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CLINICAL STUDY

Longitudinal study examining the risk factors for proliferative retinopathy and maculopathy in type-I diabetes: The Royal College of Physicians of Edinburgh Diabetes Register Group

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Abstract

Purpose **The aim of this study was to determine whether there were any differences in the risk factors for developing proliferative diabetic retinopathy or maculopathy in patients with type-I diabetes.**

Method **In all, 1632 patients aged 35 years or younger at diagnosis and treated with insulin, attending six hospital diabetes clinics in Scotland and included on the Royal College of Physicians of Edinburgh Diabetes Register were followed up for a median of 4.0 (2.5–5.5 years: interquartile range). All patients were screened at least annually for diabetic retinopathy using direct ophthalmoscopy, and positive findings were confirmed using slit lamp by an ophthalmologist.**

Results **Duration of diabetes and HbA1c were the important risk factors for developing proliferative retinopathy, while duration of diabetes, systolic blood pressure, and HbA1c were the important factors for maculopathy. The adjusted relative incidence for proliferative retinopathy with a HbA1c in the highest quartile was 26.7, while for maculopathy it was only 2.29. Carstairs deprivation score was not associated with either retinal pathology. There was a plateau effect for systolic blood pressure of 140 mmHg and for duration of diabetes of 16 years for developing either maculopathy or proliferative retinopathy.**

Conclusion **Duration of diabetes is a strong predictor for maculopathy and proliferative disease, but is relatively more important for proliferative disease. Raised systolic blood pressure is relatively more important for predicting maculopathy, while raised HbA1c is relatively more important for developing proliferative retinopathy.**

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Introduction

Blindness is one of the most feared complications of diabetes. Patients with diabetes and mild visual impairment are willing to forsake 22% of their life expectancy to restore their eyesight to normal, reflecting the impact it has on their quality of life.[1] Poor glycaemic control is an established risk factor for developing diabetic retinal disease in type-I diabetes.[2,3] Hypertension is also a risk factor in observational studies,[4,5]although there is no evidence that aggressive blood pressure-lowering therapy reduces the incidence of retinopathy in type-I diabetes. Observational data have also identified the duration of diabetes,[6] raised cholesterol,[7–9] raised

triglycerides,[9,10] and proteinuria[11] as risk factors. Smoking has previously been of borderline significance in type-I diabetes,[12,13] but may be of significance for patients who have had diabetes for less than 5 years.[14] Many of these studies have examined the risk factors for developing any sight-threatening retinopathy, but few studies have focused on the relative risks of developing proliferative retinopathy compared to maculopathy. In this longitudinal study, we compared the relationship between various risk factors and the development of diabetic maculopathy and diabetic proliferative disease.

Materials and methods

Using the Royal College of Physicians of Edinburgh Diabetes Register, data were collected from six hospital-based diabetes centres in Scotland on patients with type-1 diabetes. The register has been described in detail elsewhere.[15,16] Type-I diabetes was defined as requiring insulin treatment and being diagnosed under the age of 35 years. Data were collected on 2314 people with type-I diabetes for demographic information, smoking status, HbA1c, blood pressure, urinary albumin, and serum cholesterol. Baseline data for these factors were compared to developing retinal status as assessed in a clinic by the diabetologist, using dilated direct ophthalmoscopy. If patients were referred to an ophthalmologist, findings were verified or altered according to slit lamp examination, and the final decision recorded. Post codes were recorded for each patient and used to calculate the Carstairs deprivation score.[17] Patients were examined yearly and followed up longitudinally. Data collection started in 1989 and finished in 1996 and patients were followed up for a median of 4.0 years (2.5–5.5 years: interquartile range). End points were classified as the progression from normal or background retinopathy to maculopathy, from normal or background retinopathy to proliferative or preproliferative. Maculopathy was defined as any haemorrhages, exudates or circinates within one disc diameter of the fovea, which required referral to an ophthalmologist for laser photocoagulation or ongoing clinic review. Preproliferative retinopathy was defined as the presence of multiple blot haemorrhages, venous beading, intra-retinal microvascular abnormalities (IRMA), or six or more cotton–wool spots. Proliferative retinopathy was defined as the presence of new vessels at the disc or new vessels elsewhere. Preproliferative and proliferative retinopathies were grouped together.

