Diabetic Retinopathy and the Risk of Coronary Heart Disease

The Atherosclerosis Risk in Communities Study

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OBJECTIVE — We sought to examine the relation of diabetic retinopathy to incident coronary heart disease (CHD).

RESEARCH DESIGN AND METHODS — A population-based, prospective cohort study consisting of 1,524 middle-aged individuals with type 2 diabetes without prevalent CHD and stroke at baseline was conducted. Diabetic retinopathy signs were graded from retinal photographs according to the Early Treatment for Diabetic Retinopathy Study severity scale. Incident CHD events (myocardial infarction, fatal CHD, or coronary revascularization) were identified and validated following standardized protocols.

RESULTS — In our study, 214 (14.7%) participants had diabetic retinopathy. Over an average follow-up of 7.8 years, there were 209 (13.7%) incident CHD events. After controlling for age, sex, race, study center, fasting glucose, A1C, duration of diabetes, blood pressure, antihypertensive treatment, cigarette smoking, BMI, and lipid profile, the presence of diabetic retinopathy was associated with a twofold higher risk of incident CHD events (hazard rate ratio [HR] 2.07 [95% CI 1.38–3.11]) and a threefold higher risk of fatal CHD (3.35 [1.40–8.01]). Further adjustments for inflammatory markers, carotid artery intima-media thickness, or nephropathy had minimal impact on the association. The increased risk of CHD was significant in both men (1.89 [1.08–3.31]) and women (2.16 [1.16–4.02]) with diabetic retinopathy.

CONCLUSIONS — In individuals with type 2 diabetes, the presence of retinopathy signifies an increased CHD risk, independent of known risk factors. Our data support the role of microvascular disease in the pathogenesis of CHD in diabetes.

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Coronary heart disease (CHD) is a leading cause of mortality in individuals with type 2 diabetes (1–3). While macrovascular disease is the primary pathogenic mechanism underlying CHD in the general population, microvascular disease may play a prominent role in CHD development in diabetic individuals (4–9).

Diabetic retinopathy is a specific marker of microvascular disease in type 2 diabetes. It is unclear, however, if the presence of diabetic retinopathy signifies an increased risk of CHD. There are limited studies that have provided inconclusive evidence regarding the association of retinopathy with CHD risk in diabetic individuals (10–16). Some studies have used imprecise methods to detect retinopathy (e.g., direct ophthalmoscopy), and many have not explored the relationship of diabetic retinopathy with specific CHD events (e.g., myocardial infarction vs. fatal CHD). Furthermore, in the general population, retinal microvascular signs appear to predict CHD risk more strongly in women than in men (17,18). This sex difference in CHD risk is not just an isolated observation (16) but is also supported by some experimental and theoretical underpinnings (19–22). Whether such sex difference exists in the association of diabetic retinopathy with CHD is unclear, but it has been suggested in a recent study (16). To address these uncertainties, we examined the relation of diabetic retinopathy to incident CHD in a large population-based cohort of men and women with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The Atherosclerosis Risk In Communities (ARIC) Study is a population-based study of 15,792 individuals aged 45–64 years at their first examined in 1987–1989 (23). A second examination was conducted in 1990–1992 and a third in 1993–1995 when retinal photographs were taken on all participants (24). Of the 12,887 participants who returned for the third examination, 2,341 had diabetes, defined as fasting serum glucose levels ≥7.0 mmol/l, nonfasting levels ≥11.1 mmol/l, diabetes medications use, or physician diagnosis of diabetes. Of these, we excluded those without retinal photographs or ungradable photographs (n = 508), without blood pressure measurement (n = 5), and with prevalent CHD or stroke (according to the ARIC criteria) (n = 286) or silent myocardial infarction, defined as electrocardiographic interval changes consistent with an ischemic event (n = 18), leaving 1,524 participants for this analysis. Characteristics of participants with and without gradable photographs have been

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Abbreviations: ARIC, Atherosclerosis Risk In Communities; CHD, coronary heart disease; IMT, intima-media thickness.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of study population, by diabetic retinopathy severity*

	Diabetic retinopathy			
	None	Mild/moderate	Severe	*P**
n	1,242	174	40	
Age (years)	60.1 ± 5.6	60.0 ± 5.6	59.6 ± 5.5	0.86
Male (%)	47.3	40.2	40.0	0.15
African Americans (%)	30.0	48.6	50.0	<0.001
Hypertension (%)	55.3	71.9	72.5	<0.001
Mean arterial blood pressure (mmHg)	91.6 ± 9.5	93.1 ± 10.4	94.2 ± 11.7	0.04
Cigarette smoking, current (%)	16.1	12.8	22.7	0.22
Cigarette smoking, former (%)	43.4	35.7	36.4	0.95
BMI (kg/m^2)	31.4 ± 6.0	32.0 ± 6.3	31.0 ± 7.0	0.40
High school graduate (%)	74.5	65.1	79.5	0.01
Fasting glucose (mg/dl)	155.8 ± 58.0	214.0 ± 88.4	219.3 ± 80.9	<0.001
Total cholesterol (mg/dl)	209.6 ± 41.0	204.6 ± 40.9	212.4 ± 43.7	0.28

