United Kingdom Prospective Diabetes Study, 30

Diabetic Retinopathy at Diagnosis of Non–Insulin-Dependent Diabetes Mellitus and Associated Risk Factors

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Objectives: To report on the prevalence of retinopathy in patients with newly diagnosed non–insulin-dependent diabetes mellitus (NIDDM) and to evaluate the relationship of retinopathy to clinical and biochemical variables.

Design: A multicenter, randomized, controlled clinical study of therapy in patients with NIDDM.

Setting and Patients: Patients were part of the United Kingdom Prospective Diabetes Study, a 23-center study of 2964 white patients who had both eyes photographed and assessed.

Outcome Measures: The presence and severity of diabetic retinopathy were evaluated by sex, and the relationship of retinopathy to medical and biochemical parameters was assessed.

Results: Retinopathy, defined as microaneurysms or worse lesions in at least 1 eye, was present in 39% of men and 35% of women. Marked retinopathy with cotton wool spots or intraretinal microvascular abnormalities was present in 8% of men and 4% of women. The severity of retinopathy was related in both sexes to higher fasting plasma glucose levels, higher systolic and diastolic blood pressure, lower serum insulin levels, and reduced β-cell function. In addition, in men, increased alcohol consumption was related to increased severity of retinopathy, while leaner women had more severe eye lesions. Visual acuity was normal in most patients, but in men there was a trend for those with more severe retinal lesions to have worse visual acuity.

Conclusions: Diabetic retinopathy is common in patients with newly diagnosed NIDDM. Careful ophthalmic assessment at diagnosis is important.

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THE UNITED Kingdom Prospective Diabetes Study (UKPDS) is a multicenter, randomized, controlled clinical trial of therapy in patients with newly diagnosed non–insulin-dependent diabetes mellitus (NIDDM) that aims to determine whether improved blood glucose control will prevent microvascular and macrovascular morbidity and mortality and whether any specific therapy is advantageous or disadvantageous. Details of the study design and randomization have been described previously.[1,2] In brief, patients with newly diagnosed NIDDM were treated for 3 months with diet only, and if the fasting plasma glucose level was not adequately controlled at the end of this time, were randomized into treatment by diet only, oral agents, sulfonylureas (chlorpropamide, glyburide, or glipizide), or insulin. In addition, obese patients (≥120% of ideal body weight) were also randomized to be treated with the biguanide agent metformin. The study started in 1977, and retinal photography was included during 1983.

This report describes the retinal status of the patients at entry into the UKPDS and relates this to various clinical and biochemical variables. This gives insight into possible risk factors for the development of retinopathy and highlights the importance of full medical and eye examination at diagnosis of NIDDM.

RESULTS

Of the 4177 white patients, 3315 had baseline photographs, and 3185 (96.1%) of these were taken within the allowed window of 6 months before to 18 months after randomization. In 2972 patients (93.3%), photographs of both eyes could be graded. Photographs of only 1 eye could be graded in 112 patients (3.5%), and in 101 patients (3.2%) neither eye was gradable. Eight patients had photocoagula-

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PATIENTS AND METHODS

Patients with newly diagnosed NIDDM (fasting plasma glucose level >6 mmol/L [>108 mg/dL] on 2 occasions) between the ages of 25 and 65 years were recruited into the study between 1977 and 1991. Exclusion criteria were severe vascular disease, accelerated hypertension, preproliferative or proliferative or previously photocoagulated retinopathy, renal failure (serum creatinine level >175 µmol/L [>2.0 mg/dL]), life-threatening disease, disease requiring steroid treatment, or occupation precluding treatment with insulin (eg, bus driver). The patients gave informed consent, and the study was approved by the ethics committee of each participating center.

A total of 5102 patients were recruited into the study. Of these, 4177 were white, while the others were mostly Asian from the Indian subcontinent or Afro-Caribbean. The present analysis deals only with the 2964 whites who entered after 1983 (when retinal photography started) and who had both eyes photographed and assessed.

EYE EXAMINATION

Best corrected visual acuity was measured using the Snellen chart and, since 1986, the Early Treatment Diabetic Retinopathy Study logMAR charts.[3] Earlier Snellen chart data were corrected to their equivalent logMAR values. After pupillary dilation, eye examination was carried out using direct ophthalmoscopy. Four standard 30° fields of each eye were photographed in stereo pairs (lateral to macula, macula, disc, and nasal) and analyzed centrally, as described by Aldington et al.[4] All identifying information was masked, and each photograph was allocated a unique identification number. Assessments were carried out in duplicate, with independent adjudication of differences between graders.