Statistical methodology

Criteria were established to categorise patients according to their longitudinal pattern of retinopathy. As progression from normal or background retinae to maculopathy or proliferative retinopathy is usually clearcut, single assessments at each level were used to identify patients with such disease development. The definition of any anomalous patterns was agreed by the lead clinician and statistician in the absence of any knowledge of other patient characteristics.

Baseline characteristics were collected from the single clinic visit used, to define that the patient initially had normal retinae or retinae with background disease. This was usually the first visit recorded on the RCPE Register.

Patients had both HbA1c & HbA1 measurements over the years, as well as different methods of assay, according to the clinic and date of visit. All assays were grouped separately for HbA1 and HbA1c within each assay technique. Ranking of values and division of these data into quartiles within each group allowed comparative estimates of the level of glycaemic control for the whole cohort. HbA1c was thus recorded as quartile values to allow such comparisons between centres.

A large proportion of patients had missing cholesterol values, especially during the first few years of the Register. In an attempt to estimate the possible influence of this characteristic on retinopathy, data for about one-third of patients were collected by using the first value recorded during the initial 24 months.

Follow-up started immediately after the baseline retinal status of a patient had been defined. For patients with subsequent events, the length of follow-up was defined as the time interval to the first record of maculopathy or proliferative disease. For patients who showed no such development of retinopathy, the length of follow-up was the time to the most recent retinal assessment.

Subjects were excluded from the analysis if they had maculopathy or proliferative disease at baseline or if they had insufficient information. Thus, 682 patients were excluded, leaving 1632 patients with type-I diabetes available for this study.

Cox's proportional hazards models were used to assess the effect of baseline risk factors on the development of retinopathy. As age and duration of diabetes were strongly intercorrelated, duration was selected for inclusion in the models, as it has greater clinical relevance to retinopathy. Independent variables were categorised as shown in the tables, the lowest categories being used as reference categories. All two-way interactions were tested for significance.

Results

Of three possible blood pressure variables (systolic, diastolic and pulse pressure), systolic proved marginally more important in relation to progression to

maculopathy or proliferative disease than pulse pressure, and the former is therefore included in the models presented here. Interestingly, patients with a pulse pressure of greater than 60 mmHg were shown in additional analyses, to double the risk of developing background retinopathy in patients with normal retinae (2.05** (95% confidence interval 1.20–3.50)).

The mean length of follow-up was 4.0 years. In univariate analysis, the significant risk factors for the development of maculopathy included duration of diabetes, systolic blood pressure, HbA1c, urinary albumin, smoking and ex-smoking, and cholesterol (Table 1). The adjusted relative incidences showed that duration of diabetes, blood pressure, and HbA1c remained significant in the multivariate model and urinary albumin became marginal. Duration of diabetes, systolic blood pressure, HbA1c, urinary albumin, and ex-smoking were significant factors for proliferative diabetic eye disease in univariate analysis, of which duration of diabetes and HbA1c remained significant in the multivariate model (Table 2). HbA1c and duration of diabetes were most strongly associated with the development of proliferative retinal disease. Duration of diabetes, blood pressure, and HbA1c were the most strongly associated with the development of maculopathy (Table 1). Neither proliferative eye disease nor maculopathy was associated with social deprivation.

Cholesterol was nonsignificant in multivariate analyses, largely due to its strong interrelation with duration of diabetes, though the number of cases in these models was much reduced due to the problems with cholesterol data (see Methods).

None of the two-way interactions in the multivariate models was significant following the application of the Bonferroni rule for multiple comparisons.

