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Diabetic Retinopathy and Risk of Heart Failure

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Objectives The purpose of this study was to examine the association of diabetic retinopathy with incident heart failure (HF).

Background Microvascular disease might play a more prominent role in the pathogenesis of diabetic cardiomyopathy, a major cause of HF in diabetes. Whether diabetic retinopathy, a microvascular complication of diabetes, predicts HF is unclear.

Methods A population-based study included 1,021 middle-aged type 2 diabetic persons with normal renal function and free of clinical coronary heart disease or HF at baseline. Diabetic retinopathy signs were graded from retinal photographs. Incident HF events were prospectively identified from hospital stay and death records.

Results There were 125 (12.8%) participants with diabetic retinopathy. After 9-year follow-up, 106 (10.1%) participants developed incident HF events. Persons with retinopathy were more likely to develop HF (cumulative incidence of 21.6%) than those without retinopathy (cumulative incidence of 8.5%). After controlling for age, gender, race, smoking, diabetes duration, insulin use, blood pressure, lipid profile, and other risk factors, participants with retinopathy had more than 2.5-fold higher risk of developing HF than those without retinopathy (hazard ratio [HR] 2.71; 95% confidence interval [CI] 1.46 to 5.05). This association remained significant after further adjustments for glycemic control, carotid atherosclerosis, and serum markers of endothelial dysfunction (HR 2.20, 95% CI 1.08 to 4.47).

Conclusions The presence of diabetic retinopathy signifies an excess risk of HF, independent of known risk factors. This further supports a contribution of microvascular disease to the development of HF in people with diabetes. (J Am Coll Cardiol 2008;51:1573–8) © 2008 by the American College of Cardiology Foundation

Heart failure (HF) is a major cause of morbidity, hospital stays, and mortality in diabetic populations (1–3). Although epicardial coronary stenosis and hypertension are strongly related to HF risk in the general population, diabetic hearts might fail even in the absence of epicardial coronary artery disease and other risk factors. This phenomenon has been attributed to diabetic cardiomyopathy, a complex and incompletely understood disease process recently linked to dysfunction of the coronary microcirculation (4,5). In support of this hypothesis, studies show that microvascular pathology is common in the diabetic myocardium, evidenced by presence of microaneurysms (6) and by quantitative demonstration of perfusion defects from radiological studies (5,7). Hyperglycemia has also been associated with disturbances in microvascular homeostasis in the myocardium (e.g., endothelial cell apoptosis) (8–10), which might lead to myocardial dysfunction in the absence of epicardial coronary disease or systemic hypertension (11,12).

See page 1579

Retinopathy is the most common and specific microvascular complication of diabetes. Previous studies have reported associations of diabetic retinopathy with risks of cardiovascular diseases, such as stroke and coronary heart disease (13–17). However, there are only limited data on whether this microvascular complication is related to HF risk (18–20). In the MESA (Multi-Ethnic Study of Atherosclerosis), we reported a cross-sectional association between retinopathy signs and left ventricular concentric remodeling, a precursor of clinical HF (21). Here, we

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JACC Vol. 51, No. 16, 2008
April 22, 2008:1573–8

Abbreviations and Acronyms

CI = confidence interval

HbA1c = glycosylated hemoglobin

HR = hazard ratio

IMT = intima-media thickness

examined prospectively the association of diabetic retinopathy with incident HF in a population-based cohort of diabetic persons free of clinical heart disease.

Methods

Study population. The ARIC (Atherosclerosis Risk In Communities) study is a population-based cohort study that included 15,792 persons, ages 45 to 64 years at recruitment in 1987 to 1989 (22). Retinal photographs were first obtained at the third examination (1993 to 1995) (23). Of the 12,642 participants who returned for this examination, 1,916 had diabetes mellitus, defined as fasting serum glucose levels of ≥7.0 mmol/l, nonfasting levels of ≥11.1 mmol/l, use of diabetic medications, or physician diagnosis of diabetes (23). Of these, we excluded those whose race was neither white nor African-American (n = 8) and those with HF at the time of retinal photography (n = 162) (either taking medication for HF or with manifest HF according to the Gothenburg Criteria) (24). In addition, we also excluded participants with prevalent coronary heart disease (n = 221) (25) or renal dysfunction (n = 217) (estimated glomerular filtration rate <90 ml/min/1.73 m^2) (24), because they are 2 competing causes of HF. Of the remaining 1,308 persons, photographs were gradable for at least 1 retinopathy sign in 1,021 persons. Characteristics of participants with and without gradable retinal photographs have been described elsewhere (23). Ungradable retinal photographs were due to either no photographs or photographs of insufficient quality.

