Original Article

Diabetic Retinopathy in Diabetics Referred to a Tertiary Centre from a Nationwide Screening Programme

Marcus CC Lim,[1]*MRCSEd*, Shu Yen Lee,[1]*FRCSEd*, Bobby CL Cheng,[1]*FRCSEd*, Doric WK Wong,[1]*FRCSEd*, Sze Guan Ong,[1]*FRCSEd*, Chong Lye Ang,[1]*FRCOphth*, Ian YS Yeo,[1]*FRCSEd*

Abstract

Introduction: The aim of the study was to describe the prevalence and risk factors for diabetic retinopathy in a multi-ethnic diabetic patient cohort referred for retinal evaluation from a nationwide diabetic retinopathy screening programme in Singapore. Materials and Methods: Seven hundred and forty-two patients, aged 21 to 95, referred for suspected diabetic retinopathy on annual one-field non-mydriatic 45 degree retinal photographs (Topcon TRC-NW6, Topcon Corporation, Tokyo, Japan) from primary care to the Singapore National Eye Centre diabetic retinopathy clinic were included. The photographs had been interpreted by 24 trained family physicians accredited every 2 years with a training programme. Patients underwent a standardised interview and examination. Fundi were examined with indirect ophthalmoscopy by 2 examiners. Presence and severity of diabetic retinopathy was graded into none, mild, moderate, severe, very severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. Macular oedema and clinically significant macular oedema were also graded. Results: Ninety-nine per cent of patients were type 2 diabetics. The prevalence of diabetic retinopathy was 38.1%, vision-threatening retinopathy was 11.8% and macular oedema was 6.9%. There were no racial differences. Significant predictors of any retinopathy were longer duration of diabetes, lower body mass index, being on treatment for hypertension, hypercholesterolaemia and use of diabetic medication. Predictors for vision-threatening retinopathy were younger age, longer duration of diabetes and lower body mass index. Conclusions: The use of one-field non-mydriatic 45 degree photography as a screening tool for diabetic retinopathy resulted in a cohort of which 38.1% had diabetic retinopathy. Risk factors for diabetic retinopathy of this cohort are also presented.

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Key words: Diabetic retinopathy, Epidemiology, Ethnology, Singapore, Screening

Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss in Asia. Singapore has one of the highest prevalence rates of diabetes mellitus (DM) worldwide, with 8.2% of Singapore adults between the ages of 18 and 69 having diabetes and there is little data on the prevalence of diabetic retinopathy amongst its multi-ethnic population.[1] The epidemiology of DR has been previously described, largely in white populations.[2-4] The few studies done in Asia have mostly been carried out in India.[5-11] Observational studies, again largely conducted in Caucasian populations have identified several risk factors for DR, including duration of diabetes, hyperglycaemia and hypertension (HT).[2-4,12-14] Other less consistently documented associations include hyperlipidaemia,[15-19] obesity and other cardiovascular risk factors.[18,19]

Singapore was the first country in the world to offer an annual diabetic retinal photography screening programme using one-field non-mydriatic photographs and trained readers in the early 1990's.[11] The purpose of this study was to quantify the prevalence of and risk factors for DR in a multi-ethnic patient cohort referred to tertiary care from the annual diabetic retinal photograph screening programme in Singapore.

Materials and Methods

Seven hundred and forty-two consecutive patients who presented to the diabetic retinopathy clinic at the Singapore

[1] Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore
Address for Correpondence: Dr Marcus C C Lim, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751.
Email1: marcus.lim.c.c@singhealth.com.sg
Email2: marcuslim@mac.com

National Eye Centre (SNEC) between January and July 2002 were recruited into the study. The patients were all Singaporeans or permanent residents with diagnosed diabetes who had been referred from 9 government primary care clinics for suspected diabetic retinopathy on their retinal photographs in the form of haemorrhages or exudates; or if their interpretation was difficult due to the presence of cataract. Twenty-four specially trained family physicians with accreditation every 2 years had interpreted the retinal photographs in primary care. One-field non-mydriatic 45 degree retinal photography is carried out in the government primary care clinics (polyclinics) annually on all diabetic patients using a non-mydriatic retinal camera (Topcon TRC-NW6, Topcon Corporation, Tokyo, Japan). Diabetes was defined as fasting glucose ≥7.0 mmol/L or the use of insulin or oral hypoglycaemic medication.

