Risk Factors for Incident Retinopathy in a Diabetic and Nondiabetic Population

The Hoorn Study

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Objective: To investigate the effect of glycosylated hemoglobin, age, sex, hypertension, body mass index, waist-hip ratio, serum lipid levels, and smoking on the incidence of retinopathy in persons with normal and abnormal glucose metabolism.

Methods: The incidence of retinopathy was determined in 233 individuals, aged 50 to 74 years, by ophthalmoscopy and fundus photography at baseline and after an average follow-up of 9.4 years. Relative risks for retinopathy, estimated by odds ratios, were calculated for tertiles of cardiovascular risk factors at baseline. Logistic regression analysis was used, without and with adjustment for age, sex, hypertension, and glucose metabolism.

Results: The cumulative incidences of retinopathy among individuals with normal, impaired, and diabetic glucose metabolism were 7.3%, 13.6%, and 17.5%, respectively. Adjusted odds ratios for retinopathy were 2.36 (95% confidence interval, 1.02-5.49) for hypertension and 3.29 (95% confidence interval, 1.11-9.72) and 8.67 (95% confidence interval, 1.85-40.60) for the highest tertiles of glycosylated hemoglobin level and waist-hip ratio, respectively. No consistent or statistically significant associations with retinopathy were present for age, sex, body mass index, smoking, and serum levels of triglycerides and total, high-density lipoprotein, and non–high-density lipoprotein cholesterol ($P>.05$ for all).

Conclusion: Glycemia, hypertension, and abdominal obesity are determinants for retinopathy in a general population.

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THE DIAGNOSTIC value of the plasma glucose level for diabetes mellitus (DM) is chosen based on a sharp increase of the prevalence of retinopathy above that level.[1] It is not an absolute threshold, because retinopathy occurs, albeit at a lower prevalence, also at lower glucose levels.[1] Intervention studies in diabetic patients have shown that tight glucose control reduces the risk of retinopathy, although patients newly diagnosed as having type 2 DM in the United Kingdom Prospective Diabetes Study,[2] with a mean glycosylated hemoglobin (HbA_{1c}) level of 7.0%, still had an absolute risk of 7.9 per 1000 patient-years for retinal photocoagulation. In addition, the United Kingdom Prospective Diabetes Study[3] showed that tight blood pressure control effectively reduced the risk of retinopathy. Reports[3-15] on the incidence of (diabetic) retinopathy and risk factor analyses are mainly based on findings in diabetic patients. These studies reported HbA_{1c} level, duration of DM, use of insulin, and blood pressure as determinants of retinopathy. Moreover, hypertension seems to be a risk factor, particularly at lower fasting plasma glucose levels.[9] However, only a few studies[16,17] have investigated risk factors other than hyperglycemia for the incidence of retinopathy in a general population sample, including people with a normal glucose metabolism (NGM) or an impaired glucose metabolism (IGM).

Therefore, we studied the 10-year cumulative incidence of retinopathy in individuals with baseline NGM or IGM and in patients with type 2 DM. This study evaluates the effect of glycemic status, hypertension, dyslipidemia, obesity, and smoking at baseline for incident retinopathy during 10 years of follow-up.

METHODS

SUBJECTS

Subjects were selected from the Hoorn study,[18] a population-based cohort study on glucose metabolism that has been reported in detail previously. In brief, a random selection of 3553 inhabitants aged 50 to 74 years from Hoorn,

the Netherlands, was invited, and 2484 white individuals participated. The fasting plasma glucose level was measured, and all individuals not treated with oral hypoglycemic agents or insulin underwent a 75-g oral glucose tolerance test (OGTT) to measure the 2-hour postload plasma glucose level. A sample of 708 individuals, stratified for age, sex, and postload plasma glucose levels after the OGTT, was randomly selected to study diabetic complications and possible determinants. Subjects with a postload plasma glucose level of 135 mg/dL or higher (≥7.5 mmol/L) were oversampled to increase the power of the study. Individuals in this sample who did not receive pharmacological treatment for DM underwent a second OGTT within 3 to 5 weeks after the first OGTT. A baseline ophthalmological examination was performed in 626 people from November 24, 1989, to March 9, 1992, and 478 individuals also underwent fundus photography. Retinopathy was detected in 85 individuals, and essential information was missing for 1 person.

