Five-year incidence and progression of diabetic retinopathy in a defined older population: the Blue Mountains Eye Study

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Abstract

Aims To determine 5-year incidence and progression of diabetic retinopathy in an older Australian population-based cohort.

Methods During the period 1992–1994, the Blue Mountains Eye Study examined 3654 residents aged 49+ years (82.4% of those eligible), living in two urban postcode areas, west of Sydney, Australia. Participants were subsequently invited to attend 5-year follow-up exams. After excluding 543 (14.8%) who died during the follow-up period, 2334 persons (75.0%) were re-examined during 1997–1999. The examination included a comprehensive questionnaire, blood pressure measurement, standardised refraction, Zeiss stereo retinal photographs, and estimation of fasting blood glucose. Diabetic retinopathy was graded from the retinal photographs, using the modified Early Treatment Diabetic Retinopathy Scale classification (15-step scale). **Results** Of participants with diabetes diagnosed at baseline, 150 were re-examined, including 139 with gradable fundus photographs. The cumulative 5-year incidence of diabetic retinopathy was 22.2% before 95% confidence interval (CI) 14.1–32.2%.

Retinopathy progression (1+ steps) was documented in 25.9% (95% CI 18.8–34.0%) of participants with retinopathy and gradable photographs at both visits; in 58.3% of these cases, a 2+ -step progression was documented. Progression to proliferative retinopathy occurred in only 4.1% of those with retinopathy at baseline. The only baseline risk factors associated with retinopathy progression, after adjusting for age and gender, were increase in fasting blood

glucose, odds ratio (OR) 1.2 (95% CI 1.1–1.4)/mmol/l, and increase in diabetes duration, OR 2.3 (95% CI 1.0–5.3)/10 years.

Conclusions These data provide 5-year cumulative incidence of diabetic retinopathy in a defined older population. Increase in diabetes duration and elevated baseline fasting blood glucose level predicted retinopathy incidence.

Eye (2007) 21, 465–471. doi:10.1038/sj.eye.6702771; published online 23 February 2007

Keywords: type II diabetes; diabetic retinopathy; incidence; population-based study; Blue Mountains Eye Study

Introduction

With the increasing prevalence of type II (non-insulin dependent) diabetes in most Western countries associated with the ageing population, the ocular morbidity from diabetes is likely to remain an ongoing public health issue in the future.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported a 4-year cumulative retinopathy incidence of 32.7% for diabetic subjects not using insulin in the age group 60–74 years, whereas for persons using insulin, the incidence was 45.9%.¹ Few community-based studies of older populations have reported diabetic retinopathy incidence. In the Beaver Dam Eye Study, Wisconsin reported on the prevalence of diabetic retinopathy,² but to date, have not reported diabetic retinopathy incidence. In clinic-based studies,^{1,3–8} a wide variation in diabetic retinopathy incidence has

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Received: 2 August 2005
Accepted: 17 August 2005
Published online: 23 February 2007

been reported, presumably because different criteria have been used to diagnose diabetes, to define and grade retinopathy, and because there have been both variable follow-up periods and sample selection.

We aimed to determine 5-year incidence of diabetic retinopathy among persons with diabetes (both previously detected and newly diagnosed) from a defined older community and the 5-year progression and regression of existing diabetic retinopathy lesions that were detected at the baseline examination.

Methods

Population studied

The Blue Mountains Eye study (BMES) is a population-based study of vision and common eye diseases in a defined older community of two postcode areas in the Blue Mountains region, west of Sydney, Australia. Baseline examinations were conducted between 1992 and 1994 (BMES-1) and 5-year follow-up examinations between 1997 and 1999 (BMES-2). The study methodology has been described in detail previously.^{9,10} Briefly, after a door-to-door census in the study region, permanent non-institutionalised residents born before 1 January 1943 were invited to the local hospital to undergo a detailed eye examination. Of the 4433 eligible residents, 3654 participated (82.4%), 501 refused (11.35%), whereas 210 (4.85%) had moved from the study area, and 68 (1.5%) had died after the census was carried out. Residents participating in the initial study were invited after 5 years for a follow-up examination at the same local hospital. At follow-up, 2334 of the 3654 baseline participants (63.9%) were re-examined, 543 (14.8%) had died, 394 (10.8%) refused to participate, and 383 (10.5%) had moved from the study area.^{11,12}

Procedures

Similar procedures were conducted at both the baseline and 5-year follow-up visits, including