At the initial visit, the following were recorded: age, sex, race, height, weight and type of DM (type 1 or 2). If available, recent glycosylated haemoglobin (HbA1C) levels and fasting glucose levels were obtained from the medical records. Each patient was verbally questioned according to a standardised questionnaire during history-taking by each examiner on the existence of a family history of DM, their smoking status (current, past or never), whether they were on diabetic medication or insulin, the duration of DM in years, history of treated hypertension, ischaemic heart disease, hyperlipidaemia, nephropathy, proteinuria and neuropathy. Snellen visual acuity was measured for each eye. All patients had a slit lamp examination of the anterior segment. Examination of both fundi was performed using indirect ophthalmoscopy with the slit lamp and/or binocular indirect ophthalmoscope. Pupils were dilated with 10% tropicamide drops. Retinopathy was considered to be present if any characteristic lesion as defined in the Early Treatment Diabetic Retinopathy Study (ETDRS) was present: microaneurysms (MAs), haemorrhages, cotton wool spots (CWS), intraretinal microvascular abnormalities (IRMAs), hard exudates (HEs), venous beading and new vessels.[20] The severity of diabetic retinopathy was graded into no, mild, moderate, severe, very severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) according to the modified ETDRS Airlie House classification,[21] and "unknown" due to obscuration of view by cataract. The presence of macular oedema and clinically significant macular oedema (CSME) was also graded as described by the ETDRS studies.[21] Each patient had gradings by 2 independent examiners out of a pool of 9 possible examiners (OSG, ACL, BC, IY, AK, YKT, LSY, DW) for both eyes. Discrepancies were resolved by concensus. Exclusion criteria included previous retinal laser photocoagulation.

We compared characteristics of participants by race. Differences in means were tested by the analysis of variance test and t-test if normally distributed or the Mann-Whitney U test. Differences in proportions were tested using χ^2 tests. The eye with the worse grading of DR was used for analysis. We constructed logistic regression models to determine the odds ratio (OR) and 95% confidence intervals (CI) for the 3 primary outcomes (any diabetic retinopathy, vision-threatening retinopathy and CSME) in association with putative risk factors [e.g., presence of hypertension, duration of diabetes, race, body mass index (BMI)]. This was performed for the whole sample and then for the 3 main ethnic groups. All initial models were adjusted for age, gender, sex and race (and age and gender for ethnicity-specific models). Significant predictors (P <0.10) were included in final multivariate logistic models. All analyses were performed using SPSS version 11.5 (SPSS Inc, Chicago, Illinois, USA).

Results

The characteristics of all the participants, those with any diabetic retinopathy and those with vision-threatening retinopathy, as well as participants in each of the ethnic groups, are listed in Table 1. Among the subjects, 77% were Chinese, 13% Malay, 10% Indian and 3 patients were of 'Other' ethnicity, which comprised Caucasian and Eurasian races. There were only 4 (0.5%) patients with Type 1 DM (2 were Chinese, 1 was Malay and 1 was Indian). The age range was 21 to 95 years.

Compared to those without retinopathy, participants with any retinopathy had a longer duration of DM and a lower BMI, and were more likely to be on medication, on insulin, to have a history of HT and to report having neuropathy and nephropathy. Those with vision-threatening retinopathy, when compared to those without, were more likely to be younger, have a longer duration of DM, have a lower BMI, were more likely to be on medication, and to report nephropathy and proteinuria. Chinese participants were significantly older than Malay participants, the duration of DM for Indians was significantly higher than that of Chinese or Malays, and Malays and Indians had significantly higher BMIs than the Chinese.

The prevalence of any retinopathy, macular oedema, CSME and vision-threatening retinopathy in the total sample and in each of the 4 ethnic groups is listed in Table 2. There were no significant differences between the 4 ethnic groups. The Indians had the lowest prevalence of participants without any retinopathy (44.7%) and the highest with mild to moderate retinopathy (38.2%) and CSME (10.5%) but this was not statistically significant. The Malays had the highest prevalence of vision-threatening retinopathy (14.0%) but this was not statistically significant either.