Data are means ± SD or proportions. **P* value is based on χ^2 (categorical) and ANOVA (continuous), comparing differences for individual variables across diabetic retinopathy categories.

presented elsewhere (24,25). Data regarding the presence or absence of macular edema and hard exudates were available for all the included participants. However, due to the differential gradability of retinal photographs, data regarding retinopathy severity and the presence or absence of microaneurysms and retinal hemorrhages were available for most but not all participants.

Assessment of diabetic retinopathy and CHD

One randomly selected eye was photographed using a nonmydriatic camera and evaluated by masked graders according to standardized protocols (24,25). Retinopathy was graded according to the Early Treatment of Diabetic Retinopathy Study severity scale and defined for analysis as absent or present, as well as absent, mild/moderate (minimal and moderate nonproliferative retinopathy), and severe (severe nonproliferative and proliferative retinopathy) (24). Individual retinopathy signs were defined separately. Prevoius ARIC publications have demonstrated excellent reproducibility for the detection of well-defined retinopathy signs (κ values ranging from 0.80 to 0.99 for retinal microaneurysms and hemorrhages) (26).

Detailed description of CHD ascertainment in the ARIC Study and quality control procedures have been published previously (27). An incident CHD event was defined as an incident myocardial infarction, a fatal CHD event, or a myocardial revascularization procedure (e.g., coronary angioplasty or coronary artery bypass graft surgery), subsequent to retinal photography at the third examination (17).

Assessment of cardiovascular risk factors

Participants underwent standardized evaluations for cardiovascular risk factors at all examinations (28). Duration of diabetes was defined as the number of years from age at diagnosis to the clinical examination at the third visit. If at any of the three visits the participant was diagnosed with diabetes (using the criteria described earlier), then that was taken as the time of diagnosis of diabetes, unless at the third visit interview the participant had reported an earlier age at diagnosis. Use of diabetes medications was based on self-report at the time of retinal photography. For analysis, we used data from the third examination, except for 6-year mean arterial blood pressure, averaged over the first three examinations (to provide a more representative measurement for blood pressure); A1C and carotid artery intima-media thickness (IMT) (29), measured only at the second examination; and inflammatory markers (serum white blood cell counts and fibrinogen levels), measured only at the first examination. Nephropathy was defined as an increase in serum creatinine of at least 0.4 mg/dl or a death or hospitalization due to chronic kidney disease within the 6-year period between the second and fourth examinations (30).

Statistical analysis

We compared unadjusted survival curves by presence of retinopathy and used Cox regression to determine hazard rate ratio (HR) for CHD in relation to diabetic retinopathy, initially controlling for age, sex, race, and center and additionally for education, diabetes duration, diabetes medications, fasting glucose, A1C, 6-year mean arterial blood pressure, antihypertensive treatment, cigarette smoking, BMI, total and HDL cholesterols, and triglycerides. In supplementary analyses, we further adjusted for risk factors not available on all participants and measured at different examination visits (inflammatory markers, carotid IMT, and nephropathy). We also analyzed incident myocardial infarction, fatal CHD, and myocardial revascularization procedure as separate end points. Finally, we tested for consistency of the associations in stratified analyses by categories of A1C levels, sex, race, and hypertension status. Interaction terms for these variables were also tested.

RESULTS — Participants with retinopathy were more likely to be African American and to have hypertension, higher blood pressure, and higher glucose levels than participants without retinopathy (Table 1).

Among all participants, 214 (14.7%) had diabetic retinopathy. Over 7.8 years of follow-up, there were 209 (13.7%) incident CHD events. These included 34 fatal CHD, 110 incident myocardial infarction, and 154 cardiac revascularization procedures. Figure 1 illustrates that participants with diabetic retinopathy were more likely to develop CHD than those without retinopathy.

