Retinopathy Predicts Coronary Heart Disease Events in NIDDM Patients

HEIKKI MIETTINEN, MD
STEVEN M. HAFFNER, MD
SEPPO LEHTO, MD
TAPANI RÖNNEMAA, MD
KALEVI PYÖRÄLÄ, MD
MARKKU LAAKSO, MD

OBJECTIVE — Proliferative retinopathy has been shown to be associated with increased all-cause mortality in diabetic patients. We assessed the relationship between the different degrees of retinopathic changes at baseline and serious coronary heart disease (CHD) events (CHD death or nonfatal myocardial infarction) in a prospective population-based study of NIDDM patients.

RESEARCH DESIGN AND METHODS — Our study is based on the 7-year follow-up cohort of 1,059 NIDDM patients in east and west Finland. Classification of retinopathic changes was based on clinical examination of fundi, and the findings were classified to three categories according to the status of the worse eye: no retinopathic changes, background retinopathy, and proliferative retinopathy.

RESULTS — During the 7-year follow-up, 255 (24%) patients developed serious CHD event. In patients with proliferative retinopathy at baseline, the risk of CHD events during the follow-up was statistically significantly higher compared with patients without retinopathic changes (odds ratio [OR] 2.31, 95% CI 1.21–4.40). The association between proliferative retinopathy and CHD events remained significant when other cardiovascular risk factors were controlled for.

CONCLUSIONS — Proliferative retinopathy in NIDDM patients was associated with CHD events. Our findings suggest that retinopathy and CHD may have similar pathophysiological backgrounds.

The risk of coronary heart disease (CHD) is higher in patients with NIDDM than in nondiabetic subjects (1). This excess of CHD in NIDDM patients is only in part explained by adverse effects of diabetes on the classic cardiovascular risk factors (1). Recent data suggest that in patients with NIDDM, the degree of hyperglycemia is associated with a risk of CHD (2). In prospective studies, hyperglycemia has also been shown to be associated with an increased risk of diabetic retinopathy (3). Proliferative retinopathy has been shown to be associated with all-cause mortality (4), but no data are available on whether proliferative retinopathy predicts CHD events after controlling for cardiovascular disease risk factors and hyperglycemia. The purpose of our study was to assess the relationship between different degrees of retinopathy at baseline and serious CHD events (CHD death or nonfatal myocardial infarction) during the 7-year follow-up of a population-based cohort of NIDDM patients in east and west Finland.

RESEARCH DESIGN AND METHODS

— All diabetic patients in Finland who need drug therapy are registered in a computerized central registry maintained by the Social Insurance Institution. Based on this registry, we identified all diabetic patients, aged 45–64 years, who were born and living in the Kuopio University Hospital district in east Finland or in the Turku University Central Hospital district in west Finland. The formation of our patient population consisting of 510 NIDDM patients in east Finland (participation rate 89%) and 549 patients in west Finland (participation rate 79%) has been described previously in detail (5). IDDM was excluded in all patients treated with insulin by C-peptide measurements, as described previously (6).

The baseline examination of NIDDM patients was carried out in 1982–1984. The examination included an interview on the previous medical history as well as drawing blood samples for laboratory examinations and measurements of height, weight, and blood pressure. Ophthalmoscopic examination of fundi was performed after pharmacological dilatation of pupils at the baseline visit by two experienced diabetologists (M.L., T.R.). For the purposes of this study, findings were further classified into three categories according to the status of the worse eye: no retinopathic changes, background retinopathy (microaneurysm, cotton, or hard exudates or hemorrhages), and proliferative retinopathy (neovascularization or previous laser coagulation therapy). Because of poor visibility of fundi caused by cataract, 19 patients were excluded from the further analyses, and, thus, the final study group included 1,040 patients. Consistence 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.

All medical records of subjects who reported that they had been admitted to the hospital because of symptoms suggestive for myocardial infarction were reviewed. The modified World Health Organization (WHO) Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) criteria for verified definite or possible myocardial infarction were used in the ascertainment of the diagnosis of previous myocardial

From the Department of Medicine (H.M., S.L., K.P., M.L.), University of Kuopio, Kuopio; the Department of Medicine (T.R.), University of Turku; the Research and Development Centre (T.R.), Social Insurance Institution, Turku, Finland; and the Department of Medicine (H.M., S.M.H.), Division of Clinical Epidemiology, University of Texas Health Science Center, San Antonio, Texas.

Address correspondence to Heikki Miettinen, MD, University of Texas Health Science Center at San Antonio, Department of Medicine, Division of Clinical Epidemiology, 7703 Floyd Curl Dr., San Antonio, TX 78284-7873. E-mail: miettine@uku.fi. Address reprint requests to Markku Laakso, MD, Department of Medicine, Kuopio University Hospital, FIN-70211 Kuopio, Finland.