Table 3 shows risk factor associations of any retinopathy

Table 1. Characteristics of Participants

Characteristic	Total (n = 742)	Any retinopathy (n = 283)	Vision-threatening retinopathy (n = 88)	Chinese (n = 570)	Malay (n = 93)	Indian (n = 76)	Others (n = 3)
Gender, male, n (%)	345 (46.5)	139 (49.1)	49 (55.7)	270 (47.4)	40 (43.0)	32 (42.1)	3 (100)
Age, years, mean ± SD	58.6 ± 11.2	58.2 ± 10.4	55.8 ± 9.8*	59.7 ± 11.0*	53.5 ± 11.1	56.6 ± 11.1	52.0 ± 20.1
Diabetes duration, years, mean ± SD	8.7 ± 8.0	12.0 ± 9.0*	12.0 ± 7.2*	8.4 ± 7.3	8.4 ± 8.2	11.9 ± 11.1*	12.3 ± 17.1
Body mass index, kg/m^2, mean ± SD	25.6 ± 4.1	25.1 ± 3.6*	24.4 ± 3.4*	25.0 ± 3.7	27.9 ± 4.8*	26.6 ± 4.7*	24.8 ± 3.3
On medication, n (%)	674 (90.8)	274 (96.8)*	86 (97.7)*	515 (90.4)	87 (93.5)	70 (92.1)	2 (66.7)
Hypertension, n (%)	476 (64.2)	196 (69.3)*	57 (64.8)	376 (66.2)	56 (60.2)	44 (57.9)	0 (0)
Insulin, n (%)	38 (5.1)	24 (8.5)*	8 (9.1)	23 (4.0)	9 (9.7)	6 (7.9)	0 (0)
Ischaemic heart disease, n (%)	171 (23.0)	69 (24.4)	22 (25.0)	133 (23.3)	18 (19.4)	19 (25.0)	1 (33.3)
Hyperlipidaemia, n (%)	330 (44.5)	115 (40.6)	39 (44.3)	252 (44.2)	47 (50.5)	30 (39.5)	1 (33.3)
Neuropathy, n (%)	67 (9.0)	39 (13.8)*	13 (14.8)	49 (8.6)	13 (14.0)	5 (6.6)	0 (0.0)
Nephropathy, n (%)	28 (3.8)	16 (5.7)*	8 (9.1)*	22 (3.9)	4 (4.3)	2 (2.6)	0 (0.0)
Proteinuria, n (%)	36 (4.9)	17 (6.0)	11 (12.5)*	27 (4.7)	6 (6.5)	3 (3.9)	0 (0.0)
Current cigarette smoker, n(%)	63 (8.5)	23 (8.1)	8 (9.1)	52 (9.1)	7 (7.5)	4 (5.3)	0 (0.0)

* P <0.05 based on χ^2, t-test or Mann-Whitney U test, comparing differences between subjects with vision-threatening retinopathy/any retinopathy and those without.

Table 2. Prevalence and Severity of Diabetic Retinopathy and Macular Oedema

Characteristic	TotalSample (n = 742), n (%)	Chinese (n = 570), n (%)	Malay (n = 93), n (%)	Indian (n = 76), n (%)	Others (n = 3), n (%)	*P*
No retinopathy	459 (61.9)	360 (63.2)	55 (59.1)	42 (55.3)	2 (66.7)	0.546
Retinopathy	283 (38.1)	210 (36.8)	38 (40.9)	34 (44.7)	1 (33.3)	
None	459 (61.9)	360 (63.2)	55 (59.1)	42 (55.3)	2 (66.7)	0.309
Mild to moderate	220 (29.6)	160 (28.1)	31 (33.3)	29 (38.2)	0 (0)	
Severe to proliferative	63 (8.5)	50 (8.8)	7 (7.5)	5 (6.6)	1 (33.3)	
No macular oedema	643 (86.7)	503 (88.2)	78 (83.9)	60 (78.9)	2 (66.7)	0.114
Macular oedema present	51 (6.9)	36 (6.3)	6 (6.5)	8 (10.5)	1 (33.3)	
CSME	48 (6.5)	31 (5.4)	9 (9.7)	8 (10.5)	0 (0)	
Vision-threatening retinopathy	88 (11.9)	65 (11.4)	13 (14.0)	9 (11.8)	1 (33.3)	0.607