Table 2 shows that after adjustments for risk factors, diabetic retinopathy was associated with incident CHD (HR 2.07). The risks of CHD were higher in individuals with more severe retinopathy (HR 1.96 for mild retinopathy vs. 2.69 for moderate/severe retinopathy). Higher

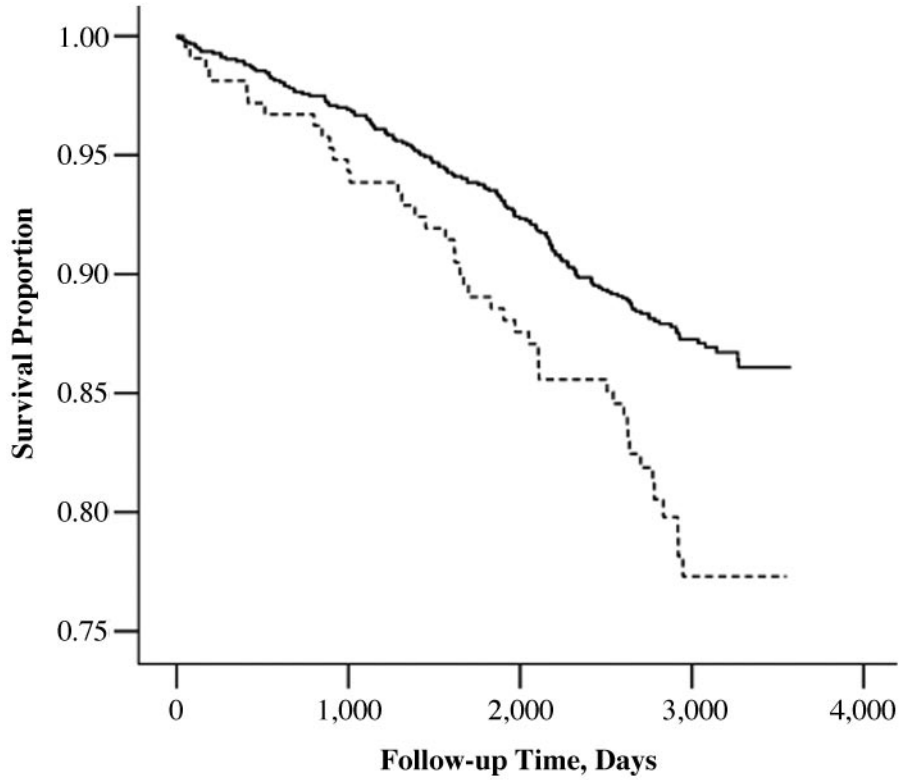

Figure 1—*CHD-free survival in participants with (solid line) and without (dashed line) diabetic retinopathy.*

risks were also seen for most retinopathy lesions but were statistically significant only for retinal microaneurysms.

The pattern of association of diabetic retinopathy with fatal CHD was similar but stronger overall (Table 2). Diabetic retinopathy was also associated with specific events: incident myocardial infarction (HR 1.88 [95% CI 1.06–3.32]) and

Table 2—*Incidence and HRs of CHD by presence of diabetic retinopathy*

		Incident CHD events			Fatal CHD	
	No. at risk	No. (%) of events	Age-sex-race HR (95% CI)*	Multivariate HR (95% CI)†	No. (%) of events	Multivariate HR (95% CI)†
Diabetic retinopathy						
Absent	1,242	153 (12.3)	1.0	1.0	19 (1.5)	1.0
Present	214	44 (20.6)	2.21 (1.56–3.14)	1.99 (1.33–3.00)	13 (6.1)	3.00 (1.27–7.09)
Retinopathy grade						
Absent	1,242	153 (12.3)	1.0	1.0	19 (1.5)	1.0
Mild/moderate	174	34 (19.5)	1.98 (1.34–2.93)	1.89 (1.22–2.92)	9 (5.2)	2.55 (0.99–6.53)
Severe	40	10 (25.0)	3.50 (1.83–6.67)	2.57 (1.25–5.27)	4 (10)	5.38 (1.54–18.82)
Microaneurysms						
Absent	1,276	160 (12.5)	1.0	1.0	21 (1.6)	1.0
Present	183	39 (21.3)	2.27 (1.58–3.28)	1.99 (1.30–3.06)	11 (6.0)	2.75 (1.10–6.83)
Retinal hemorrhages						
Absent	1,345	175 (13.0)	1.0	1.0	23 (1.7)	1.0
Present	155	29 (18.7)	1.97 (1.31–3.96)	1.41 (0.90–2.22)	9 (5.8)	2.55 (1.03–6.29)
Hard exudates						
Absent	1,408	186 (13.2)	1.0	1.0	25 (1.8)	1.0
Present	116	23 (19.8)	1.94 (1.24–3.03)	1.35 (0.84–2.19)	8 (2.2)	2.43 (0.96–6.15)
Macular edema						
Absent	1,443	195 (13.5)	1.0	1.0	28 (1.9)	1.0
Present	81	14 (17.3)	1.39 (0.79–2.44)	1.00 (0.56–1.79)	5 (6.2)	1.82 (0.60–5.55)

*HRs (95% CIs), adjusted for age, sex, race, and examination center. †HRs (95% CIs), adjusted for age, sex, race, examination center, BMI, 6-year mean arterial blood pressure, use of antihypertensive treatment, duration of diabetes, diabetes medications, cigarette smoking status, education status, and levels of serum fasting glucose, A1C, total cholesterol, HDL cholesterol, and triglycerides.

cardiac revascularization (1.93 [1.17–3.19]) (data not shown).