Photographs were initially assessed for quality and adherence to protocol, then were graded in comparison to Early Treatment Diabetic Retinopathy Study standard photographs[5] for severity of retinopathy features. Subsequently, a computer algorithm assigned a numerical level to each eye (the modified Wisconsin level),[6] summarizing the severity of the lesions found. A simplified description of the levels allocated is shown in **Table 1**. As a modified Wisconsin level was assigned to each eye individually, for the purpose of this report, results are categorized based on the worse eye/better eye system.[7] Thus, 10/10 indicates absence of any retinopathy in both eyes; 20/10, microaneurysms in 1 eye only; and 20/20, both eyes with microvascular abnormalities only. Similarly, 31/<31 indicates that the worse eye has some retinal hemorrhages and/or hard exudates in addition to microvascular abnormalities, with the better eye having less retinopathy, while 31/31 also indicates those features, but in both eyes. This yields a possible 21-point scale (10/10 to 75/75) for each patient.

MEDICAL EXAMINATION

At entry, a full medical history was obtained, including details of physical activity. Patients were categorized as sedentary (rarely participates in physical activity), moderately active (on their feet less than half the day, weekend exercise only), active (on their feet more than half day, bicycle to work, regular exercise), or fit (manual worker, or regular and vigorous exercise at least 3 times each week). The history also included smoking (never, ex-smoker,

Table 1. Retinopathy Grades*

Grade	Features
10	No retinopathy
20	≥1 Microaneurysm only
31	Microaneurysms plus minimal hemorrhages and/or hard exudates
41-45	More severe than 31+ minimal or mild cotton wool spots and intraretinal microvascular abnormalities
51-55	Preproliferative retinopathy with venous beading, intraretinal microvascular abnormalities, and cotton wool spots
≥61	Proliferative retinopathy

*All features were graded by comparison with standard photographs (for details see Aldington et al[4]).

Table 2. Retinopathy Distribution by Sex*

Grade†	Male, No. (%) (n=1731)	Female, No. (%) (n=1233)
10/10	1051 (60.7)	810 (65.7)
20/10	328 (8.9)	241 (19.5)
20/20	89 (5.1)	43 (3.5)
31/<31 and 31/31	126 (7.3)	84 (6.8)
41/<41 and worse	137 (7.9)	55 (4.5)

**Mantel-Haenszel* $\chi^2=15.65$, *df=1,* $P<.001$.
†*Worse eye/better eye.*

tion before randomization; these patients were excluded from the analyses. The data presented, therefore, are for the 2964 patients in whom both eyes were graded. The quality of the photographs was high; only 1.7% of photographs temporal to the macula, 3.5% of the macula photographs, 2.5% of the disc photographs, and 5.5% of the nasal photographs could not be graded. In these patients, retinopathy level was assigned on the basis of the remaining fields.

Lesions other than diabetic retinopathy were present in some eyes. The most common of these were extensive drusen, present in 270 eyes; a nevus in 52 eyes, pigment epithelial defects in 55 eyes, and retinal branch vein occlusion in 5 eyes. None of these conditions or other nondiabetic conditions excluded grading for diabetic retinopathy.

RETINOPATHY PREVALENCE

Retinopathy was present in 39% of the men and 35% of the women. However, 19% of the men and 20% of the women had microaneurysms in 1 eye only, with no other features of diabetic retinopathy. In most of these patients (97%) there were only 3 or fewer microaneurysms. More severe forms of retinopathy were significantly more common in men (χ^2 for trend, $P<.001$), with a retinopathy grade of 41/<41 or more severe in 7.9% of men and 4.5% of women (**Table 2**).

current smoker) and alcohol consumption (none, occasional or social, regular, heavy). A full medical examination was carried out, including measurement of height and weight. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters.

BIOCHEMICAL MEASUREMENTS

Each participating center measured fasting plasma glucose levels. These measurements were monitored by the UKPDS glucose quality assurance scheme, with an interlaboratory coefficient of variation of approximately 4%.[1] All other samples were transported to the coordinating laboratory overnight at 4°C. Assays were monitored by trilevel quality-control serum samples with Westgard rules[8] for acceptance and by external quality-control schemes where possible.