Received for publication 6 May 1996 and accepted in revised form 25 July 1996.

CHD, coronary heart disease; OR, odds ratio; MONICA, Multinational Monitoring of Trends and Determinants of Cardiovascular Disease; WHO, World Health Organization.

Table 1—*Distribution of retinopathy categories and characteristics of NIDDM patients by different degrees of retinopathy at baseline*

	Retinopathy				
	No	Background	Proliferative	All	*P* value
Distribution of subjects with retinopathy					
Men	417 (73)	131 (23)	25 (4)	573 (100)	
Women	336 (72)	111 (24)	20 (4)	467 (100)	
Risk factors					
Previous myocardial infarction (%)	15	14	17		0.872
Smoking (%)	21	13†	5 †		0.001
Hypertension (%)	60	59	63		0.092
Treatment of diabetes					
Diet (%)	17	8	0		<0.001
Oral drugs (%)	76	67	47		
Insulin (%)	7	25	53		
Fasting glucose (mmol/l)	11.3 ± 0.1	12.4 ± 0.2‡	13.9 ± 0.6‡		<0.001
Total cholesterol (mmol/l)	6.73 ± 0.06	6.75 ± 0.10	6.87 ± 0.24		0.868
HDL-cholesterol (mmol/l)	1.20 ± 0.01	1.26 ± 0.02*	1.30 ± 0.05		0.017
Triglycerides (mmol/l)					
Mean ± SE	2.71 ± 0.10	2.26 ± 0.18	2.57 ± 0.10		0.503
Median (5%;95% percentiles)	2.02 (0.81; 5.77)	1.93 (0.78; 4.60)	2.02 (0.66; 7.20)		
Urinary protein (mg/l)					
Mean (SE)	232 ± 26	415 ± 46‡	652 ± 104‡		0.006
Median (5%;95% percentiles)	140 (0; 680)	170 (0; 1 800)	200 (0; 3 830)		
Duration of DM (years)	7.0 ± 0.1	9.6 ± 0.3‡	12.6 ± 0.6‡		<0.001
HbA_1 (%)	9.8 ± 0.1	10.0 ± 0.1	11.1 ± 0.18‡		<0.001

Data are means ± SE, n (%), or %. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ compared to subjects with no retinopathy at baseline. Risk factors are adjusted for study area, age, and sex.

infarction (7). Subjects were classified as having hypertension if they were receiving drug treatment for hypertension or if their systolic blood pressure was ≥160 mmHg or diastolic blood pressure was ≥95 mmHg.

Serum lipids and lipoproteins were determined from fresh serum samples drawn after a 12-h overnight fast, as described previously (5). Fasting plasma glucose was determined by the glucose oxidase method (Boehringer Mannheim, Mannheim, Germany). HbA_1 was estimated by ion exchange chromatography (Isolab, Akron, OH; reference range 5.5–8.5%). Total urinary protein concentration was measured from the morning spot urine specimen by the Coomassie brilliant blue method (Bio-Rad, Richmond, CA).

The methods used to obtain follow-up data are previously described in detail (6). In short, the follow-up status for all the participants of the original study cohort on 31 December 1989 was confirmed using a postal questionnaire and computerized cross-linkage of our database with nationwide Hospital Discharge Register and National Death Register using social security codes unique to all individuals in Finland. All medical records of the subjects who reported that they had been hospitalized because of chest pain symptoms or those with discharge diagnosis codes ICD 410–414 were reviewed. Copies of death certificates of subjects who died between baseline examination and 31 December 1989 were obtained from the Central Statistical Office of Finland. In the final classification of the causes of deaths, hospital and autopsy records were also used, if available. Diagnostic classification of coronary events was based on the modified WHO MONICA criteria for verified definite and possible myocardial infarction (7).

Statistical analyses were conducted with SAS statistical software (SAS Institute, Cary, NC). Differences between the groups were assessed by χ^2 test or by analysis of covariance by using age, sex, and area as covariates. Triglyceride and urinary protein values were log-transformed for statistical analyses. The association between the different stages of retinopathic changes and serious CHD events (CHD death or nonfatal myocardial infarction) was studied with multiple logistic regression analysis. For the analyses of overall association between CHD events and different degrees of retinopathy (trend), retinopathy was coded as follows: 1 = no retinopathy, 2 = background retinopathy, and 3 = proliferative retinopathy.