- Detailed interview by trained interviewers covering both ocular and systemic medical history and medication usage.
- Comprehensive eye examination with measures of height, weight, and seated blood pressure.
- 30° fundus photographs taken using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany) through dilated pupils, including stereo-photographs of Diabetic Retinopathy Study (DRS) fields 1 (centred on the optic disc) and 2 (centred on the macula) and nonstereo photographs of fields 3 (temporal), 4 and 5 (upper and lower vascular arcades, respectively), and a field nasal to the optic disc. Fields 4 and 5 were

modified to accommodate the vascular arcade slightly closer to the centre of each photograph.¹⁰

- Fasting pathology tests for blood glucose, serum lipids, creatinine, and fibrinogen levels, within 8 weeks of the clinic visit. A fasting blood glucose level ≥ 7.0 mmol/l (hexokinase method) was used to diagnose new cases of diabetes mellitus.¹³

Examination findings and recommendations were sent to each participant, and his/her general practitioner and eye care practitioner.

Grading

Fundus photographs of all participants with diabetes diagnosed by history or fasting blood glucose ≥ 7.0 mmol/l were regraded in a masked manner using an adaptation of the modified Airlie House Classification used in the Early Treatment Diabetic Retinopathy Study (ETDRS).¹⁴ Intra-grader reliability of our earlier grading has been reported.¹⁰ Questionable retinopathy lesions were adjudicated and other definite lesions reviewed by the senior authors (PM, LC), before the final retinopathy grade was determined. In grouping participants according to the retinopathy level, we followed the ETDRS summary,¹⁴ with an additional severity level (14: haemorrhages without microaneurysms; and 15: hard exudates, soft exudates, or intraretinal microvascular abnormalities, in the absence of any microaneurysms) to define presence of 'questionable' diabetic retinopathy. As in the WESDR,⁸ the retinopathy level for each participant was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight, as shown in Table 1. This scheme provides a 15-step scale (10/10, 14–15/10, 14–15/14–15, 20/ <20, 20/20, 35/ <35, 35/35, 43/ <43, 43/43, 47/ <47, 47/47, 53/ <53, 53/53, 60+ / <60+ , 60+ /60+), with all levels of proliferative retinopathy grouped as one step. The higher level of retinopathy for the two eyes thus determines the level of retinopathy for each participant.

For the purposes of this study, an increase of one or more steps on the 15-step scale over the 5-year period from the baseline examination was considered to indicate progression of retinopathy. Progression rates of two or more steps were also calculated. Retinopathy level was considered ungradable if the photographs from both eyes could not be graded or were missing, or if the photographs of one eye could not be graded (or was missing), whereas the fellow eye had retinopathy level <20.

Statistical analysis

Statistical analysis system (SAS, version 6.12, SAS Institute Inc., Cary, NC, USA) was used to perform all

Table 1 Adaptation from the ETDRS classification of diabetic retinopathy¹⁴

Retinopathy level	Severity	15-Step scale	
		Lower	Higher
10	No retinopathy	10/10	
14–15	Questionable diabetic retinopathy	14–15/10	14–15/14–15
20 ^a	Minimal NPDR	20/ <20	20/20
35 ^a	Mild NPDR	35/ <35	35/35
43 ^a	Moderate NPDR	43/ <43	43/43
47 ^a	Moderately severe NPDR	47/ <47	47/47
53 ^a	Severe NPDR	53/ <53	53/53
60 ^a	PDR	60+ / <60+	60+ /60+

Abbreviations: NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

^aIncludes presence of microaneurysms.**Table 2** Baseline characteristics of diabetic participants who (1) returned to 5-year examinations (*n* = 150), (2) did not return (*n* = 65), or (3) died (*n* = 69)

Baseline characteristics	Participants (<i>n</i> = 150, 147 with gradable photos)	Non-participants (<i>n</i> = 65, 61 with gradable photos)	*P-value	Died (<i>n</i> = 69, 60 with gradable photos)	*P-value
Age (years) (mean ± SD)	66.2 ± 8.4	65.9 ± 8.3	NS	73.6 ± 7.3	0.0001
Age at diagnosis (years) (mean ± SD)	60.4 ± 11.2	60.5 ± 10.3	NS	65.7 ± 13.1	0.005
Duration of diabetes (years) (mean ± SD)	5.8 ± 7.5	5.4 ± 6.8	NS	7.9 ± 10.8	NS
Fasting blood glucose (mmol/l) (mean ± SD)	8.1 ± 3.3	9.7 ± 4.2	0.009	9.5 ± 4.5	0.04
Systolic blood pressure (mm Hg) (mean ± SD)	150.5 ± 21.9	150.6 ± 20.9	NS	155.0 ± 29.7	NS
Diastolic blood pressure (mm Hg) (mean ± SD)	83.4 ± 10.9	85.1 ± 8.2	NS	83.5 ± 13.0	NS
Sex (M:F) %	52.7: 47.3	44.6: 55.4	NS	60.9: 39.1	NS
Retinopathy present (number (%))	50 (34.0)	23 (37.7)	NS	30 (50.0)	0.05
<i>Retinopathy severity</i>					
None (number (%))	97 (64.7)	38 (58.5)		30 (43.5)	
NPDR (number (%))	49 (32.7)	23 (35.4)		27 (39.1)	
PDR (number (%))	1 (0.6)	0 (0)		3 (4.4)	
Ungradable (number (%))	3 (2.0)	4 (6.1)		9 (13.0)	