Analytical methods were upgraded during the study, and data were realigned according to new methods after relevant laboratory comparisons.[9] Data in this report are presented using laboratory methods previously described.[9]

Glycosylated hemoglobin levels were measured by high-pressure liquid chromatography (Biorad Diamat automated glycosylated hemoglobin analyzer, Biorad Laboratories Ltd, Hemel Hempstead, England) (normal range, 0.045-0.062 [n=145], 2.5-97.5 percentiles). Urine albumin concentrations were expressed relative to the mean creatinine concentration of 8 mmol/L (90 mg/dL) in women and 11 mmol/L (125 mg/dL) in men to allow for urine dilution.[9] Fasting insulin levels were measured by double antibody radioimmunoassay (PhRIA 100, Pharmacia Ltd, Milton Keynes, England) with 100% cross-reactivity to proinsulin (normal range, 21-111 pmol/L [2.9-15.5 μU/mL]). β-cell function and insulin sensitivity were assessed using fasting plasma glucose and insulin levels by homeostasis model assessment.[10] This assesses, in a structural model of glucose-insulin relationships, the degree of impairment of β-cell function and insulin sensitivity required to produce each patient's fasting plasma glucose and insulin levels. The model was calibrated to give β-cell function and insulin sensitivity of 100% in a group of normal subjects aged 18 to 25 years. Plasma lipid and lipoprotein, urine albumin, and urine creatinine levels were measured by standard laboratory techniques.[9]

STATISTICAL ANALYSES

All data were analyzed using software from SAS Institute Inc[11] and BMDP Statistical Software Inc.[12] Continuous variables are described in the form mean (SD) if approximately normally distributed or in the form geometric mean (1-SD range) if approximately log-normal. We used a polychotomous logistic regression model to identify important variables and to estimate odds ratios. In detail, this entailed examining the association between retinopathy level and covariates 1 by 1 in a univariate model (procedure PR in the BMDP software) to investigate, for example, whether those with more severe retinopathy at diagnosis had higher levels of plasma glucose. Since the variables measured at diagnosis were not independent, this model was then used, with stepwise selection of variables, to arrive at a subset of variables that together best explained the retinopathy level. The continuous variables chosen by this method were split into quartiles, and the PR procedure was used to calculate the odds ratios. $P<.02$ was considered statistically significant.

Table 3. Biometric and Biochemical Variables in Subjects With Retinal Photographs at Diagnosis of Type 2 Diabetes

	Male	Female	*P* for Difference Between Sexes
No. of patients	1731	1233	. . .
Age, y*	52.4 (9.0)	53.5 (8.8)	.002
Body mass index, kg/m²*	28.4 (5.0)	30.8 (6.4)	<.001
Systolic blood pressure, mm Hg*	134 (19)	139 (20)	<.001
Diastolic blood pressure, mm Hg*	82 (10)	83 (10)	.02
Fasting plasma glucose, mmol/L [mg/dL]*	11.6 (3.6) [209 (65)]	12.3 (3.7) [222 (67)]	<.001
Hemoglobin A_{1c}*	0.091 (0.022)	0.093 (0.022)	.02
Insulin, pmol/L [μU/mL]†	91 (53-156) [12.7 (7.4-21.8)]	112 (61-178) [14.5 (8.5-24.8)]	<.001
Insulin sensitivity, %†‡	24 (17-34)	20 (15-29)	<.001
β-Cell function, %†‡	36 (21-61)	36 (21-56)	.48
High-density lipoprotein cholesterol, mmol/L [mg/dL]*	1.01 (0.24) [39.2 (9.3)]	1.09 (0.26) [42.2 (10.1)]	<.001
Urine albumin, mg/L‡	20 (6-66)	18 (5-60)	.001
Alcohol intake, % of patients			
None	12	28	<.001
Occasional or social	58	66	
Regular	27	6	
Heavy	3	0	

**Results are presented as mean (SD).*
†Results are presented as geometric mean (1-SD interval).
‡The model was calibrated to give β-cell function and insulin sensitivity of 100% in a group of normal subjects aged 18 to 25 years.