Table 3 explores the possible threshold levels for each of the major risk factors for maculopathy and proliferative retinopathy. The duration of diabetes reaches a plateau in determining the relative incidence after 16 years duration. Only systolic blood pressures above 140 mmHg were significant as risk factors for maculopathy and proliferative retinopathy, but there was a nonsignificant trend at lower pressures and no augmented risk at blood pressure levels above this. A urine albumin excretion of 30 mg/l or above was associated with the development of diabetic eye disease.

Discussion

Our study attempts to identify whether there are different risk factors for the development of proliferative retinal disease compared to maculopathy in patients with type-I diabetes. The most important adjusted risk factors for proliferative retinopathy appear to be duration of diabetes and HbA1c. Duration of diabetes, blood pressure, and HbA1c were important risk factors for the development of maculopathy. The adjusted relative incidences for blood pressure were greater in maculopathy, and for HBA1c were greater in the development of proliferative disease. The relatively greater importance of HbA1c for proliferative retinopathy, and blood pressure for maculopathy, is intriguing. In the DCCT, HbA1c was also an important risk factor for the development and progression towards proliferative disease and maculopathy, with intensive control of blood glucose lowering the incidence of both.[3] Our study helps confirm the association of raised blood pressure as a risk factor for retinopathy in type-I diabetes which has been demonstrated elsewhere,[8,18] but an interventional study to demonstrate the benefits of blood pressure lowering is required.

Our study was performed in clinical practice, with all the inherent weaknesses and strengths of such an approach. Although there is a move away from using direct ophthalmoscopy for screening purposes, it is still the commonest modality used for detecting retinopathy in diabetes clinics and primary care, especially during the duration of this study. All cases identified as having proliferative disease or maculopathy were verified by a consultant ophthalmologist, such that there would not have been any false-positive cases recorded. It is possible that some cases of sight-threatening eye disease may have been missed, but it is likely that the majority of these would have been identified in a longitudinal study such as this. If some cases were missed, however, there is no obvious bias, which would have affected the results.

The number of individuals with recorded cholesterol at baseline was low, reflecting the fact that data collection started in 1989, before the importance of lowering serum cholesterol had been demonstrated. However, in univariate analysis, high cholesterol concentrations were associated with maculopathy, but not with proliferative eye disease. Some longitudinal studies have established an association between serum cholesterol and triglycerides with the development of any retinopathy,[7,8,10] and some have associated serum cholesterol concentrations with visual loss[9,18] in a small number of individuals with diabetes. Cholesterol concentrations are also associated with the development of hard exudates.[19] Our study helps link these findings by defining an association between cholesterol and clinically relevant macular disease that requires laser photocoagulation or ongoing care by an ophthalmologist. Studies examining the effect of cholesterol lowering on the development of maculopathy are required.

Univariate analysis also identified smoking and ex-smoking as risk factors for maculopathy, and ex-smoking as a risk factor for proliferative eye disease. The

Table 1 Proportional hazards analysis of risk factors for the development of retinopathy (from normal or background retinae at baseline to maculopathy)

