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RESEARCH

Incidence and progression of diabetic retinopathy within a private diabetes mellitus clinic in South Africa

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Objective: The study objective was to examine the influence of glycaemic control and ethnic variations on the incidence and progression of diabetic retinopathy (DR).
Design, subjects and setting: Eight hundred and ninety-two persons with type 1 diabetes mellitus, and 1 998 persons with type 2 diabetes mellitus, who were enrolled in a private diabetes mellitus management programme in South Africa, participated in the study. Survival analyses were conducted to assess the relationship between the risk factors and the incidence of DR and referable DR, and the progression of DR.
Outcome measures: Cumulative incidence of diabetic retinopathy and referable diabetic retinopathy.
Results: The seven-year cumulative incidence of DR and referable DR was 536 and 50 cases per 1 000 persons with type 1 diabetes mellitus without DR at baseline, and 351 and 47 cases per 1 000 persons with type 2 diabetes mellitus. The seven-year cumulative incidence of referable DR was 332 cases per 1 000 persons with type 1 diabetes mellitus with background DR at baseline, and 360 cases with type 2 diabetes mellitus, representing a seven- and eightfold increase compared to no DR at baseline. After controlling for known risk factors for DR, a high baseline haemoglobin A_{1c} (HbA_{1c}) and non-Caucasian ethnicity were associated with the incidence of referable DR in patients with type 1 and type 2 diabetes mellitus.
Conclusion: It was revealed in the first study to report on the incidence and progression of DR in South Africa that a high baseline $HbA_{1c,}$ ethnicity, and the presence of background DR increased the risk of the development of referable DR.

Keywords: diabetes mellitus, diabetic retinopathy, epidemiology, incidence, risk factors, South Africa

Introduction

In South Africa, diabetic retinopathy (DR) is the fourth leading cause of blindness, after cataracts, glaucoma and age-related macular degeneration; and visual impairment, after refractive errors, cataracts and glaucoma; and the third leading cause of severe visual impairment, after refractive errors and cataracts in persons aged ≥ 50 years.[1]

The prevalence rate of DR in South Africa is estimated to be between 5% and 10%,[2] and has been reported to vary in different ethnic groups.[3–6] There are no reports of incidence rates in the country. Incidence rates reported elsewhere in the world have mainly been based on Caucasian populations.[7–9] Emerging evidence suggests that there are ethnic variations in the development of DR.[10] However, it remains unclear whether these variations represent true differences, or are associated with glycaemic control or a genetic predisposition to microvascular complications, including DR.

Good control of glycaemia, blood pressure and cholesterol has been demonstrated to reduce the risk of of DR progressing, and is the cornerstone of good diabetes mellitus care.[11] However, a rapid improvement in glycaemic control in those with prior evidence of DR associated with poor glycaemic control may increase the risk of existing retinopathy progressing.[12]

The aim of this study was to examine the incidence of DR and the progression of existing DR within a population undergoing screening for DR in a private healthcare setting in Johannesburg, South Africa. The effect of glycaemic control and ethnic variations on the incidence and progression of DR were examined in persons with type 1 and type 2 diabetes mellitus.

Subjects, materials and method

The Centre for Diabetes and Endocrinology is a private, multi-specialist centre based in Johannesburg, South Africa. Details of the diabetes mellitus management programme and DR screening protocol of the Centre for Diabetes and Endocrinology have been published previously.[3,13]

The study participants were classified as type 1 or type 2 diabetes mellitus patients on clinical assessment, according to the American Diabetes Association,[14] who had undergone at least one subsequent DR screening event after the initial baseline assessment.

Screening for DR was conducted on an annual basis with one 45° macular digital image captured using a Canon® CR6 -45 NM camera without mydriasis, between 2001 and 2010. All retinal images were independently reviewed and graded by one of three senior retinal graders according to a modified UK standard DR grading protocol, used by the Diabetic Retinopathy Screening Service for Wales.[3] Levels of DR were classified as:

- *No DR:* If no lesions were detected.
- *Any DR:* When at least 1 microaneurysm and/or a blot haemorrhage was detected.
- *Background DR:* mild or moderate background DR with or without possible maculopathy (M1).

- *Referable DR:* Pre-proliferative DR, proliferative DR, as well as exudative maculopathy (M2), were classified as referable DR. RDR was the level at which further assessment by an ophthalmologist was deemed to be necessary.

The haemoglobin A_{1c} (HbA_{1c}), lipid analyses, serum creatinine concentrations and albumin to creatinine ratio were determined at baseline. The change in HbA_{1c} was calculated using the HbA_{1c} concentration either at the time that the referable DR was first identified, or if referable DR did not develop from the last known screening event, minus the baseline HbA_{1c} level. Study participants were considered to have hypertension if their blood pressure was found to be above 140/90 mmHg, taken in the right arm after they had been seated for five minutes of rest, and/or if they were already receiving antihypertensive therapy.