Abbreviations: NPDR, non-proliferative diabetic retinopathy; NS, non-significant; PDR, proliferative diabetic retinopathy.

*P-value in comparison with participants.

analyses, including *t*-tests, χ^2 -test, and logistic regression. Age, sex, fasting blood glucose level, and duration of diabetes were included in the multivariate logistic regression model. Odds ratios (OR) and 95% confidence intervals (CI) are reported.

Results

At the baseline examination, a total of 284 participants had diabetes (8.8%), including 218 who gave a history of diabetes and 66 whose diabetes was diagnosed from the fasting blood glucose test performed at the study. By the time the 5-year follow-up examination was conducted, 69 (24.3%) had died, 40 (14.1%) had moved from the study area, and 25 (8.8%) refused to attend, 150 were re-examined, which represents 52.8% of all baseline participants with diabetes or 70% of 215 surviving participants with diabetes. Selected baseline

characteristics of participants and non-participants (deaths and others) at the 5-year follow-up examination are shown in Table 2. Those who died were older, more likely to have retinopathy at baseline and had slightly higher fasting glucose levels than participants. Of others not examined, slightly higher fasting blood glucose was the only significant difference found between participants and non-participants ($P < 0.01$). Of the 284 baseline participants with diabetes, 24.3% died during the 5-year follow-up period, compared to a mortality rate of only 14.1% among persons without diabetes. Of subjects with diabetes who died, 46.9% had retinopathy at baseline, whereas 34.9% of survivors had retinopathy at baseline. The proportions with diabetic retinopathy were similar between baseline participants and those who returned to the 5-year examinations: that is, 103/284 (36.3%) compared to 50/147 (34.0%) returning participants with

Table 3 Progression of retinopathy in 139 diabetic participants examined at both baseline and 5-year visits with retinal photographs available from both examinations

Baseline retinopathy level	n	Retinopathy level at the 5-year follow-up visit				
		DR absent (%)	NPDR questionable, minimal, or mild (%)	NPDR moderate or severe (%)	PDR (%)	Macular oedema (%)
DR absent	90	77.8	22.2	—	—	
NPDR—quest, min, mild	39	30.8	56.4	12.8	—	
NPDR—moderate, severe	9	—	22.2	55.6	22.2	
PDR	1				100	
Total	139					
Macular oedema (%)	5.3					4.0

Abbreviations: DR, diabetic retinopathy; n, number of participants with gradable photos; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; quest, questionable diabetic retinopathy.

Table 4 Risk factors for progression of retinopathy level^a in participants after 5-year follow-up

Variable	Progression (mean $\pm$ SD) (n = 36)	No progression (mean $\pm$ SD) (n = 103)	P-value ^b
Age (years)	66.7 $\pm$ 8.2	65.5 $\pm$ 8.1	0.45
Duration of diabetes (years)	7.4 $\pm$ 6.4	5.6 $\pm$ 8.0	0.17
Systolic blood pressure (mm Hg)	150 $\pm$ 21	150 $\pm$ 23	0.92
Diastolic blood pressure (mm Hg)	84 $\pm$ 12	83 $\pm$ 11	0.81
Fasting blood glucose (mmol/l)	9.5 $\pm$ 4.3	7.6 $\pm$ 2.8	0.02
HDL Cholesterol (mmo/l)	1.2 $\pm$ 0.4	1.3 $\pm$ 0.4	0.58
Cholesterol (mmol/l)	5.8 $\pm$ 1.2	5.7 $\pm$ 1.0	0.87
Triglyceride (g/l)	2.4 $\pm$ 1.7	2.3 $\pm$ 1.3	0.59
Fibrinogen (g/l)	3.8 $\pm$ 0.9	4.0 $\pm$ 1.0	0.24
Body mass index (kg/m ²)	28.8 $\pm$ 5.8	27.9 $\pm$ 4.8	0.40
Sex (% female)	44.4	48.5	NS
Current smoking (%)	11.1	13.0	NS
Hypertension definite (%)	44.4	54.4	NS
Family history 1st generation (%)	27.8	36.9	NS

Abbreviations: HDL, high density lipoprotein; NS, non-significant.