and vision-threatening retinopathy in the participants. After adjusting for age and gender, there were no differences between the ethnic groups, although Malay subjects had a greater risk of having any retinopathy (OR, 1.30; CI, 0.78 to 2.17) and vision-threatening retinopathy (OR, 1.27; CI, 0.63 to 2.54) as compared to the Chinese. After adjustment for age, gender and race, significant predictors for having any retinopathy were longer duration of diabetes, being on diabetic medication, treatment for hypertension and treatment for hypercholesterolaemia. Significant predictors for vision-threatening retinopathy included longer duration of diabetes. Being in the fourth quartile for BMI (>27.9) seemed to be associated with a lower risk of vision-threatening retinopathy. We performed the multivariate logistic regression on each race. For any retinopathy, a lower age, hypertension, being on diabetic medication and duration of diabetes were predictors for the Chinese. For the Malays, there were no significant variables while in the Indians, duration of diabetes was the only significant variable. For vision-threatening retinopathy, younger age and duration of diabetes were predictors for the Chinese. For the Malays and Indians, there were no significant variables. Significant predictors for CSME were longer duration of diabetes (P = 0.005) and having a lower BMI (P = 0.02) (data not shown).

Final multivariate models for any retinopathy and vision-threatening retinopathy are shown in Table 4. Significant independent predictors of any retinopathy were longer

Table 3. Risk Factors for Diabetic Retinopathy and Vision-threatening Retinopathy (n = 742)

	Any retinopathy				Vision threatening Retinopathy			
Risk factor	**N**	**%**	**OR (95% CI) ***	***P* value**	**N**	**%**	**OR (95% CI)***	***P***
Gender								
Male	139	40.3	1.18 [0.84-1.66]	0.34	49	14.2	1.40 [0.86-2.27	0.18
Female	144	36.3	1.00		39	9.8	1.00	
Race								
Chinese	210	36.8	1.00	0.76	65	11.4	1.00	0.48
Malay	38	40.9	1.30 [0.78-2.17]		13	14.0	1.27 [0.63-2.54]	
Indian	34	44.7	1.07 [0.62-1.83]		9	11.8	0.81 [0.37-1.79]	
Others	1	33.3	1.59 [0.12-21.67]		1	33.3	5.61 [0.40-78.29]	
Duration of diabetes, years								
Less than 3 years	28	14.7	1.00	0.00	8	4.2	1.00	0.00
3-6 years	50	29.6	2.49 [1.46-4.26]		14	8.3	2.00 [0.80-4.97]	
7-11 years	96	49.0	5.61 [3.35-9.39]		30	15.3	3.92 [1.70-9.06]	
12 years or longer	109	58.6	8.74 [5.15-14.85]		36	19.4	5.70 [2.46-13.19]	
Diabetes medication								
No	9	13.2	1.00	0.01	2	2.9	1.00	0.13
Yes	274	40.7	2.96 [1.37-6.43]		86	12.8	3.13 [0.72-13.70]	
Hypertension status								
Absent	87	32.7	1.00	0.00	31	11.7	1.00	0.14
Present	196	41.2	2.01 [1.39-2.91]		57	12.0	1.48 [0.88-2.49]	
Hypercholesterolaemia								
Absent	168	40.8	1.00	0.02	49	11.9	1.00	0.91
Present	115	34.8	0.67 [0.47-0.95]		39	11.8	0.97 [0.59-1.60]	
Body mass index, kg/m^2								
1st quartile, <22.8	71	38.6	1.00	0.50	31	16.8	1.00	0.08
2nd quartile, 22.8-25.0	80	43.2	1.26 [0.80-1.99]		22	11.9	0.67 [0.36-1.23]	0.19
3rd quartile, 25.1-27.8	72	38.1	1.01 [0.64-1.61]		22	11.6	0.64 [0.35-1.19]	0.16
4th quartile, >27.9	60	32.6	0.87 [0.53-1.42]		13	7.1	0.38 [0.18-0.80]	0.01
Ischaemic heart disease status								
Absent	214	37.5	1.00	0.98	66	11.6	1.00	0.87
Present	69	40.4	0.99 [0.66-1.49]		22	12.9	1.05 [0.59-1.88]	
Cigarette smoking								
Past/Never	260	38.3	1.00	0.43	80	11.8	1.00	0.54
Current	23	36.5	0.78 [0.42-1.45]		8	12.7	0.77 [0.33-1.80]	

