003			
All	1.49 (1.18–1.88)	0.001	1.34 (1.04–1.73)	0.024	2.91 (1.79–4.71)	<0.001	**0.039**	**0.021**	0.561
Model II									
Men	1.49 (1.03–2.17)	0.036	1.30 (0.86–1.96)	0.207	3.32 (1.62–6.78)	0.001			
Women	1.80 (1.24–2.59)	0.002	1.71 (1.17–2.51)	0.006	3.17 (1.38–7.30)	0.007			
All	1.65 (1.28–2.14)	<0.001	1.52 (1.15–1.99)	0.003	3.43 (2.01–5.85)	<0.001			
CHD mortality									
Model I									
Men	1.06 (0.71–1.60)	0.771	0.94 (0.60–1.48)	0.791	1.94 (0.89–4.25)	0.096			
Women	2.19 (1.49–3.22)	<0.001	1.96 (1.30–2.96)	0.001	5.01 (2.29–10.96)	<0.001			
All	1.51 (1.15–2.00)	0.003	1.34 (0.99–1.81)	0.056	3.05 (1.76–5.29)	<0.001	**0.012**	**0.020**	**0.080**
Model II									
Men	1.32 (0.85–2.04)	0.220	1.18 (0.74–1.89)	0.493	2.54 (1.07–6.04)	0.034			
Women	1.96 (1.27–3.04)	0.003	1.79 (1.13–2.85)	0.014	4.98 (2.06–12.06)	<0.001			
All	1.63 (1.20–2.20)	0.002	1.47 (1.06–2.03)	0.020	3.45 (1.87–6.36)	<0.001			

Two levels of adjustment are used (model I: age, sex [in the analysis for all], and area of residence; model II: model I + A1, current smoking, hypertension, total cholesterol, HDL cholesterol, duration of diabetes, and urinary protein [log]). Bold data indicate significant interaction at $P < 0.10$.

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Table 4—*Studies on retinopathy predicting CVD in type 2 diabetes*

Reference	Study subjects	Follow-up; study end points	Relative risk (95% CI)	Adjusting factors
Miettinen et al. (8)	1,040 Finnish type 2 diabetic subjects	7-year follow-up of CHD events	Background 1.38 (0.95–2.00); proliferative 2.12 (1.02–4.39)	Age, area, sex, total cholesterol, HDL cholesterol, triglycerides, smoking, hypertension, urinary protein, A1C
Klein et al. (39)	The Wisconsin Epidemiologic Study of Diabetic Retinopathy: 1,370 subjects with age of onset of diabetes >30 years	16-year follow-up of all-cause, CHD, and stroke mortality	All-cause mortality: mild nonproliferative 1.34 (1.29–1.71) and proliferative 1.89 (1.43–2.50); CHD mortality: mild nonproliferative 1.21 (0.95–1.53) and proliferative 1.43 (0.94–2.17); stroke mortality: mild nonproliferative 1.30 (0.92–1.85) and proliferative 1.88 (1.03–3.43)	Age, sex, duration of diabetes, A1C, systolic blood pressure, prior CVD, smoking (pack-years), diuretic use
Fuller et al. (5)	The World Health Organization Multinational Study of Vascular Disease in Diabetes: 1,390 type 2 diabetic subjects	12-year follow-up of CVD mortality	1.2 (0.8–1.8) in men and 2.7 (1.8–4.1) in women	Age, duration of diabetes, systolic blood pressure, cholesterol, smoking, proteinuria, electrocardiographic abnormalities, glucose
van Hecke et al. (4)	The Hoorn Study: 631 nondiabetic and diabetic subjects	10.7-year follow-up (median) of all-cause and CVD mortality	All-cause mortality in diabetic subjects 2.05 (1.23–3.44); CVD mortality in diabetic subjects 2.20 (1.03–4.70)	Age and sex
Cusick et al. (40)	The Early Treatment Diabetic Retinopathy Study (ETDRS): 2,267 type 2 diabetic subjects	5-year follow-up of all-cause mortality	Moderate nonproliferative 1.27 (0.94–1.72); severe nonproliferative 1.48 (1.03–2.15); mild proliferative 1.28 (0.80–2.06); moderate/high proliferative 2.02 (1.28–3.19)	Age, sex, BMI, A1C, total cholesterol, triglycerides, fibrinogen, cigarette smoking, daily insulin use, the use of antihypertensive medications, other baseline diabetes complications
Targher et al. (9)	The Valpolicella Heart Study: 248 type 2 diabetic subjects who developed CVD during follow-up and 496 type 2 diabetic control subjects	5-year follow-up of CVD events	Nonproliferative 1.8 (1.2–2.3); proliferative 4.1 (2.0–8.9)	Age, sex, BMI, smoking history, plasma lipids, A1C, diabetes duration, diabetes treatment

that the evaluation of retinopathy was based on fundoscopy. Although the κ-coefficient between the retinopathy categories determined by the two observers was high (0.84), it is possible that subtle changes may have been missed. On the other hand, the findings of our study were consistent with other studies evaluating retinopathy with more sophisticated techniques (Table 4). Moreover, if subtle retinopathy changes would have remained unnoticed, this would have weakened rather than strengthened our findings.

In conclusion, in type 2 diabetes proliferative retinopathy in men and background, proliferative, and overall retinopathy in women predicted all-cause, CVD, and CHD death. These associations were independent of conventional CVD risk factors, glycemic control, duration of diabetes, and proteinuria. Thus, it is likely that retinopathy indicates the presence of such common factors in the pathophysiology of diabetic microvascular and macrovascular disease that are not included in the conventional risk factor assessment of CVD. The sex difference observed in the association of background retinopathy with macrovascular disease warrants closer examination.

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