Assessment of diabetic retinopathy. One randomly selected eye was photographed with a 45-degree nonmydriatic camera and evaluated by masked graders according to standardized protocol (13,14,23). Retinopathy was graded according to the Early Treatment of Diabetic Retinopathy Study severity scale and defined for analysis as absent or present and also as absent, mild (minimal nonproliferative retinopathy), moderate (moderate nonproliferative retinopathy), and severe (severe nonproliferative or proliferative retinopathy) (23). Individual retinopathy signs and the presence of macular edema were defined separately.

Assessment of HF. Detailed description of HF ascertainment in the ARIC study and quality control procedures has been published elsewhere (18,24). In brief, an incident HF event was defined as a hospital discharge diagnosis coded as HF (ICD-9, code 428 or 518.4) (hospital stay and emergency room visits) or a death certificate with an underlying primary or secondary cause of death coded as HF (ICD-9-CM code 428 or ICD-10 code I50) from the time of retinal photography (third examination, 1993 to 1995) to December 31, 2003.

Assessment of cardiovascular risk factors. Participants underwent standardized evaluations for blood pressure and other cardiovascular risk factors at all examinations (26,27). For analysis, we used data collected from the third examination (when retinal photography was performed), except for data (glycosylated hemoglobin [HbA1c], fibrinogen, white blood cells, von Willibrand factor, factor VIII, carotid intima-media thickness [IMT]) that were only available from the second examination (1990 to 1992) (14). The mean difference in time between second and third examinations was 3.03 years (95% confidence interval [CI] 3.02 to 3.05).

Statistical analysis. We compared unadjusted survival curves by absence or presence of retinopathy. Follow-up time was defined as the number of days from retinal photography to the date of the first HF event, last contact, or December 31, 2003. We used Cox regression to determine hazard ratio (HR) and its 95% CI for HF in relation to diabetic retinopathy, initially controlling for age, gender, race, and study center (Model 1). The proportional hazard assumption was checked by plotting the "log-minus-log" plot of the estimated survival functions against log time. Our multivariate analysis included additional adjustments for traditional cardiovascular risk factors measured at the third examination when retinal photography was performed (Model 2) and further adjustments for glycemic control (HbA1c), carotid atherosclerosis (IMT), and biomarkers of endothelial dysfunction (factor VIII and von Willebrand factor) measured at the second examination (Model 3). In supplementary analysis, we performed stratified analyses by gender, race and hypertension status, adjusting for Model 2 covariates. We also tested for potential interactions for these variables.

Results

Participants with retinopathy at baseline were more likely to be women, African Americans, current smokers, insulin users, and to have hypertension and higher levels of serum HbA1c, von Willebrand factor and factor VIII than participants without retinopathy (Table 1). Over the 8.9 years (SD 2.3) of follow-up, there were 106 incident HF cases identified. Of the 125 participants who developed HF, 36 (34%) died. Persons with retinopathy were more likely to develop HF (cumulative incidence of 21.6%) than those without retinopathy (cumulative incidence of 8.5%), as shown in Figure 1.

Table 2 shows that after initial adjustments for age, gender, and race/center (Model 1) and further adjustments for cardiovascular risk factors (Model 2), the presence of diabetic retinopathy was significantly associated with incident HF, with higher risks seen for some specific retinopathy lesions, such as retinal microaneurysms and hard exudates. The association remained significant after further adjustments for HbA1c, carotid IMT, and biomarkers of endothelial dysfunction (Model 3).