Patient characteristics at baseline (first year)	*Univariate relative incidence (95% CI) (n = 1537, 72 events)*	*All factors in model (n = 1537, 72 events) Adjusted relative incidence (95% CI)*	*Significant factors in model[a] (n = 1537, 72 events) Adjusted relative incidence (95% CI)*
Sex			
Female (701)	1.00	1.00	
Male (836)	1.29 (0.80–2.06)	1.25 (0.76–2.04)	
Smoking habit			
Non-smoker (804)	1.00	1.00	
Ex-smoker (209)	2.25** (1.21–4.18)	1.87 (0.97–3.60)	
Smoker (508)	1.71* (1.01–2.89)	1.55 (0.90–2.68)	
Not known (16)	$	$	
Duration of diabetes (years)			
<4.9 (492)	1.00	1.00	1.00
5.0–9.9 (283)	1.69 (0.64–4.51)	1.46 (0.54–3.95)	1.58 (0.59–4.22)
10.0–14.9 (282)	2.77* (1.15–6.69)	2.69* (1.10–6.58)	2.77* (1.14–6.71)
15.0–19.9 (196)	5.98*** (2.63–13.6)	5.43*** (2.34–12.6)	5.46*** (2.38–12.5)
20.0 + (264)	5.21*** (2.33–11.6)	3.74** (1.60–8.76)	4.07*** (1.78–9.29)
Not known (20)	$	$	$
Blood pressure (mm Hg) systolic			
< 120 (470)	1.00	1.00	1.00
120–129 (355)	1.49 (0.64–3.44)	1.24 (0.53–2.92)	1.38 (0.59–3.22)
130–139 (294)	1.82 (0.78–4.21)	1.21 (0.51–2.87)	1.35 (0.57–3.18)
140 + (379)	4.46*** (2.21–8.98)	2.91** (1.38–6.12)	3.12** (1.51–6.43)
Not known (39)	2.17 (0.47–9.91)	2.65 (0.54–13.1)	2.31 (0.48–11.0)
Hba1/a1c (quartile)			
First (380)	1.00	1.00	1.00
Second (349)	0.60 (0.25–1.41)	0.53 (0.22–1.25)	0.56 (0.24–1.33)
Third (324)	1.19 (0.58–2.44)	1.06 (0.51–2.20)	1.06 (0.51–2.17)
Highest (350)	2.19* (1.16–4.17)	2.48** (1.28–4.82	2.29* (1.20–4.38)
Not known (134)	1.71 (0.75–3.90)	1.79 (0.72–4.47)	1.49 (0.63–3.53)
Urinary albumin (ug/l)			
<20.0 (938)	1.00	1.00	1.00
20.0–54.9 (169)	2.06* (1.12–3.79)	1.72 (0.91–3.22)	1.80 (0.97–3.34)
55.0 + (62)	3.20** (1.43–7.16)	1.78 (0.77–4.12)	2.17 (0.96–4.93)
Not known (368)	1.02 (0.53–1.95)	0.88 (0.44–1.76)	0.84 (0.43–1.65)
Carstairs deprivation score (quintile)			
1 (250)	1.00	1.00	
2 (271)	0.77 (0.34–1.71)	0.83 (0.37–1.89)	
3 (466)	0.90 (0.46–1.77)	0.92 (0.46–1.84)	
4 (322)	0.79 (0.38–1.67)	0.73 (0.33–1.59)	
5 (174)	0.99 (0.42–2.31)	0.93 (0.38–2.27)	
Not known (54)	$	$	
Cholesterol[b]			
<5.0 (236)	1.00	1.00	
5.0–5.9 (178)	2.06 (0.75–5.67)	1.58 (0.56–4.44)	
6.0 + (148)	3.84** (1.49–9.90)	2.06 (0.77–5.51)	
Not known (975)	1.39 (0.59–3.28)	0.74 (0.30–1.83)	

*$P<0.05$, **$P<0.01$, ***$P<0.001$. $ No events in 'not known' category.
[a]Due to large proportion of missing data, cholesterol values taken from up to 2 years after enrolment.
[b]None of the two-way interactions significant.

Table 2 Proportional hazards analysis of risk factors for the development of retinopathy (from normal or background retinae at baseline to proliferative disease)

