Diabetic retinopathy in native and non-native Sarawakians - Findings from the Diabetic Eye Registry

P S Mallika, MS*, S Aziz, MS, P P Goh, MPH***, P Y Lee, M Fam Med****, W L Cheah, PhD*****, M S Chong, MS**, A K Tan, MS***

*Department of Ophthalmology, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Kuching, Sarawak, Malaysia, **Department of Ophthalmology, Sarawak General Hospital, Sarawak, Malaysia, ***Department of Ophthalmology, Selayang Hospital, Selangor, Malaysia, ****Department of Family Medicine, Faculty of Medicine and Health Sciences, University Putra Malaysia, Malaysia, *****Department of Community Medicine and Public Health, Faculty of Medicine and Health Sciences, University Malaysia Sarawak, Malaysia

SUMMARY

This study aims to determine the risk factors associated with diabetic retinopathy (DR) among natives and non-natives Sarawakians who were seen at 3 public hospitals and one health clinic in Sarawak. It is a cross sectional study where data on patients with DM were collected by staff at these healthcare facilities and entered into the web-based Diabetic Eye Registry. Univariate and multivariate analysis was used to determine the association factors for DR. DR was significantly less associated with natives (24.4%) compared to non-native Sarawakians (34.1%) (p <0.001). The odds of getting DR was higher in patients whose duration of DM was more than 20 years (OR=2.6), who have renal impairment (OR= 1.7) and non-natives (OR =1.4).

KEY WORDS:
Diabetic retinopathy; prevalence; Diabetic registry; Sarawak natives

INTRODUCTION

Diabetes mellitus (DM) is a global health problem. The population of diabetic individuals is increasing rapidly, from 30 million in 1985, 135 million in 1995, 171 million in 2000 and is estimated to increase to 366 million in 2030 [1] . According to World Health Organization (WHO), there will be a projected rise of people with DM by 42% in developed countries and 170% in developing countries [2]. Prevalence of DM in Malaysia has shown an increase from 0.6% in 1960 to 14.9% in 2006 [3]. Based on the National Health and Morbidity Survey in 2006, the prevalence of DM in Sarawak was 10%[4]. The World Health Organisation (WHO) has estimated that in the year 2030, Malaysia would have a total of 2.48 million people with DM compared to 0.94 million in 2000, a 164% increase[5].

The major factors associated to the raise in DM are increase in population older than 65 years, rapid urbanization and increasing prevalence of obesity [1]. Annually, about 4 million deaths are attributable to complications of DM [6]. Diabetes mellitus causes an array of long-term complications which include among others ischemic heart disease, stroke, diabetic nephropathy and diabetic retinopathy (DR).

Diabetic retinopathy is the leading cause of blindness among working age group Americans of 20 to 74 years [7, 8]. DR is responsible for 1.8 million (4.8%) of the 37 million blind people [9]. DR evolves through several stages from non proliferative diabetic retinopathy (NPDR), namely mild, moderate, severe and very severe to proliferative diabetic retinopathy (PDR). Some patients also develop diabetic maculopathy beside DR. DR is a characteristic of an early onset disease whereas maculopathy occurs in late onset disease [10]. NPDR, PDR and maculopathy are categorized as vision threatening retinopathy (VTR).

There is little information on the average duration of each stage of DR, but studies have shown that after 20 years of DM, the cumulative incidence of any form of diabetic retinopathy is 34.5% and PDR is 5% [11]. Multicentre studies like Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS) show that laser photocoagulation reduces the risk of severe and moderate visual loss by more than 50% [12, 13]. The slow progression of DR and the effectiveness of early treatment suggest that blindness due to DR can be reduced by effective screening programs.

According to a study on diabetes control and complications in private primary health care in Malaysia, DR was the second commonest complication of DM, following neuropathy[14]. Based on findings from the Diabetic Eye Registry (DER) in 2007, the proportion of patients who had DR was 36.8%, of which 7.1 % had PDR and 14.7% had VTR[15].

Sarawak, the largest state in Malaysia has a population of 2.07 million and comprises of nearly 29 different ethnic groups [16]. The natives of Sarawak consist of Ibans and Bidayuhs and they contribute to 50% of the total population in Sarawak. As there are no published report on DR among native and non natives Sarawakians, we present this paper on associated factors for the occurrence of DR among native and non-native Sarawakians.