Demographic and Clinical Variables

Demographic and clinical results are shown in **Table 3**. Women were older and more obese at diagnosis and had higher blood pressure than men. They had higher fasting plasma glucose levels ($P<.001$) and slightly higher glycosylated hemoglobin levels ($P<.02$). Plasma cholesterol levels and both high-density lipoprotein and low-

Table 4. Severity of Retinopathy Related to Medical and Biochemical Parameters

	Retinopathy Grade		
	10/10	20/10	20/20
			Men
No. % of patients	1051 (61)	328 (19)	89 (5)
Age, y*	52.4 (9.0)	52.1 (9.2)	50.1 (8.6)
Body mass index, kg/m^2*	28.5 (5.0)	28.7 (5.4)	28.4 (4.8)
Systolic blood pressure, mm Hg*	134 (18)	132 (19)	133 (17)
Diastolic blood pressure, mm Hg*	82 (10)	81 (10)	83 (9)
Fasting plasma glucose, mmol/L [mg/dL]*	11.5 (3.7) [207 (67)]	11.5 (3.5) [207 (63)]	10.3 (3.1) [186 (56)]
Hemoglobin A_{1c}*	0.091 (0.023)	0.091 (0.022)	0.083 (0.022)
Insulin, pmol/L [μU/mL]†	93 (54-164) [13.0 (7.5-22.8)]	92 (54-156) [12.8 (7.5-21.8)]	85 (50-142) [11.8 (7.0-19.8)]
Insulin sensitivity, %†‡	24 (16-34)	24 (17-33)	28 (19-36)
β-Cell function, %†‡	38 (22-63)	37 (24-60)	44 (26-72)
High-density lipoprotein cholesterol, mmol/L [mg/dL]*	1.00 (0.25) [39 (10)]	1.02 (0.24) [39 (9)]	1.00 (0.22) [39 (9)]
Urine albumin, mg/L‡	20 (6-66)	19 (6-61)	17 (6-53)
Alcohol intake, % of patients			
None	13	10	18
Occasional or social	60	61	49
Regular	25	26	32
Heavy	2	3	1
			Women
No. (%) of patients	810 (66)	241 (20)	43 (3)
Age, y*	53.3 (8.8)	53.5 (8.8)	53.0 (9.2)
Body mass index, kg/m^2*	31.1 (6.7)	31.0 (5.9)	30.8 (6.4)
Systolic blood pressure, mm Hg*	138 (19)	140 (21)	142 (20)
Diastolic blood pressure, mm Hg*	83 (10)	84 (11)	85 (10)
Fasting plasma glucose, mmol/L [mg/dL]*	12.1 (3.7) [218 (67)]	12.2 (3.7) [220 (67)]	12.9 (3.8) [232 (68)]
Hemoglobin A_{1c}*	0.092 (0.021)	0.092 (0.022)	0.100 (0.025)
Insulin, pmol/L [μU/mL]†	108 (62-184) [15.0 (8.7-25.6)]	101 (60-173) [14.1 (8.3-24.1)]	91 (50-154) [12.7 (7.5-21.5)]
Insulin sensitivity, %†‡	20 (14-29)	20 (16-30)	21 (17-33)
β-Cell function, %†‡	38 (23-60)	36 (21-56)	25 (18-39)
High-density lipoprotein cholesterol, mmol/L [mg/dL]*	1.1 (0.3) [43 (12)]	1.1 (0.3) [43 (12)]	1.0 (0.2) [39 (8)]
Urine albumin, mg/L‡	16.6 (5.2-53.0)	17.5 (4.5-68.1)	22.6 (6.8-75.5)
Alcohol intake, % of patients			
None	27	34	30
Occasional or social	68	60	61
Regular	5	7	9
Heavy	0	0	0

**Results are presented as mean (SD).*
†Results are presented as geometric mean (1-SD interval).
‡The model was calibrated to give β-cell function and insulin sensitivity of 100% in a group of normal subjects aged 18 to 25 years.

density lipoprotein cholesterol levels were higher in women ($P<.001$ for all). Women also had higher insulin levels and were more insulin resistant ($P<.001$ for both). Women were less active but smoked and drank less than men; more women were treated with diuretic agents, and more were receiving antihypertensive therapy ($P<.001$ for all).