Four hundred sixty-three individuals who were still alive and did not move out of the region received a personal written invitation with additional information for a second examination session for DM and DM-related complications in 2000 and 2001. The session consisted of 4 visits to the Diabetes Research Center in Hoorn, with an ophthalmological examination, including ophthalmoscopy combined with fundus photography, at the second visit. People who did not respond to the written invitation were contacted by telephone. This article describes the 540 individuals who did not have retinopathy at baseline. Of these individuals, 233 participated in the second ophthalmological examination (56.3% of surviving subjects, still living in the region). Of the 307 nonparticipants, 91 (29.6%) had died and 35 (11.4%) had moved out of the region. Among the 181 remaining nonparticipants, the most frequently stated reasons for nonparticipation were lack of motivation and health or mobility problems. The nonparticipants (including those who died) had a higher baseline age (65.7 vs 62.1 years), fasting glucose level (120 vs 112 mg/dL [6.7 vs 6.2 mmol/L]), and HbA_{1c} level (5.90% vs 5.67%), and more of them experienced hypertension (42.3% vs 30.5%), compared with participants at follow-up ($P<.05$ for all differences). The Hoorn study was approved by the Ethical Review Committee of the VU University Medical Center. Written informed consent was obtained from all participants.

OPHTHALMOLOGICAL EXAMINATIONS

After mydriasis with tropicamide and phenylephrine hydrochloride eyedrops, the retina was examined by ophthalmoscopy (indirect ophthalmoscopy and biomicroscopy). In addition, 2 photographs were made of each eye, one centered on the macula and the other nasal on the optic disc.

Examinations at baseline were performed by ophthalmologists of the Department of Ophthalmology, VU University Medical Center. Baseline photography was performed with a 45° fundus camera with a green filter (Kowa Pro; Kowa Optical Industry, Tokyo, Japan), and retinopathy was graded from 11×11-cm photographs from black-and-white 35-mm films (Kodak Tri-X400 ASA; Eastman Kodak, Rochester, NY).

At follow-up, a fundus examination and photography of the same fields as at baseline were performed by an ophthalmologically trained physician (H.A.v.L.). A 45° nonmydriatic retinal camera (CR5; Canon Inc, Tokyo) was used, interfaced to a 3CCD color video camera (DXC-950P; Sony Corp, Tokyo). The quality of each photograph was checked immediately on a connected color video monitor (Trinitron; Sony Corp), and a new photograph was taken if the quality was insufficient. The photographs were digitized, compressed (10:1 JPEG [Joint Photographic Experts Group]), and stored on a disc using a magneto-optical videodisk recorder (MV-300P Viewfile system; TEAC Corp, Tokyo). These follow-up photographs were graded for retinopathy using a 43-cm monitor (resolution, 600×800 pixels; 16-bit color) and a software program (Adobe Photoshop 4.0 LE).

Baseline and follow-up photographs were analyzed independently by an ophthalmologically trained physician (H.A.v.L.) and an ophthalmologist (A.C.M. or B.C.P.P.). The agreement for the presence of retinopathy from digital images at follow-up was 96.0% (κ, 0.59) for right eyes and 97.3% (κ, 0.71) for left eyes. In cases of disagreement, the independent judgment of another ophthalmologist (A.C.M. or B.C.P.P.) was decisive. All graders were masked for patient characteristics such as age, type of glucose metabolism, and presence of hypertension. Retinopathy was considered present when at least one microaneurysm, hemorrhage, or hard exudate was present (minimal nonproliferative retinopathy) or occurred in combination with cotton-wool exudates, venous beading, or intraretinal microvascular abnormalities (moderate nonproliferative retinopathy) or, in case of neovascularization, fibrous proliferation or laser coagulation scars detected by photography or ophthalmoscopy, according to the classification that was used in the EURODIAB (EUROpe and DIABetes) study.[19] Six individuals with symptoms of hypertensive retinopathy and 7 with symptoms of vascular occlusion (flame-shaped hemorrhages) were scored as not having (diabetic) retinopathy. In each subject, the retinopathy level of the worst eye, according to ophthalmoscopy or fundus photography, was scored. In case of discrepancies between ophthalmoscopy and photography, ophthalmoscopic findings were corrected if corresponding photographically visible retinal lesions seemed to be symptoms of other underlying pathological conditions.