Patient characteristics at baseline (first year)	*Univariate relative incidence (95% CI) (n = 1598, 80 events)*	*All factors in model (n = 1598, 80 events) Adjusted relative incidence (95% CI)*	*Significant factors in model[a] (n = 1598, 80 events) Adjusted relative incidence (95% CI)*
Sex			
Female (733)	1.00	1.00	
Male (865)	1.00 (0.65–1.56)	1.03 (0.65–1.63)	
Smoking habit			
Non-smoker (833)	1.00	1.00	
Ex-smoker (224)	1.99* (1.14–3.48)	1.57 (0.88–2.81)	
Smoker (524)	1.14 (0.68–1.90)	0.98 (0.57–1.68)	
Not known (17)	1.87 (0.26–13.6)	2.03 (0.26–15.9)	
Duration of diabetes (years)			
<4.9 (493)	1.00	1.00	1.00
5.0–9.9 (290)	6.60* (1.40–31.1)	5.45* (1.15–25.9)	5.95* (1.26–28.0)
10.0–14.9 (292)	10.8** (2.44–47.9)	10.7** (2.39–47.5)	10.4** (2.34–46.0)
15.0–19.9 (211)	24.8*** (5.84–105.6)	27.2*** (6.31–117.2)	25.6*** (6.01–108.9)
20.0 + (291)	27.9*** (6.71–116.2)	25.2*** (5.88–108.0)	29.4*** (7.06–122.5)
Not known (21)	18.2* (1.65–201.7)	15.7* (1.33–185.6)	11.5* (1.04–126.9)
Blood pressure (mm Hg) systolic			
< 120 (483)	1.00	1.00	
120–129 (365)	1.41 (0.69–2.89)	1.23 (0.58–2.58)	
130–139 (304)	1.39 (0.65–2.95)	0.96 (0.44–2.10)	
140 + (405)	2.87*** (1.54–5.33)	1.71 (0.86–2.10)	
Not known (41)	1.44 (0.33–6.36)	1.56 (0.32–7.69)	
Hba1/a1c (quartile)			
First (382)	1.00	1.00	1.00
Second (356)	5.59* (1.23–25.5)	4.70* (1.02–21.5)	4.78* (1.05–21.8)
Third (335)	8.89** (2.03–38.9)	7.91** (1.80–34.8)	7.74** (1.77–33.8)
Highest (382)	26.3*** (6.37–108.4)	29.2*** (7.03–121.5)	26.7*** (6.47–110.4)
Not known (143)	11.6** (2.51–53.8)	12.6** (2.59–61.2)	9.84** (2.13–45.6)
Urinary albumin (ug/l)			
<20.0 (970)	1.00	1.00	
20.0–54.9 (178)	1.85* (1.01–3.39)	1.58 (0.85–2.93)	
55.0 + (67)	1.93 (0.77–4.89)	1.02 (0.39–2.68)	
Not known (383)	1.41 (0.82–2.43)	1.19 (0.66–2.13)	
Carstairs deprivation score (quintile)			
1 (260)	1.00	1.00	
2 (287)	1.48 (0.70–3.13)	1.84 (0.86–3.97)	
3 (483)	1.24 (0.62–2.50)	1.41 (0.68–2.89)	
4 (330)	0.94 (0.43–2.07)	1.16 (0.51–2.63)	
5 (180)	0.90 (0.35–2.32)	0.96 (0.35–2.61)	
Not known (58)	1.13 (0.31–4.03)	1.94 (0.52–7.25)	
Cholesterol[b]			
<5.0 (241)	1.00	1.00	
5.0–5.9 (190)	2.04 (0.80–5.18)	1.74 (0.66–4.60)	
6.0 + (153)	2.35 (0.91–6.06)	1.13 (0.42–3.03)	
Not known (1014)	1.45 (0.66–3.20)	0.78 (0.34–1.82)	

*$P<0.05$, **$P<0.01$, ***$P<0.001$. [a]Two-way interaction not significant.
[b]Due to large proportion of missing data, cholesterol values taken from up to 2 years after enrolment.

Table 3 Proportional Hazards Analysis of risk factors for the development of retinopathy (from normal or background retinae at baseline) Investigation of possible threshold levels in independent variables