^aProgression of retinopathy level using the 15-step-scale in Table 1.

^bt-Tests for continuous variable, χ^2 for categorical variable.

gradable retinal photographs had diabetic retinopathy at baseline.

Retinopathy developed in 20 of 90 participants with no diabetic retinopathy present at baseline (22.2%, 95% CI 14.1–32.2%). After excluding those with other isolated retinopathy lesions but no microaneurysms, the 5-year cumulative incidence was only 14.4%.

A total of 139 participants who had retinal photographs available at both the baseline and the 5-year examinations were considered for the analysis of progression of retinopathy, including progression from no retinopathy (step 10/10) to minimal or worse levels. Progression of diabetic retinopathy level in the worse eye of these 139 participants is shown in Table 3. The second column of this table presents the number of subjects with various retinopathy levels at baseline, and the remaining five columns represent the proportion with each retinopathy level 5 years later. Owing to the collapse of some retinopathy levels in Table 3, numbers with

progression or regression calculated from this table are slightly different from the number and proportions described below, calculated according to retinopathy levels presented in Table 1. After the 5-year follow-up period, the retinopathy in 36 (25.9%, 95% CI 18.8–34.0) had progressed one or more steps higher on the scale, 16 had regressed (11.5%, 95% CI 6.7–18.0), and 87 remained at the same level as at the baseline examination (62.6%, 95% CI 54.0–70.7). Among those participants who progressed after 5 years, 58.3% progressed by two or more steps (not shown in Table 3, owing to collapse of some levels in this table). Two of the nine participants (22.2%) with moderate or severe non-proliferative retinopathy progressed to proliferative retinopathy. This number also accounted for 4.2% of participants with presence of any retinopathy lesion progressing to proliferative retinopathy.

Table 4 shows baseline characteristics of participants with and without progression of retinopathy level at

Table 5 OR with confidence intervals (CI) of selected risk factors predicting progression of retinopathy in multivariate model

Risk factors	Progression (% (number))		OR (95% CI) age-sex adjusted	OR (95% CI) multivariate model
	With factor	Without factor		
Diabetes duration > 10 years	41.2 (14)	21.0 (22)	2.7 (1.1–6.2)	2.4 (1.0–6.1)
Fasting glucose ≥ 10.0	44.4 (12)	21.3 (23)	3.3 (1.3–8.4)	3.2 (1.3–8.4)

follow-up. The mean fasting glucose level was higher in those whose retinopathy progressed than in those without progression, 9.4 ± 4.2 vs 7.6 ± 2.8 mmol/l, respectively, $P < 0.05$. Although diabetes duration, body mass index, and the proportion of women were all slightly higher among participants exhibiting progression, these differences were not statistically significant.

After adjusting for age and gender, fasting blood glucose level (OR 1.2, 95% CI 1.1–1.4) and the duration of diabetes (OR 1.04, 95% CI 1.0–1.1, per year) were the only statistically significant risk factors for progression. The relative risk for progression was even greater for participants with duration of diabetes ≥ 10 years at follow-up (OR 2.7, 95% CI 1.1–6.2) or for baseline fasting blood glucose levels ≥ 10 mmol/l (OR 3.4, 95% CI 1.3–8.4). Other potential risk factors that were not statistically significantly related to progression were history of hypertension, serum cholesterol, triglycerides and HDL cholesterol, body mass index, and a first-degree family history of diabetes. The risk of progression was found to be 2.8 times higher (after 5 years of follow-up) when both fasting blood glucose ≥ 10 mmol/l and duration of diabetes ≥ 10 years were present at the baseline examination (Table 5).