OTHER BASELINE ASSESSMENTS

Fasting and 2-hour postload venous plasma glucose levels were determined with a glucose dehydrogenase method (Merck, Darmstadt, Germany). For statistical analyses, the mean of 2 fasting and 2 two-hour glucose levels was used. Subjects were classified into 3 categories (NGM, IGM, or DM), in accordance with the World Health Organization 1999 criteria.[20] Known diabetic individuals at baseline (n=16), treated with oral glucose-lowering medication, insulin, or a diet, were included in the DM group. Glycosylated hemoglobin and lipid levels were determined in the fasting blood sample during the first OGTT. The HbA_{1c} level was determined by ion-exchange high-performance liquid chromatography (Modular Diabetes Monitoring system; Bio-Rad, Veenendaal, the Netherlands) (normal range, 4.3%-6.1%). Total cholesterol, high-density lipoprotein (HDL) cholesterol (after precipitation of the low- and very low-density proteins), and triglycerides were measured by enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany). The non-HDL cholesterol level was calculated by subtracting the HDL cholesterol level from the total cholesterol level. The non-HDL cholesterol level, which includes the low-density lipoprotein cholesterol level and the very low-density lipoprotein remnants, was chosen because it may be a more reliable predictor for mortality from cardiovascular disease than low-density lipoprotein cholesterol level alone.[21] Systolic and diastolic (Korotkoff V) blood pressure measurements were determined on the right arm of seated subjects, after at least 5 minutes of rest, using a random-zero sphygmomanometer. The average of 4 measurements was used for analysis. Hypertension was defined as a systolic pressure of 160 mm Hg or higher, a diastolic pressure of 95 mm Hg or higher, and/or the use of antihypertensive medication. Height, weight, body mass index (BMI), and waist-hip ratio (WHR) were determined to assess the presence of obesity and fat distribution. Information on smoking behavior and use of medication

Table 1. Baseline Characteristics of People With and Without Incident Retinopathy After 10 Years*

Baseline Characteristic	Retinopathy: Yes (n = 27)	Retinopathy: No (n = 206)	*P* Value
NGM/IGM/DM ratio	8:9:10	102:57:47	. . .
Female sex†	48.1	46.6	>.99
Age, y	64.8 (± 6.1)	61.8 (± 6.8)	.03
Glucose level, mg/dL			
Fasting	123 (± 32)	110 (± 31)	.08
2 h‡	153 (± 59)	146 (± 72)	.64
HbA_{1c} level, %	6.1 (± 1.0)	5.6 (± 1.0)	.03
Blood pressure, mm Hg			
Systolic	141.6 (± 17.7)	133.7 (± 16.4)	.02
Diastolic	84.6 (± 9.9)	81.5 (± 9.4)	.11
Hypertension†	51.9	27.7	.02
Use of antihypertensive agents†	37.0	18.9	.06
BMI	27.8 (± 3.9)	26.6 (± 3.4)	.10
WHR	0.96 (± 0.07)	0.91 (± 0.09)	<.01
Circumference, cm			
Waist	97.8 (± 10.1)	92.1 (± 10.8)	<.01
Hip	102.0 (± 8.1)	101.3 (± 6.2)	.60
Cholesterol level, mg/dL			
Total	259 (± 49)	254 (± 40)	.54
HDL	47 (± 10)	50 (± 14)	.27
Non-HDL	212 (± 49)	203 (± 41)	.30
Triglycerides, mg/dL§	133 (± 89)	142 (± 89)	.69
(Ever) smoked cigarettes†	70.4	58.7	.34

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; IGM, impaired glucose metabolism; NGM, normal glucose metabolism; WHR, waist-hip ratio.