In supplementary analyses, the association of diabetic retinopathy with incident CHD remained significant after additional adjustments for inflammatory markers (HR 2.08 [95% CI 1.39–3.12]), carotid artery IMT (1.99 [1.30–3.04]), and nephropathy (1.91 [1.18–3.08]).

Finally, in stratified analyses, the association of retinopathy with CHD was present in individuals with A1C ≤7% (HR 1.93 [95% CI 1.08–3.44]) and A1C >7% (2.10 [1.14–3.86]), in men (1.89 [1.08–3.31]) and women (2.16 [1.16–4.02]), in Caucasians (2.16 [1.36–3.42]) and African Americans (1.59 [0.67–3.82]), and in individuals with (2.08 [1.33–3.23]) and without (2.10 [1.00–4.43]) hypertension. Interaction terms for these variables were not statistically significant ($P > 0.15$).

CONCLUSIONS — Our data show that in individuals with type 2 diabetes, the presence of signs of retinopathy was associated with a twofold higher risk of incident CHD and threefold higher risk of fatal CHD, independent of glycemic levels, cardiovascular risk factors, and large-vessel atherosclerosis. This association appears to be graded with retinopathy severity and was significant in men and women, even in those without hypertension. Our findings support the theory that microvascular disease may contribute to the development of CHD in people with diabetes.

Epidemiological data from previous studies have provided inconclusive evidence regarding the association of retinopathy with CHD in people with type 2 diabetes (10–16). Studies in Finland (10,16) and Milan (11) have reported an increased CHD risk among diabetic individuals with retinopathy, while controlling for cardiovascular risk factors. Other studies, however, suggest that the association of diabetic retinopathy with CHD is largely due to shared risk factors (12,13,15). A recent study of 824 type 2 diabetic patients, using fundoscopic examinations to evaluate retinopathy, showed a sex difference in the association of background diabetic retinopathy with CHD death, raising the possibility that microvascular disease might be more important in the development of CHD in women than in men (16). However, in our study, based on standardized assessment of retinal photographs, a significantly excess risk of CHD was observed in both men and women. Although a slightly higher risk of CHD was observed in women with diabetic retinopathy, which is consistent with a recent report (16), we found no statistically significant interaction with sex.

Our findings are consistent with observations that diabetic retinopathy is associated with subclinical coronary pathology. Studies have shown that diabetic individuals with retinopathy are more likely to have myocardial perfusion defects (11,31,32), poorer coronary flow reserve (33), and lower coronary collateral score (34) than those without retinopathy. Moreover, diabetic retinopathy has also been associated with higher degrees of coronary calcification (35) and more diffuse and severe coronary artery stenosis on angiograms (36). These observations, in conjunction with ours, support the concept that micro- and macrovascular complications of diabetes share common pathogenic mechanisms (16,37) beyond those related to the risk factors adjusted for in our multivariate models. It is uncertain what these pathways may be (e.g., endothelial dysfunction, oxidative stress, and platelet dysfunction), but one potential candidate that has gained recent interest involves the advanced glycation end products, which can cause both micro- and macrovascular injury in diabetes (38). Further research is clearly required to elucidate the exact pathophysiological mechanisms underlying the development of micro- and macrovascular complications of diabetes.

Strengths of our study include a large population-based cohort, standardized ascertainment of diabetic retinopathy and CHD events, and detailed collection and adjustment of potential confounders. Potential limitations of our study should also be discussed. First, diabetic retinopathy was graded from a single retinal photograph taken without pharmacological pupil dilation, and a significant proportion of photographs were ungradable. Thus, retinopathy might have been underestimated. Such misclassification bias might have potentially weakened our results, and, therefore, the real effect of diabetic retinopathy on CHD risk could be stronger than what we presented herein. Second, selection biases could have distorted the associations, as retinal photography was performed at the third examination, while some variables used in our analyses (A1C and carotid IMT) were available only at the second examination. However, we have no reason to believe that such biases are differential in nature. Lastly, the definition of nephropathy used in our study is not specific for nephropathy caused by diabetes. While microalbuminuria and/or proteinuria are more specific indicators of diabetic nephropathy, the ARIC Study did not assess these measures for all the participants. Therefore, residual confounding from diabetic nephropathy, though unlikely to be substantial, cannot be totally excluded.

In conclusion, we demonstrate an association of diabetic retinopathy with increased risk of CHD events, independent of cardiovascular risk factors, diabetes duration and control, and large artery atherosclerosis. Our data support the concept that microvascular disease may also contribute to CHD risk and suggest that individuals with diabetic retinopathy may warrant a more careful cardiovascular assessment and follow-up.

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