Statistical analysis

All data was anonymised before statistical analysis was conducted using SPSS® version 16. The population characteristics were described using means and standard deviations for continuous variables, and percentages for categorical variables. The Kaplan-Meier estimator was used to calculate the cumulative incidence rates per 1 000 persons. The results are reported with 95% confidence intervals (CIs). The log rank test was used to test for equivalence between the survival curves of categorical variables. Cox proportional hazards regression was used to assess the association of clinical risk factors and the development of referable DR with hazard ratios and 95% CI calculated for each category of diabetes mellitus. Continuous variables, i.e. the duration of diabetes mellitus and age at diagnosis were stratified as duration of diabetes mellitus (< 7, 7–15 and > 15 years) for patients with type 1 diabetes mellitus, and (< 3, 3–8 and > 8 years) for those with type 2 diabetes mellitus; and age at diagnosis of diabetes mellitus (≤ 11, 12–20, 21–32 and ≥ 33 years) for participants with type 1 diabetes mellitus, and ≤ 42, 43–50, 51–58 and ≥ 59 years for participants with type 2 diabetes mellitus. These categories were used to ensure an equal distribution among the groups. Associations were considered to be significant if the *p*-value was < 0.050.

Results

Between 2001 and 2010, 5 515 persons with diabetes mellitus (1 537 type 1 and 3 978 type 2) underwent retinal screening. The characteristics of the full population at baseline have been reported previously.[3] The persons included in this analysis had no evidence of DR (2 339, 81%) or pre-existing background DR (551, 19%) at baseline and after at least one further screening event. Of the total population (2 890), 892 (31%) had type 1 diabetes mellitus and 1 998 (69%) had type 2 diabetes mellitus. The baseline characteristics according to DR status for both type 1 and type 2 diabetes mellitus on entry are shown in Table 1. There was a longer duration of diabetes mellitus in persons with type 1 diabetes mellitus with pre-existing DR at baseline, and they were younger at diagnosis than those without previous DR. A higher baseline albumin to creatinine ratio was also reported in those with pre-existing DR, and they were more hypertensive than those without previous DR. There was also a longer duration of diabetes mellitus in persons with pre-existing DR with type 2 diabetes mellitus, and they were younger at diagnosis than those without previous DR. A higher baseline HbA_{1c} level and albumin to creatinine ratio were also reported for those with pre-existing DR than for those without previous DR.

Incidence and progression of diabetes retinopathy

Thirty-five per cent of persons with type 1 diabetes mellitus without previous DR developed any DR, i.e. 32% with background DR, and 3% with referable DR, during the course of the study (Table 1). Of those with referable DR, 0.6% had pre-proliferative DR, 2.0% maculopathy, and 0.5% pre-proliferative DR with maculopathy. The seven-year cumulative incidence of any DR, background DR and referable DR in those without DR at baseline was 536; 511 and 50 cases per 1 000 persons, respectively (Table 2). Twenty-three per cent of those with pre-existing background DR developed referable DR. Of those with referable DR, 8% had pre-proliferative DR, 66% maculopathy, 14% pre-proliferative DR with maculopathy, 5% proliferative DR and 7% proliferative DR with maculopathy. The seven-year cumulative incidence of referable DR in those with background DR at baseline was 332 cases per 1 000 persons. The seven-year cumulative incidence of referable DR in persons with type 1 diabetes mellitus was sevenfold higher in persons with pre-existing background DR than in those with no previous DR.

15.3% of those without previous DR with type 2 diabetes mellitus developed any DR, consisting of 13.6% background DR and 1.5% referable DR (Table 1). The category of referable DR consisted of 1.40% with maculopathy, and 0.06% pre-proliferative DR with maculopathy. No one developed proliferative DR during the study. The seven-year cumulative incidence of any DR, background DR and referable DR in those without DR at baseline was 351, 331 and 47 cases per 1 000 persons (Table 2). 19.9%t of those with pre-existing background DR developed referable DR, which consisted of 3.0% with pre-proliferative DR, 14.9% maculopathy, 1.7% pre-proliferative DR with maculopathy, and 0.3% proliferative DR. The seven-year cumulative incidence of referable DR in those with background DR at baseline was 360 cases per 1 000 persons. The seven-year cumulative incidence of referable DR in persons with type 2 diabetes mellitus was eightfold higher in those with pre-existing DR than in those without previous DR.

Glycaemic control

The change in HbA_{1c} over the course of the study period was minimal in both persons with type 1 and type 2 diabetes mellitus [median of 0.1%, interquartile range (IQR) of −0.8 to 0.9%, and median of 0.1% (IQR of −0.6 to 0.8%), respectively]. The crude hazard ratio for a change in HbA_{1c} failed to reach significance over the course of the study using Cox regression analysis (Table 3). The crude hazard ratio for a 1% increase in baseline HbA_{1c} was associated with a 1.27 (95% CI: 1.16–1.39) and 1.54 (95% CI: 1.36–1.74) increased risk of developing referable DR for participants with type 1 and type 2 diabetes mellitus, respectively. There was a 1.44 (95% CI: 1.27–1.62) and a 1.33 (95% CI: 1.15–1.54) increased hazard of developing referable DR for patients with type 1 and type 2 diabetes mellitus, respectively, following a change in HbA_{1c}, DR status on entry and the presence of hypertension for every 1% increase in baseline HbA_{1c}, after adjusting for age at diagnosis of diabetes mellitus, gender and duration of diabetes mellitus.