Stratified analyses showed that the association of retinopathy with HF was present in both whites (HR 2.39, 95% CI

Table 1 Baseline Characteristics of Study Population by Diabetic Retinopathy

	Diabetic Retinopathy		
	Absent (n = 854)	Present (n = 125)	p Value*
Men, %	47.4	37.6	0.04
African Americans, %	25.4	47.2	<0.001
Hypertension, %	49.4	33.6	0.001
Cigarette smoking, current, %	40.8	56.0	0.006
Insulin use, %	41.1	58.9	<0.001
Age, yrs	59.8 (5.7)	58.9 (5.2)	0.09
6-yr MABP, mm Hg	91.2 (9.1)	92.1 (10.5)	0.32
Body mass index, kg/m^2	30.9 (5.7)	31.5 (6.2)	0.32
Glycosylated hemoglobin, %	6.3 (1.3)	8.6 (2.1)	<0.001
HDL cholesterol, mg/dl	45.8 (14.9)	48.8 (16.9)	0.04
Triglyceride, mg/dl	178.5 (125.0)	157.8 (103.6)	0.08
Total cholesterol, mg/dl	209.0 (40.8)	206.9 (42.6)	0.59
Fibrinogen, mg/dl	308.2 (62.2)	308.2 (61.3)	0.99
White cell count, 10^9 cells/dl	6.4 (2.2)	6.1 (1.8)	0.16
von Willebrand factor, mg/dl	120.2 (44.8)	136.0 (49.6)	<0.001
Factor VIII, mg/dl	137.5 (37.5)	153.2 (46.9)	<0.001
Creatinine, mg/dl	109.5 (9.2)	110.9 (8.8)	0.11
Common carotid IMT, mm	0.76 (0.18)	0.77 (0.17)	0.69

Data are means (SD) or proportions (%). *The p value on the basis of chi-square (categorical), and analysis of variance (continuous), comparing differences for individual variables across diabetic retinopathy categories.

HDL = high-density lipoprotein; IMT = intima-media thickness; MABP = mean arterial blood pressure.

1.04 to 5.51) and African Americans (HR 7.88, 95% CI 2.40 to 25.92), hypertensive (HR 2.22, 95% CI 1.08 to 4.54) and normotensive (HR 5.59, 95% CI 1.86 to 16.82) participants, and in both women (HR 2.98, 95% CI 1.34 to 6.64) and men (HR 3.67, 95% CI 1.22 to 11.01). Potential interactions were also tested for these stratified variables and for glomerular filtration rate, and there were no significant ($p < 0.10$) interactions found.

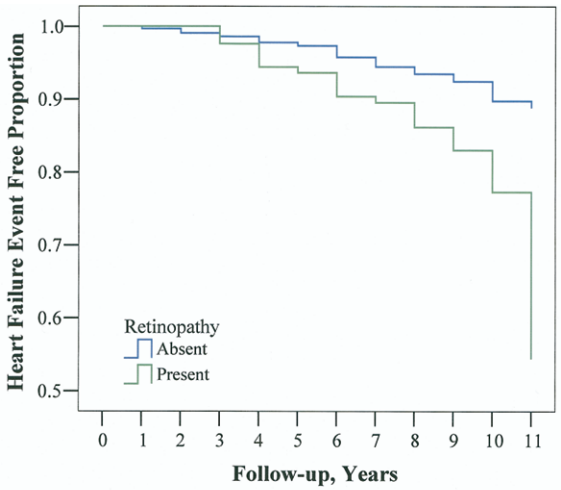
Discussion

In this prospective cohort study of diabetic persons without clinical heart disease and renal dysfunction, we report an association of diabetic retinopathy with incident HF events. Participants with diabetic retinopathy were more than twice as likely to develop HF as those without retinopathy, even after controlling for conventional cardiovascular risk factors, diabetes duration, glycemic control, carotid atherosclerosis, and markers of endothelial dysfunction. This association was somewhat stronger in people without hypertension than those with hypertension.