Discussion

There have been few similar community-based incidence studies of defined older population samples with which to compare these findings. Our cumulative incidence rate of 22.2% is somewhat lower than the cumulative incidence of 32.7% reported for non-insulin-treated diabetic participants aged 60–74 years who were examined after 4 years in the WESDR.¹ However, the rate from our study is identical to the 5-year incidence of 22.2% reported from a Japanese population sample aged 60 years or older⁶ and is very similar to the 4-year incidence rate of 19.2% reported from a Taiwanese study³ and to the 5-year incidence rate from a Korean study of older-onset diabetes.¹⁵ Our cumulative incidence rate is also close to 26.2% reported in a 4-year follow-up of a sample of non-Hispanic whites with a mean age of 59 years,¹⁶ and lower than the 4-year rate of 30.8% incidence reported from a Swedish clinic study of 369 older-onset

non-insulin-treated diabetic subjects.¹⁷ In a large Australian clinic-based study of 1210 persons with diabetes (all age groups), which achieved a 70% follow-up rate after 4 years,⁵ the incidence of new diabetic retinopathy lesions in those without retinopathy was 8% per person-year of follow-up,⁵ a somewhat higher projected rate than in the current study. This earlier study was reported from a period when the control of type II diabetes was typically poorer than in the last decade.

Although our diabetic sample is relatively small compared with many of these earlier studies, including the WESDR,^{1,8} its population-based design provides an unbiased estimate of the 5-year cumulative incidence of diabetic retinopathy in a community of persons aged 50 years or older.

Excluding retinopathy levels in which microaneurysms were absent was associated with a one-third decrease in the cumulative incidence to 14.4%. Thus, the outcome of incidence studies may vary substantially depending on the classification of retinopathy used. Given that retinopathy with no microaneurysms present (termed 'questionable' diabetic retinopathy) could indicate the presence of resolving non-proliferative diabetic retinopathy, we grouped this questionable level with minimal and mild non-proliferative diabetic retinopathy levels as a separate entity.

Our 25.9% 5-year cumulative rate of progression is relatively similar to 4-year follow-up rates found for non-Hispanic Whites (27.2%) and Hispanics (23.0%) aged 20–74 years in the San Luis Valley Diabetic Study,¹⁶ and to the progression rate of 23.6% reported from the Japanese study⁶ and slightly lower than the 30.3% progression rate recorded in Taiwan.³ However, in comparison to the WESDR, our 15.1% rate for progression of two or more steps after 5 years is substantially lower than the 29.1% rate reported for progression in WESDR diabetic subjects aged 34–74 years after 4 years.⁸ Although our study findings could be influenced by its relatively small number of diabetic subjects, it is also possible that this lower rate of progression could reflect improved diabetes management after the introduction of more widespread home glucose monitoring and awareness of the need to

achieve tight diabetic control than was recommended a decade ago, before the publication of findings from the Diabetes Control and Complications Trial.¹⁸

We found that longer duration of diabetes and higher fasting blood glucose level were associated with increased progression of retinopathy over the 5-year period. This finding is not unexpected, because higher levels of fasting blood glucose were shown to be statistically significantly related to presence of moderate to severe retinopathy than to mild or no retinopathy in our previous prevalence report, after adjusting for age, gender, and the duration of diabetes.¹⁰

Our findings indicate that after 5 years, for individuals with diabetes for a period of 10 years or longer, the relative risk for progression of the retinopathy level by at least one step was 2.4 compared with the progression rate among individuals with a diabetes duration of less than 10 years. Similarly, for diabetic subjects with baseline fasting blood glucose levels ≥ 10 mmol/l, the relative risk for progression of the retinopathy level by at least one step was 3.2 compared with the progression rate in diabetic subjects who were recorded as having fasting blood glucose levels less than 10 mmol/l. These findings are consistent with recent data on glycaemic control in older type II diabetes subjects from the United Kingdom Prospective Diabetes Study.¹⁹

Strengths of this study include its population-based sample and stereo retinal photographic documentation of the retinopathy level, graded initially by LC and adjudicated by a retinal specialist (PM). The limitation of our study is a relatively low follow-up rate among participants with diabetes compared to an overall follow-up rate of 75% in the whole study sample. Of the 284 baseline participants with diabetes, 69 died and only 150 of 215 (70.0%) survivors with diabetes returned at 5 years. Although this follow-up rate is acceptable, it could have introduced selection bias in estimating diabetic retinopathy incidence rates in the direction of either an overestimate or underestimate.

In summary, the cumulative incidence, after 5-year follow-up, of developing diabetic retinopathy lesions in this older community was 22.2%. The 5-year cumulative rate for retinopathy progression of at least one step or more was 25.9%, whereas progression from any signs of non-proliferative retinopathy to proliferative retinopathy over this period was only 4.2%. Higher baseline fasting blood glucose levels and longer duration of diabetes were the only statistically significant risk factors found for retinopathy progression after 5 years in this study.

Acknowledgements

This study was supported by the Australian National Health & Medical Research Council (Grant no. 974159)

and the Westmead Millennium Institute, University of Sydney.

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