This article was accepted: 20 March 2012
Corresponding Author: Mallika Premsenthil, University Malaysia Sarawak, Ophthalmology, Lot 77, Seksyen 22, Kuching Town Land District, Jalan Tun Ahmad Zaidi Adruce, Kuching, Sarawak 93150, Malaysia Email: pmallika@fmhs.unimas.my / drmallikaps@gmail.com

MATERIALS AND METHODS

National Eye Database (NED) is a health information system supported by Clinical Research Centre, Ministry of Health (MOH), Malaysia. It is an online clinical database hosted at www.acrm.org.my/ned ,started from January 2007 and is ongoing. It consists of six patients registries including DER. DER is designed as a multi-centered cross sectional study with online data entry, concurrent descriptive data analysis and downloadable real time reports [17]. Data were captured by doctors who saw the patients. The determination of native and non native ethnicity was based on patients' identify cards. Data entry was done by trained healthcare providers. The data were entered either directly into the web based registry or into case report forms which are later entered into the website. The DER collected data on patients who were seen for the first time at 36 MOH Ophthalmology departments, 12 health clinics with optometry service and a non-governmental organization. A total of 22,870 diabetic patients i.e. 10,856 in 2007 and 12,014 in 2008 were registered to DER.

The source data providers (SDP) for the Sarawak state are Sarawak General Hospital, Sibu Hospital, Bintulu Hospital, Sri Aman Hospital, Miri Hospital and Sarawak Society for the Blind.From 2007 to 2009, 2081 diabetic patients from these SDP were registered to DER.

Our study was a cross-sectional study conducted from January 2007 to December 2009. All the diabetic patients seen in the eye clinic for the first time were included in the study and patients who are already under treatment or follow-up for diabetic retinopathy in the eye clinic were excluded from the study. Our study included 519 eligible patients.

The criteria for referral of patients with DM to eye clinics by primary doctors were the same for natives and non-natives patients. The more frequent reasons for referral were: poor vision, patient having some form of DR, or patients who need a diabetic eye screening as stated in the Clinical Practice Guidelines. We did not think whether natives or non -natives were more likely to turn up to eye clinics but would presume that there was no selection bias as these patients were from Kuching and Sri Aman and not from the interior part of Sarawak where natives may choose not to attend clinics due to logistic reasons.

Information collected included: socio-demographic details, type of diabetes, duration of diabetes, treatment of diabetes, source of referral, systemic co-morbidity, ocular co-morbidity, previous fundus examination, risk factors, unaided and aided visual acuity, presence of maculopathy, presence of rubeosis and management plan.

DR was graded based on the International Clinical Diabetic Retinopathy Disease severity Scale [18]. Visual loss was categorized into normal (6/6), mild (6/9 to 6/12), moderate (6/18 to 6/60) and severe (worse than 6/60). The eyes with better vision were used to categorise visual status of the patients. When both eyes have DR, the eye with more severe stage of DR was taken for analysis.

Statistical analysis

Data analysis was done using SPSS version 17.0 for windows. Socio-demographic characteristics of the study sample were analyzed and presented using descriptive statistics. Mean and standard deviation were used for normally distributed continuous variables and frequency and percentage were used for categorical variables. Chi-square tests and Fischer exact test were used for univariate analysis. Multiple logistic regression was used to elucidate the various associated factors for DR. All the variables listed in the table that are included in the multivariable analysis were adjusted. The variables were adjusted for each other. Variables with a p value of < 0.05 were included in a multivariable e model. All hypotheses tests were based on two-sided test and p value less than 0.05 was considered to be statistically significant.

RESULTS

Table I shows the demography of the patients. Our study sample had more females (56.3%) than males (43.7%). The ethnicity distribution of our sample consisted predominantly non-natives (66.7%) (Chinese, Malays, Indians, and others) and the remaining were natives (Iban, Bidayuh, Melanau and other native groups) (33.3%). Among the non-natives Chinese contributed 44.6% and Malays 21.9%.The age of our study population ranged from 8 to 90 years. More than half of the patients were in the working age group of 30 to 60 years and patients above 60 years of age contributed 37.8% (n=738). Majority of them had Type 2 DM and more than three quarter of them had diabetes for less than 10 years. Systemic hypertension was the most common co-morbidity found in our study sample. Cataract was the predominant ocular co-morbidity present in 353 patients (17%). Almost all the referrals (97%) were from government outpatient clinics and hospital.