Ethnicity

The characteristics of Caucasians and non-Caucasians at baseline in persons with type 1 and type 2 diabetes mellitus are shown in Table 4. Eighty-three per cent of type 1 diabetes mellitus patients were Caucasian, and 17% non-Caucasian. A significantly lower HbA_{1c} on entry was recorded in Caucasians [mean of 8.4% (68 mmol/mol) ± 1.0%] than non-Caucasians [mean of 9.2% (77 mmol/mol) ± 2.4%], ($p < 0.001$). Over the course of the study, there was a minimal increase in HbA_{1c} of 0.07% (± 1.6%) in Caucasians, and a minimal reduction of 0.40% (± 2.2%) in non-Caucasians (*p* 0.013). Seventy-three per cent of type 2 diabetes mellitus patients were Caucasian, and 27% were non-Caucasian. A significantly lower baseline HbA_{1c} was recorded in Caucasians

Table 1: Baseline characteristics of those with at least two clinic visits presenting without diabetic retinopathy, and with background diabetic retinopathy

Characteristics	Type 1 diabetes mellitus			Type 2 diabetes mellitus		
	No DR	Background DR	*p*-value	No DR	Background DR	*p*-value
n (%), 95% confidence interval	637 (66.0), 63.0–68.9	255 (26.4), 23.7–29.3		1 702 (80.9), 79.2–82.5	296 (14.1), 12.7–15.6	
Age (years)*	33.5 (15.2)	37.9 (14.0)	< 0.001	56.8 (11.5)	57.6 (10.8)	0.271
Gender			0.438			0.191
Male, (*n*, %)	344 (54.0)	145 (56.9)		1 136 (66.7)	209 (70.6)	
Female (*n*, %)	293 (46.0)	110 (43.1)		566 (33.3)	87 (29.4)	
Ethnicity			0.448			< 0.001
Caucasian (*n*, %)	521 (81.8)	219 (85.9)		1 271 (74.7)	189 (63.9)	
Indigenous African (*n*, %)	51 (8.0)	13 (5.1)		186 (10.9)	43 (14.5)	
Indian Asian (*n*, %)	47 (7.4)	17 (6.7)		192 (11.3)	42 (14.2)	
Mixed race (*n*, %)	16 (2.5)	6 (2.4)		46 (2.7)	20 (6.8)	
Duration of diabetes mellitus (years)*	10.0 (9.6)	18.22 (9.0)	< 0.001	5.2 (5.7)	10.6 (7.6)	< 0.001
Age at diagnosis of diabetes mellitus (years) *	23.5 (14.0)	19.7 (11.9)	0.223	51.5 (11.5)	46.9 (12.1)	< 0.001
Baseline HbA_{1c} percent (*n*, %)*	8.5 (2.1)	8.7 (1.9)	0.179	7.6 (1.7)	8.1 (1.7)	< 0.001
Baseline HbA_{1c} (mmol/mol)	69	72		60	65	
Total cholesterol (mmol/L)*	5.0 (1.0)	5.3 (1.0)	0.005	4.9 (1.1)	4.8 (1.1)	0.170
Albumin to creatinine ratio*	1.9 (4.8)	3.8 (7.7)	0.013	3.1 (6.8)	6.5 (16.7)	0.029
Hypertension (*n*, %)	84 (13.2)	52 (20.4)	0.007	896 (52.6)	175 (59.1)	0.039
Smoking status (*n*, %)	107 (16.8)	46 (18.0)	0.657	229 (13.5)	45 (15.2)	0.420
Other therapies (*n*, %)						
ACE inhibitors	73 (11.5)	40 (15.7)	0.086	687 (40.4)	140 (47.3)	0.025
Aspirin	10 (1.6)	2 (0.8)	0.357	286 (16.8)	42 (14.2)	0.262
Incidence of any DR (*n*, %)	221 (34.8)			260 (15.3)		
Incidence of background DR	201 (31.6)			231 (13.6)		
Incidence of or progression to referable DR	20 (3.1)	58 (22.7)		25 (1.5)	59 (19.9)	
Development of referable DR (*n*, %)						
Pre-proliferative DR with or without maculopathy	4 (20.0)	5 (8.6)		0	9 (15.3)	
Maculopathy with background DR	13 (65.0)	38 (65.5)		24 (96.0)	44 (74.6)	
Pre-proliferative DR with or without maculopathy, plus maculopathy with background DR	3 (15.0)	8 (13.8)		1 (4.0)	5 (8.5)	
Proliferative DR	0	3 (5.2)		0	1 (1.7)	
Proliferative DR plus maculopathy, with background DR	0	4 (6.9)		0	0	