SI conversion factors: To convert cholesterol (total, HDL, and non HDL) to millimoles per liter, multiply by 0.0259; to convert glucose (fasting and 2-hour) to millimoles per liter, multiply by 0.0555; and to convert triglycerides to millimoles per liter, multiply by 0.0113.

*Data are given as mean (± SD) unless otherwise indicated.

†Data are given as percentage of individuals.

‡Individuals with known DM were excluded.

§Data are given as median (± interquartile range).

was obtained from a questionnaire completed by the participants.

STATISTICAL ANALYSES

The cumulative incidence of retinopathy was calculated in categories of glucose metabolism. The baseline characteristics of individuals with retinopathy at follow-up were compared with those of individuals who had not developed retinopathy, by using a *t* test, a χ^2 test with continuity correction, or a Mann-Whitney test in case of a skewed distribution (triglyceride levels). $P<.05$ (2 sided) was considered statistically significant. Logistic regression was used to calculate the odds ratios (ORs) for retinopathy, with a 95% confidence interval, for women compared with men, for 10-year age groups compared with the youngest age group (50-59 years), for IGM and DM compared with NGM, for tertiles of HbA_{1c} level compared with the lowest tertile, and for individuals with hypertension compared with those without hypertension. The OR is a good estimate for the relative risk when the cumulative incidence is less than approximately 20%.[22] When the cumulative incidence is higher, the OR is an overestimation of the relative risk. The univariate association of lipid levels, obesity, and smoking with retinopathy was investigated by calculating ORs for tertiles of triglycerides; total, HDL, and non-HDL cholesterol levels; BMI; and WHR compared with the lowest tertile, and for smokers and ex-smokers compared with never smokers. Tertiles of determinants were analyzed to evaluate possible linear trends. Odds ratios were adjusted for age and sex and subsequently for hypertension and glucose metabolism (glucose metabolism category or HbA_{1c} level). Hypertension was chosen for adjustment, because it combined systolic and diastolic blood pressure measurements and the use of antihypertensive medication in one variable. To investigate the effect of DM duration, the OR for incident retinopathy was calculated per year with DM in individuals with known DM. In all analyses, Statistical Product and Service Solutions software, version 10.1 for Windows (SPSS Inc, Chicago, Ill), was used.

RESULTS

Twenty-seven (11.6%) of 233 individuals had developed retinopathy after an average follow-up of 9.4 years (range, 7.9-11.0 years). Twenty-four people had minimal nonproliferative retinopathy, and one individual had moderate nonproliferative retinopathy; 2 people were treated with photocoagulation. For baseline characteristics, individuals who developed retinopathy had a higher mean age, HbA_{1c} level, systolic blood pressure, WHR, and waist circumference, and they more frequently had hypertension, than individuals who did not develop retinopathy (**Table 1**). If we consider only nondiabetic individuals, serum fasting glucose level ($P=.04$), diastolic blood pressure ($P=.009$), and BMI ($P=.04$) were significantly higher in individuals with retinopathy as well, but the mean age was not (data not shown).

The cumulative incidence of retinopathy was similar for men and women, and was highest in those aged

Table 2. Incidence of and ORs for Incident Retinopathy by Categories of Cardiovascular Risk Factors

Risk Factor at Baseline	Incidence, %*	OR†		
		Crude	Adjusted 1	Adjusted 2
Sex				
Male‡	11.3 (124)	1.00	1.00	1.00
Female	11.9 (109)	1.06 (0.48-2.38)	0.97 (0.43-2.19)	0.99 (0.43-2.28)
Age, y				
50-59‡	7.0 (100)	1.00	1.00	1.00
60-69	16.3 (98)	2.59 (1.02-6.61)	2.60 (1.02-6.67)	2.23 (0.85-5.85)
≥70	11.4 (35)	1.71 (0.47-6.25)	1.72 (0.47-6.34)	1.46 (0.39-5.56)
Glucose metabolism category				
NGM‡	7.3 (110)	1.00	1.00	1.00
IGM	13.6 (66)	2.01 (0.74-5.50)	1.90 (0.69-5.25)	1.68 (0.60-4.71)
DM	17.5 (57)	2.71 (1.01-7.31)	2.36 (0.86-6.48)	1.91 (0.68-5.41)
HbA_{1c} level, %				
4.3-5.2‡	6.0 (83)	1.00	1.00	1.00
5.3-5.7	7.4 (68)	1.24 (0.34-4.47)	1.18 (0.32-4.28)	1.13 (0.31-4.19)
5.8-13.1	20.7 (82)	4.08 (1.43-11.65)	3.80 (1.31-11.00)	3.29 (1.11-9.72)
Hypertension				
No‡	8.0 (162)	1.00	1.00	1.00
Yes	19.7 (71)	2.82 (1.25-6.36)	2.66 (1.17-6.06)	2.36 (1.02-5.49)