RESULTS — At baseline, 23% (131) of male NIDDM patients had background retinopathy, and 4% (25) had proliferative retinopathy. Among NIDDM women, the prevalence rates were 24% (111) and 4% (20), respectively. Other baseline characteristics are shown in Table 1. NIDDM patients with background or proliferative retinopathy were slightly older than NIDDM patients without this complication (58.6 ± 0.2 [mean ± SE] vs. 57.6 ± 0.2 years, $P < 0.01$). During the 7-year follow-up, 255 (24%) NIDDM patients developed a serious CHD event. The risk of a CHD event during the follow-up was higher in NIDDM patients with proliferative retinopathy than in patients without retinopathy (OR 2.31, 95% CI 1.21–4.40, Table 2). The association between proliferative retinopathy and CHD events remained significant when all other cardiovascular risk factors as well as duration of diabetes, metabolic control of diabetes (as measured by HbA_1), and urinary protein concentration were included in the model. The risk of CHD events among

Table 2—*Adjusted odds ratios (95% CI) for background or proliferative retinopathy and CHD events obtained by using different models in logistic regression analysis in nondiabetic and NIDDM subjects*

Variables included in the model	NIDDM
Retinopathy, sex, age, area	
OR for background vs. no retinopathy	1.32 (0.94–1.85)
OR for proliferative vs. no retinopathy	2.31 (1.21–4.40)
P value for trend	0.006
Retinopathy, gender, age, area, previous myocardial infarction, total cholesterol, HDL cholesterol, triglycerides, smoking, hypertension, urinary protein concentration	
OR for background vs. no retinopathy	1.45 (1.02–2.07)
OR for proliferative vs. no retinopathy	2.07 (1.30–5.09)
P value for trend	0.002
Retinopathy, gender, age, area, previous myocardial infarction, total cholesterol, HDL cholesterol, triglycerides, smoking, hypertension, urinary protein concentration, duration of diabetes, HbA_1	
OR for background vs. no retinopathy	1.38 (0.95–2.00)
OR for proliferative vs. no retinopathy	2.12 (1.02–4.39)
P value for trend	0.019

Interaction term area · retinopathy was not significant in any of the models ($P > 0.05$). *P* value for trend: retinopathy coded as 1 = no retinopathy, 2 = background retinopathy, and 3 = proliferative retinopathy.

NIDDM patients with background retinopathy was not increased compared with patients without retinopathy.

We also compared association of retinopathic changes to the risk of CHD events in subjects with low (<300 mg/l) and high (≥300 mg/l) urinary protein concentration (Fig. 1). The association between different degrees of retinopathy and incidence of CHD events increased stepwise. However, the association was statistically significant only in NIDDM patients with low urinary protein concentration (<300 mg/l). The lack of significance in subjects with high proteinuria (≥300 mg/l) probably was mostly due to low statistical power of analysis due to the small number of subjects ($n = 17$) having both high proteinuria and proliferative retinopathy.

CONCLUSIONS — It has been suggested that in diabetic patients, proliferative retinopathy, albuminuria, and CHD are consequences of similar widespread vascular damage (8). We assessed the relationship between different degrees of retinopathy at baseline and serious CHD events in the 7-year follow-up study in which we had a unique opportunity to use extensive data on cardiovascular risk factors in NIDDM patients at baseline to control confounding factors. We found a stepwise association between the different degrees of retinopathy and the incidence of CHD events. The stepwise association was more apparent in the patients without clinical proteinuria. In patients with proteinuria, the stepwise association between the different degrees of retinopathy and CHD events was also found but it was not statistically significant. This finding suggests either that clinical proteinuria is a sign of severe vascular damage, enough to mask the association between retinopathy and CHD events, or that the number of patients with proteinuria is too small for statistical analysis. Proliferative retinopathy was associated with the incidence of CHD events statistically significantly even after other cardiovascular risk factors were controlled for.

Only few prospective studies describing the association between retinopathy and CHD or other cardiovascular diseases have previously been published. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, diabetic proliferative retinopathy predicted all-cause mortality during a 6-year follow-up in older onset diabetic patients (OR 1.3, 95% CI 1.21–1.45) (4). On the other hand, in that study, diabetic patients with proliferative retinopathy did not have a significantly increased risk for myocardial infarction during the 4-year follow-up (OR 1.2, 95% CI 0.5–3.4) (9).

Data on risk factors for retinopathy in NIDDM patients are contradictory. Retinopathy has been associated with duration of diabetes (9), glycemic control (3,10), and hypertension (11,12), which also are associated with a higher risk of CHD. In our study, retinopathy at baseline