Note: DR: diabetic retinopathy, HbA_{1c}: haemoglobin A_{1c}
*: Numbers are presented as mean (± standard deviation)

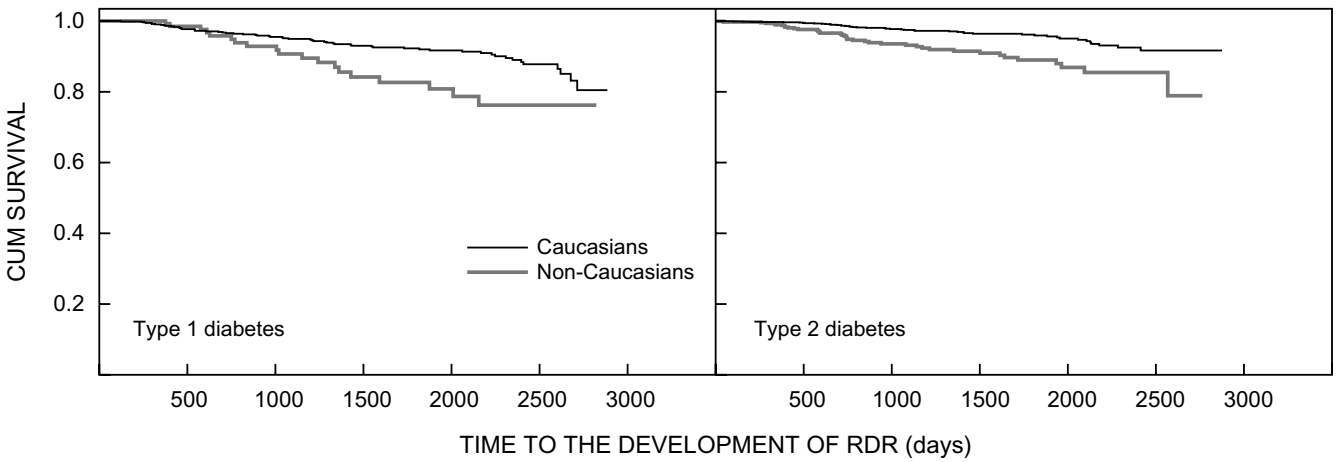
Table 2: Annual and cumulative incidence of any diabetic retinopathy, background diabetic retinopathy, referable diabetic retinopathy and proliferative diabetic retinopathy in persons with type 1 (top) and type 2 (bottom) diabetes mellitus without diabetic retinopathy (left) at baseline and with background diabetic retinopathy at baseline (right)

	Baseline no DR				Baseline background DR			
Type 1 diabetes mellitus	**Incidence of any DR (*n* = 223)**		**Incidence of background DR (*n* = 203)**		**Incidence of referable DR (*n* = 20)**		**Progression to referable DR (*n* = 58)**	
Time since last screen (years)	**Annual incidence**	**Cumulative incidence (95% CI)**	**Annual incidence**	**Cumulative incidence (95% CI)**	**Annual incidence**	**Cumulative incidence (95% CI)**	**Annual incidence**	**Cumulative incidence (95% CI)**
1	29	29 (28.91–29.09)	28	28 (27.91–28.09)	2	2.0 (1.99–2.01)	28	28 (27.77–28.22)
2	134	163 (162.37–163.63)	124	152 (151.39–152.61)	7	9.0 (8.96–9.03)	72	100 (99.04–100.96)
3	91	254 (252.87–255.13)	88	240 (238.89–241.11)	9	18.0 (17.92–18.08)	51	151 (149.41–152.59)
4	65	319 (317.34–320.66)	59	299 (297.38–300.62)	7	25.0 (24.87–25.13)	68	219 (216.18–221.82)
5	77	396 (393.37–398.63)	73	372 (369.40–374.60)	6	31.0 (30.79–31.21)	21	240 (236.43–243.58)
6	77	473 (468.68–477.32)	73	445 (440.72–449.28)	14	45.0 (44.55–45.45)	27	267 (261.82–272.18)
7	63	536 (518.59–553.41)	66	511 (493.51–528.49)	5	50.0 (48.78–51.23)	65	332 (315.28–348.72)
Type 2 diabetes mellitus	**Incidence of any DR (*n* = 261)**		**Incidence of background DR (*n* = 236)**		**Incidence of referable DR (*n* = 25)**		**Progression to referable DR (*n* = 59)**	
Time since last screen (years)	**Annual incidence**	**Cumulative incidence (95% CI)**	**Annual incidence**	**Cumulative incidence (95% CI)**	**Annual incidence**	**Cumulative incidence (95% CI)**	**Annual incidence**	**Cumulative incidence (95% CI)**
1	18	18 (17.98–18.02)	17	17 (16.98–17.02)	1	1.0 (0.99–1.00)	21	21 (20.85–21.15)
2	59	77 (76.88–77.12)	52	69 (68.89–69.11)	4	5.0 (4.99–5.01)	86	107 (105.99–108.01)
3	62	139 (138.71–139.29)	57	126 (125.73–126.27)	6	11.0 (10.98–11.02)	77	184 (181.97–186.03)
4	39	178 (177.47–178.53)	34	160 (159.51–160.49)	2	13.0 (12.96–13.04)	50	234 (230.69–237.31)
5	35	213 (212.06–213.94)	35	195 (194.12–195.88)	4	17.0 (16.92–17.08)	45	279 (273.29–284.71)
6	55	268 (265.89–270.11)	56	251 (248.96–253.04)	20	37.0 (36.69–37.31)	81	360 (344.95–375.05)
7	83	351 (341.29–360.71)	80	331 (321.56–340.44)	10	47.0 (45.56–48.44)	0	360 (284.74–435.26)