Abbreviations: DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; IGM, impaired glucose metabolism; NGM, normal glucose metabolism; OR, odds ratio.
*Data in parentheses are the absolute number at risk.
†Data in parentheses are 95% confidence intervals. The crude OR is the OR after univariate logistic regression, and the adjusted OR is the OR after adjustment for sex and age (1) and for sex, hypertension, age, and glucose metabolism category (2). The determinant HbA_{1c} level was adjusted for sex, hypertension, and age only.
‡Referent.

60 to 69 years (**Table 2**). In individuals with IGM, the cumulative incidence was almost twice as high as in individuals with NGM ($P=.17$). The cumulative incidence increased from 6.0% for those in the lowest to 20.7% for those in the highest tertile of HbA_{1c} level ($P=.005$ for trend), and was significantly higher in people with hypertension than in people without hypertension (Table 2). A univariate logistic regression analysis showed higher ORs for the development of retinopathy in older persons (Table 2). The crude ORs for retinopathy were 2.01 and 2.71 for individuals with IGM and DM, respectively, compared with individuals with NGM. Risk also increased with HbA_{1c} level, particularly for those in the highest tertile of HbA_{1c} level, and more than doubled in individuals with hypertension compared with individuals without hypertension (Table 2). After adjustment for age and sex, and for age, sex, glucose metabolism category, and hypertension, in multivariate models, the ORs did not change considerably. When we limited the analyses to the nondiabetic subjects, the OR for those in the highest tertile of HbA_{1c} level compared with those in the lowest tertile was 3.95, and the OR for those with hypertension compared with those without hypertension was 3.84 (**Table 3**).

No associations were observed between BMI, serum triglycerides, and total, HDL, and non-HDL cholesterol levels and incident retinopathy (**Table 4**). The ORs for retinopathy were significantly higher for those in the higher tertiles of WHR, which did not change after adjustment for age, sex, HbA_{1c} level, and hypertension (Table 4). Cigarette smokers and ex-smokers had higher, but nonsignificant, ORs for incident retinopathy than never smokers, particularly after adjustment for age, sex, HbA_{1c} level, and hypertension. When we limited the analyses to the nondiabetic subjects, comparable results were observed (data not shown).

Regarding DM duration, the OR for incident retinopathy was 1.06 (95% confidence interval, 0.73-1.52) per year of DM among persons with known DM. The number of persons with known DM was, however, too small (n=16) for a detailed analysis of this risk factor.

COMMENT

Not only patients with type 2 DM, but elderly individuals with IGM and NGM in general, have a substantial risk of developing retinopathy. Our findings indicate that a high HbA_{1c} level, hypertension, and a high WHR are determinants of the incidence of retinopathy.

Little research has been performed on the incidence of (diabetic) retinopathy and its association with cardiovascular risk factors in populations, including nondiabetic people as well. To our knowledge, only 2 studies describe the incidence of retinopathy in nondiabetic subjects. The Beaver Dam Eye Study[17] reports a 5-year incidence of 6.0%, and a study[16] in Finland reports an incidence of 6.5% after 10 years, which agrees with the observations for individuals with NGM in the present study. In the present study, the incidence of retinopathy was comparable in men and women, in accordance with findings in diabetic patients.[9,11,13] In contrast to these studies, however, the incidence in our study had a tendency to increase with older age in the 50- to 70-year-old people. Our study confirmed the well-known positive association between HbA_{1c} level

Table 3. Incidence of and ORs for Incident Retinopathy by Categories of Cardiovascular Risk Factors in People Without DM