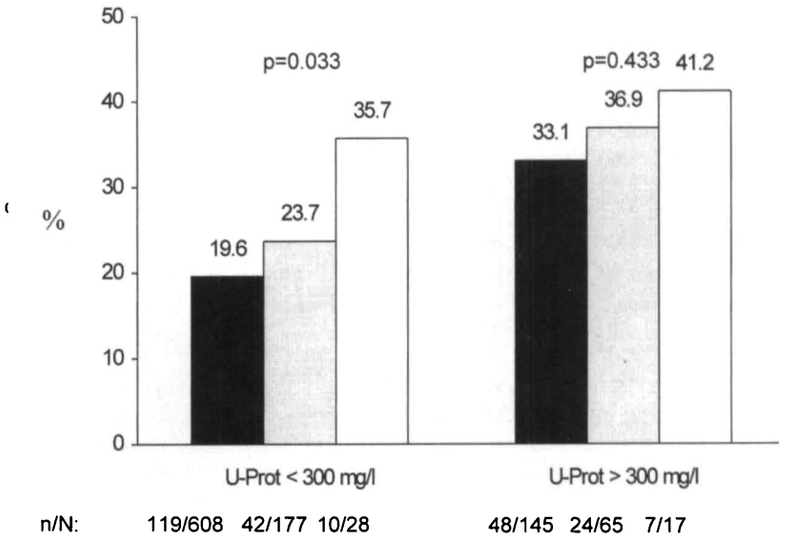

Figure 1—*The incidence of CHD events in different retinopathy categories by urinary protein concentration (n/N = number of CHD events/number of participants).* ■, *no retinopathy;* ▨, *background retinopathy;* □, *proliferative retinopathy.*

was associated with a longer duration of diabetes and elevated HbA_1, fasting glucose, urinary protein concentration, and HDL cholesterol. Increased risk of CHD as well as the risk of other atherosclerotic vascular diseases in NIDDM patients is only in part explained by adverse effects of diabetes on the classic cardiovascular risk factors (1). Several reports have suggested that in NIDDM patients, an increased urinary albumin excretion is associated with high cardiovascular disease mortality, independently of other cardiovascular risk factors (13,14). Furthermore, the degree of hyperglycemia has been shown to be associated with the risk of CHD in patients with NIDDM (2). However, even after adjustment for all these variables, the association between proliferative retinopathy and CHD events remained significant.

In conclusion, proliferative retinopathy was associated with CHD events in NIDDM patients. Since the association between retinopathy and CHD events was affected little by adjusting for CHD risk factors, our findings support the hypothesis that retinopathy and CHD may have similar pathophysiological backgrounds related to widespread vascular damage (8,15).

Acknowledgments— This study was supported by grants from the Academy of Finland, Aarne and Aili Turunen Foundation, and the Finnish Heart Research Foundation.

References

1. Pyörälä K, Laakso M, Uusitupa M: Diabetes and atherosclerosis: an epidemiological view. *Diabetes Metab Rev* 3:463–524, 1987
2. Kuusisto J, Mykkänen L, Pyörälä K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:962–967, 1994
3. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 260:2864–2871, 1988
4. Klein R, Moss SE, Klein BEK, DeMets DL: Relation of ocular and systemic factors to survival. *Arch Intern Med* 149:266–272, 1989
5. Laakso M, Rönnemaa T, Pyörälä K, Kallio V, Puukka P, Penttilä I: Atherosclerotic vascular disease and its risk factors in non-insulin-dependent diabetic and nondiabetic subjects in Finland. *Diabetes Care* 11:449–463, 1988
6. Laakso M, Rönnemaa T, Lehto S, Puukka P, Kallio V, Pyörälä K: Does NIDDM increase the risk for coronary heart disease similarly in both low- and high-risk populations? *Diabetologia* 38:487–493, 1995
7. Tuomilehto J, Arstila M, Kaarsalo E, Kankaanpää J, Ketonen M, Kuulasmaa K, Lehto S, Miettinen H, Mustaniemi H, Palomäki P, Puska P, Pyörälä K, Salomaa V, Torppa J, Vuorenmaa T: Acute myocardial infarction (AMI) in Finland: baseline data from the FINMONICA AMI register in 1983–1985. *Eur Heart J* 13:577–587, 1992
8. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage: the Steno hypothesis. *Diabetologia* 32:219–226, 1989
9. Klein R, Klein BEK, Moss SE: Epidemiology of proliferative diabetic retinopathy. *Diabetes Care* 15:1875–1891, 1992
10. Haffner SM, Fong D, Stern MP, Pugh JA, Hazuda HP, Patterson JK, van Heuven WAJ, Klein R: Diabetic retinopathy in Mexican Americans and Non-Hispanic Whites. *Diabetes* 37:878–884, 1988
11. Knowler WC, Bennett PH, Ballintine EJ: Increased incidence of retinopathy in diabetics with elevated blood pressure: a six-year follow-up study in Pima Indians. *N Engl J Med* 302:645–650, 1980
12. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 102:527–532, 1984
13. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 310:356–360, 1984
14. Gall MA, Borch-Johnsen K, Hougaard P, Nielsen FS, Parving H-H: Albuminuria and poor glycemic control predict mortality in NIDDM. *Diabetes* 44:1303–1309, 1995
15. Deckert T, Kofoed-Enevoldsen A, Norgaard K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen T: Microalbuminuria: implications for micro- and macrovascular disease. *Diabetes Care* 15:1181–1191, 1992