Note: CI: confidence interval, DR: diabetic retinopathy

[7.5% (58 mmol/mol) ± 1.5%] than in non-Caucasians [8.0% (64 mmol/mol) ± 2.0%], ($p < 0.001$). There was a minimal increase in HbA_{1c} of 0.08% over the course of the study period in Caucasians, and a minimal reduction in HbA_{1c} of 0.03% in non-Caucasians. However, this difference was not significant ($p = 0.244$).

Caucasians were less likely to develop referable DR than non-Caucasians in both type 1 ($p = 0.006$) and type 2 diabetes mellitus ($p < 0.001$). However, this separation did not occur until after three years of follow-up in type 1 diabetes mellitus patients (Figure 1). Using Cox regression, the crude hazard ratio for the development of referable DR was increased in non-Caucasians when compared to Caucasians at 2.0% (95% CI: 1.19–3.56) vs. 2.7% (95% CI: 1.75– 4.16) for type 1 and type 2 diabetes mellitus, respectively (Table 3). After adjusting for age at diagnosis of diabetes mellitus, gender, duration of diabetes mellitus, HbA_{1c} at baseline and the change in $HbA_{1c,}$ as well as DR status on entry



Note: RDR: referable diabetic retinopathy

Figure 1: Kaplan-Meier curves for the development of referable diabetes retinopathy in Caucasian and non-Caucasian persons with type 1 (left) and type 2 (right) diabetes mellitus

Table 3: Cox regression analysis (expressed as hazard ratio (95% CI)) for the development of referable diabetic retinopathy

	Referable DR (*n* = 76)				Referable DR (*n* = 79)		
Type 1 diabetes mellitus	**Crude**	***n***	**Adjusted***	**Type 2 diabetes mellitus**	**Crude**	***n***	**Adjusted***
Gender				**Gender**			
Male	1	472	1	Male	1	1 259	1
Female	1.04 (0.66–1.63)	386	1.11 (0.70–1.75)	Female	1.02 (0.64–1.61)	617	0.98 (0.60–1.60)
Ethnicity				**Ethnicity**			
Caucasian	1	714	1	Caucasian	1	1 379	1
Non-Caucasian	2.00 (1.19–3.56)	144	1.77 (1.01–3.08)	Non-Caucasian	2.70 (1.75–4.16)	497	2.40 (1.37–3.54)
Duration of diabetes mellitus (years)				**Duration of diabetes mellitus (years)**			
≤ 7	1	326	1	≤ 7	1	685	1
8–16	4.18 (1.95–8.98)	299	2.80 (1.22–6.40)	8–16	4.38 (1.96–9.79)	692	3.11 (1.29–7.49)
≥ 17	4.37 (2.00–9.52)	233	3.01 (1.19–7.64)	≥ 17	6.27 (2.80–14.05)	499	2.35 (0.92– 5.97)
Age at diagnosis (years)				**Age at diagnosis (years)**			
≤ 11	1	216	1	≤ 11	1	446	1
12–20	0.64 (0.32–1.28)	209	0.72 (0.35–1.47)	12–20	0.91 (0.55–1.49)	473	1.29 (0.76–2.20)
21–32	1.10 (0.61–1.98)	237	1.56 (0.84–2.92)	21–32	0.34 (0.17–0.67)	452	0.64 (0.30–1.35)
≥ 33	1.11 (0.60–2.06)	196	1.54 (0.78–3.02)	≥ 33	0.33 (0.16–0.67)	505	1.02 (0.44–2.34)
Baseline HbA_{1c}	1.27 (1.16–1.39)		1.44 (1.27–1.62)	Baseline HbA_{1c}	1.54 (1.36–1.74)		1.33 (1.15–1.54)
Average HbA_{1c}	1.38 (1.23–1.56)			Average HbA_{1c}	1.54 (1.36–1.74)		
Change in HbA_{1c}	0.97 (0.84–1.12)		1.18 (1.01–1.62)	Change in HbA_{1c}	0.91 (0.81–1.03)		1.06 (0.92–1.23)
DR status at baseline				**Baseline DR grade**			
No DR	1	607	1	No DR	1	1 595	1
Background DR	8.07 (4.81–13.55)	251	5.56 (3.15–9.80)	Background DR	14.93 (9.34–23.84)	281	11.94 (7.09–20.08)
Total cholesterol (mmol/L)				**Total cholesterol (mmol/L)**			
≤ 5.02	1			≤ 4.87	1		
≥5.03	2.71 (1.31–5.63)			≥ 4.88	0.83 (0.48–1.46)		
Albumin to creatinine ratio				**Albumin to creatinine ratio**			
≤ 0.90	1			≤ 1.07	1		
≥ 0.91	3.60 (1.73–7.51)			≥ 1.08	1.01 (0.54–1.90)		
Hypertension				**Hypertension**			
Yes	1	724	1	Yes	1	861	1
No	2.47(1.52– 4.03)	134	1.92 (1.11–3.31)	No	0.80 (0.52–1.23)	1 015	0.73 (0.45–1.17)
Smoking status	0.79 (0.42– 1.50)			Smoking status	1.51 (0.88–2.60)		
ACE inhibitors	1.50 (0.84– 2.67)			ACE inhibitors	0.60 (0.38–0.96)		