Our findings are consistent with previous studies that have reported associations of diabetic retinopathy with heart disease. Over 2 decades ago, the Framingham Heart and Eye Study showed that diabetic retinopathy was associated with prevalent cardiovascular disease (odds ratio 14.3, 95% CI 2.7 to 101.9), an end point that included HF, coronary heart disease, intermittent claudication, and stroke (19). Studies in Finland (16), Milan (15), and the U.S. (14,28) have all reported an excess risk of coronary heart disease among diabetic persons with retinopathy compared with those without retinopathy. These studies, however, did not specifically evaluate associations of diabetic retinopathy with HF.

Earlier clinical studies have indicated that diabetic retinopathy (or other microvascular complications) is associated with left ventricular diastolic dysfunction (29,30) and presence of diabetic cardiomyopathy (2,31–33). Furthermore, there is evidence from radiological and histological studies that diabetic retinopathy is associated with subclinical coronary microvascular pathologies (6,7,34–37). However, there are limited prospective data on the relationship of diabetic retinopathy with clinical HF events. Therefore, our study addresses an important gap in the published data.

We have previously reported an association of retinopathy signs with incident HF in the general population (HR 1.96, 95% CI 1.51 to 2.54) (18). In this study, the interpretation of results from sub-group analysis of the diabetic participants was limited, because a number of important confounders (e.g., renal dysfunction, large artery atherosclerosis), including ones that are specific for diabetic populations (diabetes duration and glycemic control), were not accounted for. In addition, retinopathy severity was also not evaluated in our previous analysis. In our current study specifically focusing on diabetic participants with longer follow-up, we confirm that diabetic retinopathy, even in its mildest form (minimal nonproliferative), predicts a higher risk of HF, independent of traditional and nontraditional



No. at Risk by Follow-up Years

	0	1	2	3	4	5	6	7	8	9	10
Retinopathy	125	125	125	122	118	116	109	106	83	44	14
No Retinopathy	854	851	846	842	833	821	798	778	763	490	192

Figure 1 Heart Failure Free Survival in Participants With and Without Diabetic Retinopathy

Participants with diabetic retinopathy were more likely to develop incident heart failure than those without retinopathy in the Atherosclerosis Risk In Communities Study.

JACC Vol. 51, No. 16, 2008
April 22, 2008:1573–8

Table 2 Incidence and HRs of Heart Failure by Presence of Diabetic Retinopathy, the Atherosclerosis Risk in Communities Study

	At Risk (n)	Incident Heart Failure			
		Events n (%)	Model 1 HR (95% CI)*	Model 2 HR (95% CI)*	Model 3 HR (95% CI)*
Diabetic retinopathy					
Absent	854	73 (8.5)	1.0	1.0	1.0
Present	125	27 (21.6)	2.61 (1.74–3.93)	2.71 (1.46–5.05)	2.20 (1.08–4.47)
Retinopathy grade					
Absent	854	73 (8.5)	1.0	1.0	1.0
Mild	45	9 (20.0)	2.99 (1.49–6.03)	3.06 (1.34–6.99)	1.91 (0.65–5.62)
Moderate-severe	80	18 (22.5)	2.88 (1.70–4.87)	2.48 (1.15–5.32)	2.38 (1.04–5.42)
Microaneurysms					
Absent	873	75 (8.6)	1.0	1.0	1.0
Present	110	25 (22.7)	2.99 (1.89–4.75)	2.83 (1.45–5.53)	2.69 (1.27–5.70)
Retinal hemorrhages					
Absent	913	85 (9.3)	1.0	1.0	1.0
Present	93	19 (20.4)	2.51 (1.51–4.19)	1.56 (0.80–3.04)	1.36 (0.65–2.88)
Cotton wool spots					
Absent	958	96 (10.0)	1.0	1.0	1.0
Present	54	9 (16.7)	1.84 (0.92–3.69)	1.18 (0.49–2.87)	0.91 (0.35–2.39)
Hard exudates					
Absent	954	91 (9.5)	1.0	1.0	1.0
Present	67	15 (22.4)	2.75 (1.58–4.79)	2.19 (1.07–4.49)	2.33 (1.10–4.93)
Macular edema					
Absent	972	99 (10.2)	1.0	1.0	1.0
Present	49	7 (14.3)	1.37 (0.63–2.95)	1.13 (0.46–2.78)	1.21 (0.49–3.02)