* Adjusted for age, gender and race

duration of diabetes, lower BMI, being on treatment for hypertension, hypercholesterolaemia and use of diabetic medication. Predictors for vision-threatening retinopathy were younger age, longer duration of diabetes and lower BMI. We also carried out multivariate logistic regression models for each race separately. For the Chinese race, predictors of any retinopathy were duration of diabetes, hypertension and use of diabetic medication. For the Malay race, having a low BMI was a positive predictor for any retinopathy (OR, 0.88; CI, 0.78 to 0.98). For the Indian race, duration of diabetes was the only significant variable. For other races, the sample size was too small for a meaningful analysis.

For vision-threatening retinopathy, duration, lower BMI

Table 4. Predictors of Diabetic Retinopathy and Vision-threatening Retinopathy (n = 742)

	Any retinopathy		Vision threatening retinopathy	
Risk factor	**OR (95% CI)***	***P***	**OR (95% CI)***	***P***
Age	0.99 (0.97-1.00	0.06	0.97 (0.945-0.988)	0.00
Gender, male vs female	1.08 (0.79-1.49)	0.62	1.32 (0.83-2.09)	0.24
Race				
Chinese	1.00	0.60	1.00	0.58
Malay	1.32 (0.81-2.15)		1.41 (0.70-2.79)	
Indian	1.28 (0.76-2.17)		1.02 (0.47-2.22)	
Others	0.74 (0.04-12.60		4.02 (0.30-53.69)	
Duration of DM, per 10 years	2.16 (1.66-2.81)	0.00	1.38 (1.02-1.87)	0.04
BMI, per unit increase	0.95 (0.91-0.99)	0.02	0.89 (0.84-0.96)	0.00
Hypertension, present vs absent	1.75 (1.24-2.47)	0.00	1.49 (0.90-2.48)	0.13
Hypercholesterolaemia, present vs absent	0.69 (0.50-0.96)	0.03	1.02 (0.64-1.62)	0.95
Use of diabetes medication, yes vs no	4.13 (1.97-8.64)	0.00	4.27 (1.00-18.17)	0.05

*Of any retinopathy and vision-threatening retinopathy, adjusted for all variables listed.

and lower age were predictors for the Chinese. For Malays and Indians, none of the variables were significant.

Discussion

Our study provides new data on the prevalence and risk factors for DR in multi-ethnic patients referred to the SNEC diabetic retinopathy clinic from a nationwide screening programme. Although not population-based, the racial breakdown of this group of patients, who were all Singaporeans or permanent residents, was 77% Chinese, 13% Malay and 10% Indian. This is comparable to the racial breakdown of Singaporeans or permanent residents as Chinese 77%, Malay 14%, Indian 7.6% and "Other" 1.4%, from the Singapore Census of 2000. Because our patients were referred from primary care as "retinopathy suspects" one would expect a higher than expected prevalence of DR in our sample than in a population-based sample. In an ideal world, all of the patients referred to us would have diabetic retinopathy, with no false positives. However, only 38.1% of them had any retinopathy. A recent population-based study of Malays in Singapore showed that 35.0% had any retinopathy and 9.0% had vision-threatening retinopathy.[22] In our study, 40.9% of Malays had any retinopathy and 14.0% had vision-threatening retinopathy.