Note: ACE: angiotensin-converting enzyme, DR: diabetic retinopathy, HbA_{1c}: haemoglobin A_{1c}
*:Each variable is adjusted for all other covariates included in Table 3. For example, gender has been adjusted for ethnicity, duration of diabetes mellitus, age at diagnosis of diabetes mellitus, baseline haemoglobin A_{1c}, change in haemoglobin A_{1c} and hypertension. All variables were measured at baseline, except for the change in haemoglobin A_{1c} which is the haemoglobin A_{1c} concentration at the time that referable diabetic retinopathy developed, or the last time it was recorded in the study minus the baseline haemoglobinA_{1c} value

and the presence of hypertension, non-Caucasians with type 1 diabetes mellitus had a 1.77-fold increased hazard of developing referable DR (95% CI: 1.01–3.08), and non-Caucasian type 2 diabetes mellitus a 2.40-fold increased hazard of developing referable DR (95% CI: 1.37–3.54), compared to Caucasians.

Baseline diabetic retinopathy status

The multivariate model contained gender, ethnicity, age at diagnosis, duration of diabetes mellitus, baseline and the change in HbA_{1c}, DR status at entry and the presence of hypertension. After adjusting for all of these confounders, DR status on entry was associated with the development of referable DR. There was a hazard ratio of 5.56 and 11.94, for those with pre-existing background DR, compared to those without DR, for type 1 and type 2 diabetes mellitus respectively (Table 3).

Discussion

The seven-year cumulative incidence of referable DR in a diabetes mellitus management programme based in Johannesburg, South Africa, was similar for persons with type 1 diabetes and type 2 diabetes mellitus without previous DR at 50 and 47 cases per 1 000 persons, respectively, and 332 and 360 cases per 1 000 persons, respectively, for those with pre-existing background DR. Poor glycaemic control on entry into the diabetes mellitus management programme was associated with a greater risk of developing referable DR in both type 1 and type 2 diabetes mellitus patients. Non-Caucasians were also at an increased risk of developing referable DR compared to Caucasians, even after adjusting for confounders, such as glycaemic control. The presence of background DR on entry into the programme was the strongest association with the subsequent development of referable DR, after adjusting for all other risk factors.

Table 4: Characteristics of the population with type 1 and type 2 diabetes mellitus by ethnicity

Characteristics	Type 1 diabetes mellitus		Type 2 diabetes mellitus	
	Caucasian	Non-Caucasian	Caucasian	Non-Caucasian
n	740	150	1 460	529
Age (years)*	35.1 (15.4)	33.8 (13.9)	54.5 (10.7)	49.8 (10.6)
Gender (*n*, %)				
Male	407 (55.0)	81 (54.0)	1,003 (68.7)	336 (63.5)
Female	333 (45.0)	69 (46.0)	457 (31.3)	193 (36.5)
Duration of diabetes mellitus (years)*	13.3 (10.5)	8.1 (6.9)	6.1 (6.5)	5.8 (5.8)
Age at diagnosis of diabetes mellitus (years)*	21.7 (13.2)	25.7 (14.3)	53.4 (11.2)	44.0 (10.4)
HbA_{1c} (baseline percentage)*	8.4 (1.9)	9.2 (2.4)	7.5 (1.5)	8.3 (2.1)
HbA_{1c} (baseline, mmol/mol)	57	77	58	67
Total cholesterol (mmol/L)*	5.0 (1.0)	5.3 (1.1)	4.9 (1.1)	4.8 (1.0)
Albumin to creatinine ratio*	2.4 (5.3)	3.6 (8.4)	3.8 (10.1)	3.2 (6.0)
Hypertension (*n*, %)	112 (15.1)	24 (16.0)	826 (56.6)	241 (45.6)
Smoking status (*n*, %)	132 (17.8)	21 (14.0)	195 (13.4)	78 (14.7)
Other therapies (*n*, %)				
ACE inhibitors	97 (13.1)	16 (10.7)	656 (44.9)	171 (32.3)
Aspirin	12 (1.6)	0 (0.0)	263 (18.0)	65 (12.3)