Model 1: adjusted for age, gender, race, and study center. Model 2: adjusted for Model 1 covariates plus body mass index, smoking status, diabetes duration, insulin use, 6-year mean arterial blood pressure, antihypertensive medication use, and serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. Model 3: adjusted for Model 2 covariates plus carotid intima-media thickness and serum glycosylated hemoglobin, factor VIII, and von Willebrand factor (data obtained at the second examination, 3 years before retinal photography; see Methods). *Adjusted hazard ratio (HR) and 95% confidence interval (CI).

cardiovascular risk factors in people free of clinical heart disease or renal dysfunction at baseline. In addition, findings in this study also extend support to our previous observation in the MESA, in which we found that diabetic individuals with retinopathy were more likely to have left ventricular concentric remodeling, a precursor for HF, as determined from cardiac magnetic resonance imaging (odds ratio 1.72, 95% CI 1.20 to 2.47) (21).

As we hypothesized previously, small vessel damage seen in the retina, reflected as diabetic retinopathy signs, might represent widespread systemic microcirculatory disease that places an increased impedance burden on the heart, in part through reflected waves (21,38,39). This in turn can lead to increased load to the heart and compromise cardiac performance (e.g., impair ventricular emptying and contractility), predisposing the development and manifestation of clinical HF. Additional studies are clearly needed to verify our hypothesis and perhaps uncover other noncirculatory mechanisms (e.g., insulin resistance, sympathetic overdrive, oxidative stress, endothelin) that could also explain our findings (4,5).

Our findings are important for clinicians who treat or counsel patients with diabetes. Routine evaluation of the retina to detect retinopathy signs presents clinicians the unique opportunity to directly visualize and assess the actual pathology of microvascular damage caused by diabetes. Although the impact of diabetic retinopathy on vision is well known, the clinical significance of retinopathy signs beyond the eyes of diabetic patients is less clear. Our study showed that diabetic persons with retinopathy might have a greater risk of future HF development. Therefore, it is possible, as proposed by the investigators from the Framingham Heart and Eye Study over 2 decades ago, that retinopathy in people with diabetes might represent microvascular dysfunction not only in the retina but also in other organs, such as the heart (19). The presence of retinopathy in diabetic patients might indicate a need for a more thorough cardiac assessment and closer follow-up, a recommendation that has been suggested in previous clinical studies of diabetic patients undertaking cardiac revascularization procedures (20,40–43). In addition, a more careful cardiac assessment in asymptomatic people with diabetic retinopathy might also allow detection of subclinical left ventricular dysfunction, facilitating early implementation of treatments (e.g., beta-blockers, angiotensin-converting enzyme inhibitors) to prevent progression to overt HF.

Strengths of our study include a large population-based cohort 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. So, retinopathy might have been underestimated. Second, selection biases might have distorted the

associations, because retinal photography was performed at the third examination whereas some variables used in our analyses were available only at the second examinations (e.g., HbA1c, carotid IMT). Third, we did not have data on ventricular function (e.g., results from echocardiographic examinations) to assess whether the predominant cause of HF in our study was due to systolic or diastolic dysfunction. Finally, although in our multivariate analysis we have adjusted for antihypertensive medications and insulin use, the possibility of residual confounding from the other medical treatments cannot be totally excluded. For example, certain types of hypoglycemic agents (e.g., glitazone class) might be associated with a higher risk of HF development (44,45). However, we have no reason to believe these medications would have a major confounding effect on our results, because glitazone has not been known to affect retinopathy.

Conclusions

In summary, we demonstrate a prospective association of diabetic retinopathy with an increased risk of HF, independent of diabetes duration, glycemic control, and other traditional and nontraditional cardiovascular risk factors. These findings might provide further evidence to support a microvascular etiology of HF in diabetes and might suggest that diabetic patients with retinopathy signs might warrant a more careful cardiac evaluation and follow-up.

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JACC Vol. 51, No. 16, 2008
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