It is interesting that a prevalence of 35.0% was computed in a Taiwan population-based study of type 2 diabetics in Taiwan,[5] and the 40.3% prevalence in the US obtained from a meta-analysis of several population-based studies.[23] However, other population-based studies in India found prevalences ranging from 10.5 to 26.2%.[6-9] The fact that the percentage of subjects with confirmed DR in our clinic is as low as it is suggests that diabetic retinal photograph screening by trained primary care physicians in Singapore may have a higher than desirable false positive rate and might be reassessed as a screening tool for DR. In fact, one-field non-mydriatic retinal photography has been shown to have a high technical failure rate of 19.7% and low specificity.[24] Mydriasis has been shown to reduce the rate of ungradeable photos from 26% to 5%[25] but there is little evidence as to whether mydriasis would reduce the rate of compliance amongst diabetics. Results from the diabetic retinal photograph screening programme recently started in the United Kingdom in 2007 may answer this question as two-field mydriatic photography is being used. In our study, the low rate of retinopathy in our referred patients were due to referrals owing to ungradeable and poor quality photographs due to cataract, pupils not dilated, as well as other non-diabetic pathology and who turned out not to have any retinopathy.

The vast majority (99.5%) of our subjects were type 2 diabetics and 9.2% were not on any diabetic medication, so for all intents and purposes, our study can be assumed to be one on type 2 diabetics. We found that significant predictors of any retinopathy were longer duration of diabetes, lower BMI, being on treatment for hypertension, hypercholesterolaemia and the use of diabetic medication. Predictors for vision-threatening retinopathy were younger age, longer duration of diabetes and lower BMI. These associations have been described in the past but mostly in Western populations.

We found that a higher BMI was associated with a lower risk of vision-threatening retinopathy, but only in the Malay race. A lower BMI has been associated with an increased risk of DR.[26-28] However there is also evidence to the contrary.[14] Poorer glycaemic control has been shown to be related to an increased progression of DR and also to younger age and lower BMI.[12,29] One possible explanation for the apparently better glycaemic control in individuals with high BMI is the weight-gaining effects of taking insulin, as the United Kingdom Prospective Diabetes Study found.[30] In our sample however, there was no significant difference in BMI between subjects on insulin and subjects who were not. We also found that BP, duration of DM, being on DM medication and hypercholesterolaemia were related to DR. These factors have been consistently shown to be related to DR.[14]

There is evidence that there are racial differences in the prevalence of DR.[31-34] However, we did not find any differences in our sample. This could be because Singaporean Chinese, Malay and Indian subjects, being predominantly of South East Asian origin, are more homogenous in their genetic make-up than Afro-Caribbean, Hispanic and Caucasian subjects from previous studies. There is limited data on DR in the Chinese living in Asia.[5] One of them was a population-based study in Taiwan of type 2 diabetics over 40, which reported a prevalence rate of DR of 35.0% and the duration of diabetes was the most significant predictor of DR. A sub-analysis on our group of Chinese patients also showed that duration of diabetes as well as hypertension were predictors of DR.

In our study, there was no difference in the prevalence of DR among the races. However, the duration of DM for Indians was significantly higher than that of Chinese or Malays. This could be because the Indian subjects presented later to primary care, or developed DR later in the course of the disease. In fact, Indians in Singapore have the highest prevalence of diabetes compared to the Chinese or Malays.[1] We also found that Malays and Indians had significantly higher BMI's than the Chinese, which is consistent with findings from a national health survey that showed that Indians had the highest BMI, followed by the Malays and the Chinese.[1]

Our study was performed in a large group of patients with an ethnic mix fairly representative of the general population of Singapore. All the patients had clinical fundal examinations. However, the study was not population-based and we did not measure BP, serum lipids or HbA1C. Although we measured BMI, we did not measure waist-hip ratio, which has been associated with increased DR.[19]

In summary, our study provides new data on the prevalence of and risk factors for DR among diabetics referred from screening to a tertiary eye centre in Singapore. In our group, we found that just over 1 in 3 patients referred from primary care DR had any retinopathy and 1 in 9 had vision-threatening retinopathy. We confirmed the association of DR with classic risk factors, including duration of disease and hypertension, with some racial differences. The low rate of retinopathy picked up from our screening programme using one-field non-mydriatic photographs may be due to low specificity and high technical failure rate. More studies are needed to assess more cost-effective methods of screening for DR.

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