Note: ACE: angiotensin-converting enzyme, HbA_{1c}: haemoglobin A_{1c}
*:Data are presented as mean (± standard deviation)

A systematic review identified 61 studies in which the prevalence and incidence of DR were reported across 21 countries in the African region, with only one reported incidence of DR.[15,16] The study reported on the six-year incidence and progression of DR in Mauritius, based on three field digital images of one eye (the right), and without defining the type of diabetes mellitus. They reported that the incidence of severe non-proliferative and proliferative DR in those without previous DR was 0.4% after six years, and progression from mild or moderate non-proliferative DR was 15%. Differences between this study and ours in the methodologies of photographing the retina (one eye only, versus both eyes), the classification of DR, as well as population characteristics, may account for the lower incidence rates reported in this study.

The seven-year cumulative incidence of any DR in persons with type 2 diabetes mellitus without previous DR was reported in two previous studies. There have been no similar studies with respect to type 1 diabetes mellitus.[17,18] The seven-year incidence of any DR in persons without previous DR in the present study of 351 cases per 1 000 persons (35%) was higher than that in a Brazilian cohort at 17%,[17] but lower than that in the Norwich DR screening programme at 50%.[18] The incidence rates of referable DR reported in this study are very similar to those previously reported in populations undergoing systematic screening in the UK.[7,19,20]

It has been demonstrated in evidence from clinical trials that tight control of glycaemia reduced the risk of the incidence and progression of DR.[19,21,22] However, there was only a minimal change in glycaemic control in this study. Therefore, after controlling for other putative risk factors, baseline HbA_{1c} was a stronger predictor of the development of referable DR than the changing HbA_{1c} during the study. Also, there was an increased risk of developing referable DR in both type 1 and type 2 diabetes mellitus patients for every 1% increase in HbA_{1c} at baseline.

Non-Caucasians were at an increased risk of developing DR (both type 1 and type 2 diabetes mellitus patients) when adjusting for other putative risk factors, including glycaemic control, which has previously been shown in prevalence studies in South Africa.[3,23] There is some evidence that HbA_{1c} may vary independently of glycaemia in people of different ethnicities.[24–26] However, evidence that ethnicity modifies the relative association of HbA_{1c} with the prevalence of DR has not been found in recent studies.[27,28] Other possible explanations include ethnic differences in response to chronic glycaemia, as well as factors unrelated to glycaemia, such as the erythrocyte turnover or the rate of protein glycation, anaemia, haemolytic anaemia, thalassaemia and sickle cell anaemia.[24] An association between polymorphisms of specific genes and DR in different ethnicities, including African populations, has also been found in studies. However, the evidence is conflicting.[29] Therefore, whether the increased risk in incidence of referable DR in non-Caucasians is owing to differences in the underlying risk factors, or some sort of genetic propensity for DR, remains unknown.[15]

In this study, the seven-year cumulative incidence of referable DR was 6.6- and 7.7-fold higher in type 1 and type 2 diabetes mellitus patients, respectively, when pre-existing background DR was evident at the onset of the study compared to when no previous DR was evident. There was a 5.6 and 11.9 increased hazard ratio for developing referable DR in type 1 and type 2 diabetes mellitus patients, respectively, after controlling for all other putative risk factors, when pre-existing background DR was present compared to when no previous DR was present. This increased risk in the development of referable DR once background DR was present, has led to a suggestion that annual screening interval in persons without DR can be extended to biennial or even triennial,[7,30,31] with annual screening maintained or reinstituted if and when background DR is present.[18–20] Our findings would support this suggestion for both Caucasians and non-Caucasians.

Clearly, achieving good glycaemic and blood pressure control is the first step in reducing the risk of the development and progression of DR. Patients of non-Caucasian ancestry appear to be at higher risk of developing DR than their Caucasian

counterparts. This needs to be acknowledged. However, overall, good general diabetes mellitus care is required in order to reduce or eliminate the incidence of blindness due to diabetes mellitus, a goal of the Vision 2020 initiative.[11,32]

This represents a large longitudinal study of a multi-ethnic population undergoing screening for DR in post-apartheid South Africa, and is the first study to report on the incidence of DR within the region using standardised screening and grading protocols; recognised as a gap in the research literature.[15] The private healthcare setting and the large number of Caucasians, compared to the low number of other ethnic groups, were limitations of the study. This limits its generalisation to the majority of the population who would seek diabetes mellitus care in the public sector.