UNIVARIATE ASSOCIATION OF RETINOPATHY WITH CLINICAL AND BIOCHEMICAL VARIABLES

In both sexes the presence and severity of retinopathy and demographic variables were associated univariately (**Table 4**), with higher fasting plasma glucose levels ($P=.02$ for men, $P=.002$ for women) and higher systolic ($P=.006$ for men, $P<.001$ for women) and diastolic ($P=.009$ for men, $P=.004$ for women) blood pressures. More severe retinopathy was also associated with lower plasma insulin levels ($P=.005$ for men, $P=.002$ for women) and reduced β-cell function ($P<.001$ for men and women). In addition, in men, higher high-density lipoprotein cholesterol levels ($P=.009$) and increased alcohol consumption ($P=.005$) were also associated with more severe retinopathy, while in women there was a significant trend for those who were leaner ($P=.005$) and who had higher glycosylated hemoglobin levels ($P=.005$) to have more severe lesions. Triglyceride levels, low-density lipoprotein cholesterol levels, smoking, physical exercise, treatment with antihypertensive or diuretic therapy, and, in women, hormone replacement therapy did not appear to be related to severity of retinopathy.

When patients (both men and women) with microaneurysms in only 1 eye (level 20/10) were compared with those who had no retinopathy (level 10/10), they were not significantly different in any of the clinical variables. When they were compared with patients who had more severe retinopathy (levels ≥20/20), there were some

31/<31 and 31/31	41/<41 and Worse	*P* for Trend
126 (7)	137 (8)	. . .
54.5 (8.5)	53.1 (8.2)	.53
27.6 (4.4)	27.6 (4.5)	.41
140 (20)	139 (19)	.006
84 (10)	85 (10)	.009
12.2 (3.7) [220 (67)]	13.0 (3.4) [234 (61)]	.02
0.091 (0.020)	0.097 (0.019)	.56
83 (52-131) [11.6 (7.2-18.2)]	85 (52-135) [11.8 (7.3-18.8)]	.005
24 (20-37)	25 (19-36)	.02
29 (18-50)	27 (16-42)	<.001
1.05 (0.25) [41 (10)]	1.05 (0.27) [41 (10)]	.009
20 (6-70)	22 (6-82)	.84
8	14	.005
56	45	
34	37	
2	5	
84 (7)	55 (4)	. . .
55.1 (8.0)	53.6 (9.5)	.18
28.8 (5.4)	28.5 (4.6)	.005
143 (21)	149 (27)	<.001
84 (10)	85 (11)	.004
13.3 (3.5) [240 (63)]	13.7 (3.6) [247 (65)]	.002
0.096 (0.022)	0.103 (0.022)	.005
97 (58-163) [13.5 (8.1-22.7)]	89 (52-149) [12.4 (7.3-20.8)]	.002
22 (16-30)	22 (17-31)	.05
26 (17-46)	27 (16-38)	<.001
1.1 (0.3) [43 (12)]	1.2 (0.3) [46 (12)]	.34
21.6 (5.8-80.8)	23.9 (5.6-101.8)	.02
30	25	.32
67	67	
4	7	
0	0	

differences (Table 4), suggesting that patients with a retinopathy level of 20/10 resembled those without retinopathy.

MULTIVARIATE ANALYSIS OF ASSOCIATIONS OF RETINOPATHY WITH CLINICAL AND BIOCHEMICAL VARIABLES

Table 5 presents the results of a polychotomous logistic regression analysis that associates increasing severity of retinopathy with variables commonly measured in routine clinical practice, blood pressure and fasting plasma glucose level. After adjusting for systolic blood pressure and fasting plasma glucose level, female subjects presented with less severe retinopathy at diagnosis. The risk of increasing severity of retinopathy increased with higher fasting plasma glucose level and was about 30% higher for those in the top half of the distribution. The odds ratio for systolic blood pressure rose steadily with each quartile of systolic blood pressure: 11% higher in the second quartile, 23% higher in the third quartile, and 31% higher for the top quartile.