Risk Factor at Baseline	Incidence, %*	OR†		
		Crude	Adjusted 1	Adjusted 2
Sex				
Male‡	10.5 (95)	1.00	1.00	1.00
Female	8.6 (81)	0.80 (0.29-2.22)	0.72 (0.25-2.02)	0.75 (0.26-2.17)
Age, y				
50-59‡	6.0 (84)	1.00	1.00	1.00
60-69	14.7 (68)	2.72 (0.88-8.39)	2.85 (0.92-8.88)	2.58 (0.81-8.21)
≥70	8.3 (24)	1.44 (0.26-7.91)	1.54 (0.28-8.58)	1.36 (0.24-7.82)
HbA_{1c} level, %				
4.3-5.2‡	6.3 (79)	1.00	1.00	1.00
5.3-5.7	6.8 (59)	1.08 (0.28-4.19)	1.08 (0.27-4.30)	1.02 (0.25-4.18)
5.8-13.1	21.1 (38)	3.95 (1.19-13.03)	4.50 (1.26-16.06)	3.54 (0.94-13.37)
Hypertension				
No‡	6.1 (131)	1.00	1.00	1.00
Yes	20.0 (45)	3.84 (1.38-10.68)	3.61 (1.28-10.17)	3.61 (1.28-10.17)

Abbreviations: DM, diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; OR, odds ratio.
*Data in parentheses are the absolute number at risk.
†Data in parentheses are 95% confidence intervals. The crude OR is the OR after univariate logistic regression, and the adjusted OR is the OR after adjustment for sex and age (1) and for sex, age, and hypertension (2).
‡Referent.

and retinopathy.[4,10,12,13,15] The 2-hour serum glucose value was not associated with incident retinopathy. The estimated risk for developing retinopathy after 10 years in individuals with hypertension was more than 2 times as high as in individuals without hypertension, which remained after adjustment for age, sex, and glucose metabolism category. This is in line with previous findings of incident retinopathy in studies[6,7,9,13] of diabetic patients and in the 2 studies[16,17] that included nondiabetic individuals.

Type 2 DM is often associated with dyslipidemia, including elevated serum triglyceride levels and low HDL cholesterol levels. The present study did not find a statistically significant association between serum triglyceride and total, HDL, and non-HDL cholesterol levels and the development of retinopathy. Associations between cholesterol or triglyceride levels and the incidence of retinopathy, although not always statistically significant in multivariate risk models, were described in studies[7,12,15,23] that included diabetic patients. Cross-sectional data[24,25] have shown that hard exudates in particular are associated with elevated cholesterol levels. In the present study, the number of individuals with incident hard exudates was too small (n=6) for detailed analysis.

The WHR is an indicator for central obesity and is associated with insulin resistance.[26] A high WHR, but not BMI, seemed to indicate a high risk of developing retinopathy after 10 years, independent of age, sex, HbA_{1c} level, and hypertension. In particular, a large waist circumference seems to play a role, because the mean hip circumference did not differ much between individuals with and without retinopathy (Table 1). The WHR was also an independent risk factor in the diabetic patients in the EURODIAB study.[12,15] In line with our study, no consistent associations between BMI and incident retinopathy have been observed in studies[9,16] that included diabetic patients. A positive association between BMI and retinopathy was found in the Diabetes Control and Complications Trial[4] cohort of patients with type 1 DM, but a negative association was found in diabetic Pima Indians.[7] The present findings of the combination of WHR, HbA_{1c} level, and hypertension as risk factors for retinopathy may suggest that insulin resistance or associated factors are implicated in the pathogenesis of retinopathy.

The present study mainly considered early phases of retinopathy. Retinal hemorrhages and exudates at this stage could be the first symptoms of hypertensive retinopathy, during which the vasoconstrictive phase is not expressed.[27] This could explain the strong association with hypertension. However, independent associations of hypertension were also found with proliferative retinopathy in diabetic populations.[7,15] Moreover, in the present study, 8 of the 17 nondiabetic individuals who developed retinopathy did not have hypertension. In addition, HbA_{1c} level and WHR were risk factors in the nondiabetic individuals.