Patient characteristics at baseline (first year)	*Maculopathy Univariate relative incidence (95% CI)*	n	*Proliferative Univariate relative incidence (95% CI)*	n
Duration of diabetes (years)				
	($n=1517$, 72 events)		($n=1577$, 79 events)	
<4.0	1.00	421	1.00	423
4.0–5.9	1.90 (0.45–7.94)	126	3.24 (0.20–51.8)	125
6.0–7.9	1.99 (0.48–8.35)	120	9.69* (1.01–93.2)	122
8.0–9.9	3.67* (1.06–12.7)	108	17.7** (2.07–151.5)	113
10.0–11.9	3.18 (0.85–11.8)	111	15.2* (1.70–135.8)	115
12.0–13.9	4.28* (1.31–14.0)	111	20.8** (2.51–172.9)	115
14.0–15.9	5.15** (1.63–16.2)	105	28.4** (3.55–226.9)	111
16.0–17.9	8.13*** (2.72–24.3)	85	43.7*** (5.59–341.5)	91
18.0–19.9	8.40*** (2.67–26.5)	66	40.2*** (4.95–326.9)	71
20.0–24.9	6.61*** (2.26–19.3)	119	46.1*** (6.10–349.4)	129
25.0+	7.36*** (2.62–20.6)	145	48.1*** (6.43–359.0)	162
Blood pressure (mm Hg) systolic				
	($n=1498$, 70 events)		($n=1557$, 78 events)	
<120	1.00	470	1.00	483
120–129	1.48 (0.64–3.44)	355	1.41 (0.69–2.89)	365
130–134	1.74 (0.72–4.19)	253	1.23 (0.55–2.78)	260
135–139	2.26 (0.50–10.3)	41	2.33 (0.67–8.12)	44
140–144	4.95*** (2.28–10.7)	172	3.47*** (1.74–6.93)	184
145–154	5.09*** (2.12–12.2)	93	1.98 (0.76–5.15)	97
155+	3.23** (1.27–8.18)	114	2.70* (1.20–6.08)	124
Urinary albumin (ug/l)				
	($n=1169$, 60 events)		($n=1215$, 61 events)	
<5.0	1.00	237	1.00	246
5.0–9.9	1.24 (0.53–2.87)	382	0.90 (0.43–1.86)	397
10.0–14.9	1.22 (0.47–3.17)	211	0.47 (0.17–1.34)	215
15.0–19.9	1.27 (0.42–3.89)	108	1.22 (0.48–3.09)	112
20.0–24.9	1.81 (0.54–6.01)	67	0.63 (0.14–2.80)	65
25.0–29.9	2.86 (0.86–9.51)	39	0.49 (0.06–3.75)	40
30.0–39.9	3.63* (1.09–12.1)	33	3.22* (1.21–8.57)	39
40.0+	3.09* (1.19–8.02)	92	2.14 (0.92–4.95)	101
Cholesterol[b]				
	($n=562$, 31 events)		($n=584$, 30 events)	
<4.0	1.00	63	1.00	64
4.0–4.9	0.67 (0.12–3.68)	173	2.12 (0.25–17.6)	177
5.0–5.9	1.57 (0.34–7.16)	178	3.77 (0.49–29.0)	190
6.0–6.9	1.60 (0.31–8.27)	89	3.23 (0.38–27.7)	93
7.0+	4.99* (1.09–22.8)	59	6.07 (0.73–50.4)	60

*$P<0.05$, **$P<0.01$, ***$P<0.001$. [a]Due to large proportion of missing data, cholesterol values taken from up to 2 years after enrolment.

relevance of smoking for the development of diabetic eye disease is controversial, especially after the UKPDS study indicated that for type-II diabetes retinal disease was less common in smokers,[20] although this may be due to a survival bias. The evidence for smoking in type-I diabetes is not clear cut. Smoking has been of borderline significance,[12] relevant only in the short term[14] or only significant depending on the statistical model used[13] in various previous studies. Our study again suggests a weak association between smoking and both proliferative disease and maculopathy in type-I diabetes, which is present on univariate analysis but not after adjustment for confounding factors.

We have also investigated threshold levels for the independent variables. The risk of proliferative retinopathy and maculopathy reached a plateau after 16 years duration of diabetes, with a systolic blood pressure of 140 mmHg and with a urinary albumin excretion of 30 mg/dl, with no increased risk at levels higher than this in each category.

We have demonstrated specific risk factors associated with the development of diabetic eye disease, and have identified different risk factors for maculopathy and proliferative retinopathy. We have also demonstrated thresholds for risk in developing diabetic eye disease, namely diabetes duration of 16 years, systolic blood pressure of 140 mmHg, and urinary albumin excretion of 30 mg/dl.

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