Table 5. Polychotomous Stepwise Logistic Regression Model to Examine the Relationship of Sex, Fasting Plasma Glucose Level, and Systolic Blood Pressure to Increasing Severity of Diabetic Retinopathy*

Variable	Odds Ratio (95% Confidence Interval)	*P*
Sex		
M	1.00	<.001
F	0.72 (0.62-0.84)	
Fasting plasma glucose, mmol/L (mg/dL)		<.001
≤8.9 (≤160)	1.00	
9.0-11.4 (161-205)	1.03 (0.83-1.26)	
11.5-14.3 (206-258)	1.25 (1.02-1.54)	
≥14.4 (≥259)	1.39 (1.13-1.71)	
Systolic blood pressure, mm Hg		.004
≤121	1.00	
122-134	1.11 (0.90-1.37)	
135-147	1.23 (1.00-1.52)	
≥148	1.45 (1.18-1.78)	

**Variables that are commonly measured in routine clinical practice were chosen. Continuous variables were partitioned into quartiles.*

A stepwise procedure was used to determine which variables found to be significant in the univariate model were significant in the multivariate model. After adjusting for sex, 3 variables remained in the model: β-cell function, fasting plasma insulin level, and systolic blood pressure (**Table 6**). Systolic blood pressure was strongly associated with steadily increasing risk of retinopathy. Fasting plasma insulin level below the top quartile was associated with higher levels of retinopathy. β-Cell function in the lower half of the distribution was associated with increased risk of retinopathy.

VISUAL ACUITY

The great majority of patients had normal visual acuity of 0.0, 0.1, or less than 0.2 on the logMAR chart (6/5 or better and 6/6 on the Snellen chart) in their worse eye at diagnosis (**Table 7**). Among the men, there was a significant trend for worsening visual acuity with increasing retinopathy severity ($P=.005$). There was no similar relationship among the women. Visual acuity was worse in the women than in the men ($P<.001$).

COMMENT

Among white patients with newly diagnosed NIDDM referred from primary care physicians, diabetic retinopathy was present at diagnosis in 39% of the men and 35% of the women. This figure is consistently higher than in other studies, which have recorded prevalences of retinopathy at diagnosis of 18% to 22%.[13,14] Most previous studies used ophthalmoscopy for the diagnosis of diabetic retinopathy. Even when it is performed by skilled observers, 1 to 3 microaneurysms may well be missed on ophthalmoscopy. It could be argued that a few micro-

Table 6. Polychotomous Stepwise Logistic Regression Model to Examine the Relationship of Fasting Plasma Insulin Level, β-Cell Function, and Systolic Blood Pressure to Increasing Severity of Diabetic Retinopathy*

Variable	Odds Ratio (95% Confidence Interval)	P
Sex		
M	1.00	<.001
F	0.72 (0.61-0.84)	
Fasting plasma insulin, pmol/L (μU/mL)		<.001
≥139 (≥19.4)	1.00	
100-138 (13.9-19.3)	1.55 (1.29-1.85)	
69-99 (9.6-13.8)	1.59 (1.26-1.99)	
≤68 (≤9.5)	1.40 (1.09-1.80)	
β-Cell function, %†		.002
≥60	1.00	
36-59	1.06 (0.85-1.32)	
21-35	1.36 (1.09-1.69)	
≤20	1.48 (1.16-1.88)	
Systolic blood pressure, mm Hg		<.001
≤121	1.00	
122-134	1.15 (0.92-1.43)	
135-147	1.28 (1.02-1.59)	
≥148	1.57 (1.26-1.95)	

**Variables were selected for inclusion in the model by a stepwise procedure. Continuous variables were partitioned into quartiles.*

†The model was calibrated to give β-cell function of 100% in a group of normal subjects aged 18 to 25 years.

Table 7. Visual Acuity at Diagnosis Assessed by LogMAR Score and Retinopathy Grade

Visual Acuity in Worse Eye	Retinopathy Grade, % of Patients 10/10	20/10	20/20	31/<31 and 31/31	41/<41 and Worse	P
Men						
LogMAR score						.005
<0	29.5	29.0	32.1	23.3	23.1	
0-0.19	37.3	37.4	34.6	35.0	31.4	
0.2-0.39	26.7	28.4	29.6	33.4	35.8	
≥0.4	6.5	5.2	3.7	8.3	9.7	
Women						
LogMAR score						.51
<0	20.8	21.2	18.0	20.2	18.9	
0-0.19	35.4	33.6	35.9	32.9	28.3	
0.2-0.39	36.7	35.9	38.5	41.8	41.5	
≥0.4	7.1	9.3	7.7	5.1	11.3	