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References

1. Cockburn N, Steven D, Lecuona K, et al. Prevalence, causes and socio-economic determinants of vision loss in Cape Town, South Africa. PLoS One. 2012;7(2):e30718.
2. Levy J, Jotkowitz AB. Diabetes in Africa: screening for diabetic retinopathy. E J Internal Med. 2010;21:145–6.
3. Thomas RL, Distiller L, Luzio SD, et al. Ethnic differences in the prevalence of diabetic retinopathy in persons with diabetes when first presenting at a diabetes clinic in South Africa. Diabetes Care. 2013;36(2):336–41.
4. Stolk RP, van Schooneveld MJ, Cruickshank JK, et al. Retinal vascular lesions in patients of Caucasian and Asian origin with type 2 diabetes: baseline results from the ADVANCE Retinal Measurements (AdRem) study. Diabetes Care. 2008;31(4):708–13.
5. Raymond NT, Varadhan L, Reynold DR, et al. Higher prevalence of retinopathy in diabetic patients of South Asian ethnicity compared with white Europeans in the community: a cross-sectional study. Diabetes Care. 2009;32(3):410–5.
6. Yau JWY, Rogers SL, Kawasaki R, et al. The Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35:556–64.
7. Thomas RL, Dunstan F, Luzio SD, et al. Incidence of Diabetic Retinopathy in people with type 2 diabetes mellitus attending the diabetic retinopathy screening service for Wales: retrospective analysis. BMJ. 2012;344:e874.
8. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. Arch Ophthalmol. 1989;107(2):244–9.
9. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1989;107(2):237–43.
10. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010;376(9735):124–36.
11. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA 2007;298(8):902–16.
12. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the diabetes control and complications trial. Arch Ophthalmol. 1998;116(7):874–86.
13. Distiller LA, Brown MA, Joffe BI, et al. Organisation and delivery of care striving for the impossible dream: a community-based multi-practice collaborative model of diabetes management. Diabetic Med. 2010;27:197–202.
14. American Diabetes Association. Clinical practice recommendations. Diabetes Care. 2010;33(Suppl 1):S11–61.
15. Burgess PI, MacCormick IJC, Harding SP, et al. Epidemiology of diabetic retinopathy and maculopathy in Afrcia: a systematic review. Diabetic Med. 2013;30:399–412.
16. Tapp R, Zimmet P, Harper C, et al. Six year incidence and progression of diabetic retinopathy: Results from the Mauritius diabetes complication study. Diabetes Res Clin Pract. 2006;73:298–303.
17. Cardoso CR, Salles GF. Predictors of development and progression of microvascular complications in a cohort of Brazilian type 2 diabetic patients. J Diabetes Complications. 2008;22(3):164–70.
18. Jones CD, Greenwood RH, Misra A, et al. Incidence and progression of diabetic retinopathy during 17 years of a population based screening program in England. Diabetes Care. 2012;35:592–6.
19. Younis N, Broadbent DM, Harding SP, et al. Incidence of sight-threatening retinopathy in Type 1 diabetes in a systematic screening programme. Diabetic Med. 2003;20(9):758–65.
20. Younis N, Broadbent DM, Vora JP, et al. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye study:a cohort study. Lancet. 2003;361:195–200.
21. UK Prospective diabetes study group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–53.
22. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
23. Kalk WJ, Joannou J, Ntsepo S, et al. Ethnic differences in the clinical and laboratory associations with retinopathy in adult onset diabetes: studies in patients of African, European and Indian origins. J Intern Med. 1997;241(1):31–7.
24. Hare MJL, Magliano DJ, Zimmet PZ, et al. Glucose-indepenent ethnic differences in HbA_{1c} in people without known diabetes. Diabetes Care. 2013;36(6):1534–40.
25. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-Independent, Black-White differences in hemoglobin A_{1C} levels; A cross sectional analysis of 2 studies. Ann Intern Med. 2010;152:770–77.
26. Chapp-Jumbo E, Edeoga C, Wan J, et al. Pathobiology of pre-diabetes in a biracial cohort (POP-ABC) reseach group. Ethnic disparity in hemoglobin A1C levels among normoglycaemic offspring of parents with type 2 diabetes mellitus. Endocr Pract. 2012;18:356–62.
27. Bower JK, Brancati FL, Selvin E. No ethnic differences in the association of glycated hemoglobin with retinopathy: The National Health and Nutrition Examination Survey 2005-2008. Diabetes Care. 2013;36:569–73.
28. Selvin E, Ning Y, Steffes MW, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. Diabetes. 2011;60(1):298–305.
29. Chen Y, Huang H, Zhou J, et al. Polymorphism of the endothelial nitric oxide synthase gene is associated with diabetic retinopathy in a cohort of West Africans. Mol Vis. 2007;13:2142–7.
30. Olafsdottir E, Stefansson E. Biennial eye screening in diabetic patients without retinopathy. 10 year experience. Brit J Ophthalmol. 2007;91(12):1599–601.
31. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. Diabetes Care. 2011;34(6):1318–9.
32. World Health Organisation. Vision 2020. The right to sight. 2006. [2013 Jan 31]. Available from: http://www.vision2020.org/main.cfm?type=WHATVISION2020.

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