Similar to other longitudinal cohort studies with relatively older populations, the associations between baseline determinants and retinopathy may be underestimated as a result of competing morbidity and mortality. One of the limitations of this study is the relatively small number of cases. Therefore, only the strongest associations with retinopathy are expected to be detected. Also, there was a rather high nonparticipation rate of 43.7% among the survivors in the region at follow-up. There may be several possible explanations. First, in contrast to previous population studies of the 60- to 85-year-old population, two thirds of our original selected subcohort had IGM or DM at baseline. We observed that health had considerably deteriorated in these groups, as also indicated by the high mortality of 40.5% in patients with known DM compared with 12.8% in those with NGM. Furthermore, the present follow-up medical examination was rather extensive, and included several visits to

Table 4. The ORs for Incident Retinopathy by Categories of Cardiovascular Risk Factors

Risk Factor at Baseline	OR*		
		Adjusted	
	Crude	1	2
Cholesterol level, mg/dL			
Total			
155-233†	1.00	1.00	1.00
234-272	0.94 (0.35-2.52)	1.03 (0.37-2.84)	0.99 (0.35-2.81)
273-371	0.94 (0.35-2.52)	1.05 (0.37-2.97)	0.74 (0.25-2.22)
HDL			
24-43†	1.00	1.00	1.00
44-52	1.26 (0.51-3.11)	1.31 (0.52-3.32)	1.56 (0.60-4.05)
53-133	0.45 (0.15-1.39)	0.43 (0.13-1.39)	0.56 (0.17-1.88)
Non-HDL			
114-186†	1.00	1.00	1.00
187-221	1.47 (0.53-4.09)	1.79 (0.62-5.16)	1.75 (0.59-5.15)
222-310	1.49 (0.54-4.15)	1.73 (0.60-5.00)	1.24 (0.40-3.82)
Triglycerides, mg/dL			
35-110†	1.00	1.00	1.00
111-163	1.00 (0.36-2.82)	1.03 (0.36-2.92)	0.99 (0.34-2.85)
164-930	1.34 (0.51-3.52)	1.45 (0.54-3.88)	0.96 (0.33-2.79)
BMI			
19.675-25.164†	1.00	1.00	1.00
25.165-27.624	1.64 (0.60-4.49)	1.44 (0.52-4.00)	1.38 (0.49-3.91)
27.625-42.810	1.30 (0.46-3.70)	1.11 (0.38-3.22)	0.73 (0.23-2.28)
WHR			
0.5829-0.8772†	1.00	1.00	1.00
0.8773-0.9570	3.63 (0.96-13.70)	5.15 (1.29-20.60)	5.14 (1.24-21.30)
0.9571-1.1330	5.40 (1.48-19.60)	9.68 (2.21-42.40)	8.67 (1.85-40.60)
Smoked cigarettes			
Yes	1.16 (0.36-3.73)	1.62 (0.47-5.62)	1.61 (0.45-5.70)
Stopped	2.01 (0.80-5.06)	2.50 (0.89-7.03)	2.44 (0.85-7.03)
Never†	1.00	1.00	1.00

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL, high-density lipoprotein; OR, odds ratio; WHR, waist-hip ratio.

SI conversion factors: To convert cholesterol (total, HDL, and non-HDL) to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113.

*Data in parentheses are 95% confidence intervals. The crude OR is the OR after univariate logistic regression, and the adjusted OR is the OR after adjustment for age and sex (1) and for age, sex, HbA_{1c} level, and hypertension (2).

†Referent.

the research center. This may have been considered too demanding, because the nonparticipants, in general, were less healthy, had already visited hospitals or health care centers more often, or had problems with mobility. The selection due to morbidity and mortality may also be an explanation for the relatively lower ORs for retinopathy in the highest age group. In conclusion, this study shows that a higher HbA_{1c} level, hypertension, and abdominal obesity, as indicated by a high WHR, are determinants for the development of retinopathy. These results suggest that, in addition to serum glucose control in diabetic patients, screening for hypertension and abdominal obesity and adequate treatment of these risk factors might prevent retinopathy in diabetic and nondiabetic individuals.

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