aneurysms without any other lesions do not indicate diabetic retinopathy. Klein et al[15] reported finding microaneurysms among subjects without diabetes. The fact that the clinical characteristics of patients with microaneurysms in only 1 eye resembled those of patients without retinopathy suggests the possibility that the microaneurysms were an incidental finding. However, follow-up of these patients[16] indicates that microaneurysms alone are important predictors of progression to more severe retinopathy. Furthermore, the 4- and 10-year follow-up data of Wisconsin patients with microaneurysms only[17,18] also emphasizes the importance of microaneurysms as a risk factor for both proliferative retinopathy and macular edema. It is unlikely that these patients had undiagnosed diabetes for a longer period than patients in other studies,[19] as the National Health Service enables patients to present early without financial disincentives. Furthermore, primary care physicians were encouraged to send all their newly diagnosed patients to the hospital in the districts of the participating centers.

Increased systolic and diastolic blood pressures were associated with the severity of retinopathy. This might signify that patients with microvascular disease in the retina may also have renal involvement and secondary higher systolic blood pressure. However, increased urine albumin concentrations showed only a weak association with retinopathy in women and no association in men, and albuminuria was not included in the multivariate model. The data therefore suggest that higher systolic blood pressure per se is probably an important determinant of retinopathy. This is in accordance with the theory that hypertension, by increasing retinal blood flow, is important in the evolution of diabetic retinopathy.[20,21]

Retinopathy was also associated with increased fasting plasma glucose levels in women and showed a similar trend in men. This would have been anticipated from the Diabetes Control and Complications Trial[22] and the Kumamoto study.[23] Measurement of β-cell function from fasting glucose and insulin levels by homeostasis model assessment[10] showed an even stronger relationship of retinopathy with impaired β-cell function. Since the increasing hyperglycemia of NIDDM is associated with progressive deterioration of β-cell function,[24] it is possible that the assessment of β-cell function provides a better guide to the severity of diabetes and the hyperglycemic exposure over the previous years than the measurement of fasting plasma glucose and glycosylated hemoglobin levels at a single clinic visit. The lesser association of retinopathy with these indices of glycemia might in part be because some patients had already restricted their diet between the time when the diagnosis was suspected by their primary care physician and their first clinic visit.

Retinopathy was more prevalent in men than women, but this could not be explained by the major risk factors, since women had higher blood pressure and glucose levels than men. Men were less obese than women, but body mass index was not related to the presence or severity of retinopathy in men, while in women the leaner subjects had more severe retinopathy. Retinopathy was not associated with greater impairment of insulin sensitivity, although this has been suggested in a small study of NIDDM patients using clamp studies.[25]

Other factors thought to be of importance in some previous studies, such as smoking[26,27] and exercise, were not found to be important. These results emphasize the importance of large studies for obtaining definitive data.

In conclusion, diabetic retinopathy was common in patients with newly discovered NIDDM, although much of this was restricted to just a few microaneurysms in 1 eye only. This high prevalence underlines the importance of detailed ophthalmic investigation of newly di-

agnosed patients. The major associated variables were higher systolic blood pressure and hyperglycemia. Ongoing large-scale trials—the Hypertension in Diabetes Study,[28] in which patients have been allocated to improved blood pressure control, and the UKPDS, in which patients are allocated randomly to improved glucose and blood pressure control—will determine whether careful attention to these risk factors will reduce the incidence of related clinical end points, such as reduced visual acuity and need for photocoagulation.

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REFERENCES

1. United Kingdom Prospective Diabetes Study Group. UK Prospective Study of Therapies of Maturity-Onset Diabetes, I: effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over 1 year. *Diabetologia.* 1983;24:404-411.
2. United Kingdom Prospective Diabetes Study Group. UK Prospective Study, VIII: study design progress and performance. *Diabetologia.* 1991;34:877-890.
3. Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol.* 1982;94:91-96.
4. Aldington SJ, Stratton IM, Holman RR, Lipinski HJ, Kohner EM. *Assessment of Diabetic Retinopathy in the United Kingdom Prospective Diabetes Study (UKPDS).* Springfield, Va: National Technical Information Service. In press.
5. Classification of diabetic retinopathy: detailed grading of stereo-color photographs. In: *Early Treatment of Diabetic Retinopathy Study Manual of Operations.* Baltimore, Md: Early Treatment of Diabetic Retinopathy Study Coordinating Center, Dept of Epidemiology and Preventive Medicine, University of Maryland; 1985:chap 18.
6. Klein BEK, Davis MD, Segal P, et al. Assessment of severity and progression of diabetic retinopathy. *Ophthalmology.* 1984;91:10-17.
7. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, II: prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984;102:520-526.
8. Westgard JO, Barry PL, Hunt MR. A multi-rule Shewart chart for quality control in clinical chemistry. *Clin Chem.* 1981;27:493-501.
9. UK Prospective Diabetes Study Group. UK Prospective Study, 11: biochemical risk factors in type II diabetic patients at diagnosis compared with age matched normal subjects. *Diabet Med.* 1994;11:534-544.
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentration in man. *Diabetologia.* 1985;28:412-419.
11. SAS Institute Inc. *SAS/STAT Users Guide.* Cary, NC: SAS Institute Inc; 1989:851-859, 1071-1126.
12. BMDP Statistical Software Inc. *BMDP Statistical Software* [computer program]. Berkeley: University of California Press; 1990.
13. Dorf A, Ballintine EJ, Bennett PH, Miller M. Retinopathy in Pima Indians: relationship to glucose level, duration of diabetes, age at diagnosis of diabetes and age at examination in a population with high prevalence of diabetes mellitus. *Diabetes.* 1976;25:554-560.
14. Owens DR, Volund A, Jones D, et al. Retinopathy in newly presenting non insulin dependent diabetic patients. *Diabetes Res.* 1988;9:59-62.
15. Klein R, Klein BEK, Moss SE, Wang Q. Hypertension and retinopathy, arterial narrowing, and arteriovenous nicking in a population. *Arch Ophthalmol.* 1994;112:92-98.
16. Matthews DR, Kohner EM, Aldington SJ, Stratton I. Relationship of microaneurysm count to progression of retinopathy over 6 years in non-insulin dependent diabetes. *Diabetes.* 1995;9(suppl 1):117A.
17. Klein R, Meuer SM, Moss SE, Klein BEK. The relationship of retinal microaneurysm counts to the 4-year progression of diabetic retinopathy. *Arch Ophthalmol.* 1989;107:1780-1785.
18. Klein R, Meuer SM, Moss SE, Klein BEK. Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. *Arch Ophthalmol.* 1995;113:1386-1392.
19. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. *Diabetes Care.* 1992;15:815-819.
20. Patel V, Rassam S, Newsom R, Wiek J, Kohner EM. Retinal blood flow in diabetic retinopathy. *BMJ.* 1992;305:678-683.
21. Rassam SMB, Patel V, Kohner EM. The effect of experimental hypertension on retinal autoregulation in humans: a mechanism for the progression of diabetic retinopathy. *Exp Physiol.* 1995;80:53-68.
22. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on development and progression of long term complications in insulin dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
23. Ohkubo Y, Kishikawa H, Araki A, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomised prospective 6 year study. *Diabetes Res Clin Pract.* 1995;28:103-117.
24. United Kingdom Prospective Diabetes Study Group. UK Prospective Study, 16: overview of 6 year therapy of type 2 diabetes: a progressive disease. *Diabetes.* 1995;44:1249-1258.
25. Maneschi F, Mashiter K, Kohner EM. Insulin resistance and insulin deficiency in diabetic retinopathy of non-insulin dependent diabetes. *Diabetes.* 1983;32:82-87.
26. Walker JM, Cove DH, Beevers DG, et al. Cigarette smoking, blood pressure and the control of blood glucose in the development of diabetic retinopathy. *Diabetes Res.* 1985;2:183-186.
27. Muhlhauser I, Sawicki P, Berger M. Cigarette smoking as a risk factor macroproteinuria and proliferative retinopathy in type 2 insulin dependent diabetes. *Diabetologia.* 1986;29:500-502.
28. The Hypertension in Diabetes Study Group. Hypertension in diabetes, I: prevalence of hypertension in newly presenting type 2 diabetic patients and the association of risk factors for cardiovascular and diabetic complications. *J Hypertens.* 1993;11:309-317.