Table II shows the visual status of patients based on status of the better eye. Mild and moderate visual loss was commonly seen in our patients than severe visual loss. Eighty seven percent of the patients did not have any previous fundus examination.

Based on the status of DR in the worse eye, majority of our patients had no apparent DR in both eyes and 124 patients (6.0%) had VTR in at least one eye (Table III). About 136 (6.6%) of the patients had maculopathy.

Among 692 natives, more than three quarter of them did not have DR and among the 1389 natives, more than half of them did not have DR. Among non-natives 28.5% had NPDR (mild, moderate and severe) and 3.3% had PDR compared to 20.4% and 2.5% in natives respectively (Table IV).

Table V shows the presence of DR and its associated factors using univariable analysis and table VI shows associated factors based on multiple logistic regression. The factors significantly associated with any diabetic retinopathy were longer duration of DM (Odd ratio 2.6, CI 1.8, 4.0), presence of renal impairment (odd ratio 1.7, CI 1.0, 2.7) and being non-natives (odd ratio=1.4 C1.1, 1.8).

The odds of developing any DR was 2.4 times higher for a patient with duration of diagnosis between 10 to 15 years when compared to patients with <5 years of diabetes and patients with duration of DM 10 to 15 years have 2.8 times risk of developing PDR and 2.5 times risk of developing NPDR. There was no difference in the proportion of men and women who have DR (p=0.59) (Table V).

The prevalence of any DR in nephropathy was 46.5% (42/91) compared to patients without renal impairment (30.2%) (600/1990) (p=0.001). The odd of developing any DR in patients with nephropathy was 1.7 times (Table VI)

Having ischemic heart disease seems to be a protective factor for not developing DR (Odd ratio of 0.5 (CI 0.3, 0.8)

Moderate visual loss (OR=2.2, CI= 1.7 to 3.0) and severe visual loss (OR=3.0, CI 2.0, 4.8) were significantly associated with presence of any DR and the odds was higher with more serious stage of DR.

Older age was significantly associated with the severity of DR but not for any form of DR. Patients younger than 50 years were at higher risk of developing PDR (OR=3.1, CI 1.7, 5.5).

Compared to the natives, non-natives had a higher risk of having any form of DR (OR=1.4, CI 1.1, 1.8) and NPDR (OR=1.4, CI 1.1, 1.7).

Non-natives were significantly associated to having DR, 34.1% (473/1389) when compared to natives (Iban, Bidayuh, Melanau and others), 24.4% (169/692) (p < 0.001). The proportion of non-natives who had NPDR was 30.8% (428/1389), significantly higher than that of natives, 22.1% (153/692) (p <0.001). The odds of developing DR among non-natives was 1.4. (Table VI)

Mode of DM treatment and presence of systemic diseases showed significant association in the univariable analysis, but were not statistically significant in the multivariate analysis.

In terms of management, 1808 patients (86.9%) were given routine follow up appointment, 89 patients (4.3%) required laser photocoagulation and 23 patients (1.1%) needed fundus fluorescence angiogram to assess the extent of retinal ischemia or maculopathy. Of the 2081 patients, only one patient needed vitrectomy surgery. Of the 89 patients who needed laser treatment, 34(38.2%) were treated with focal laser and 55 (61.8%) with pan retinal photocoagulation.

Table I: The demographic and health profile of the respondents (N=2081)

Variables	n	%
Gender		
Male	909	43.7
Female	1172	56.3
Ethnicity		
Borneo natives	692	33.3
Non-natives	1389	66.7
Type of Diabetes		
Type 1	178	8.6
Type 2	1903	91.4
Duration of DM		
Mean duration (SD)	5.72 (6.3)	
	n	%
< 5 Yrs	1384	66.5
5-9 Yrs	346	16.6
10-14 Yrs	195	9.4
15-19 Yrs	57	2.7
> 20 Yrs	99	4.8
Mean age (SD)	55.6 (12.2)	
Age group	n	%
<50	580	27.9
>50	1501	72.1
Treatment for Diabetes		
Diet only	44	2.1
Oral medications	1813	87.1
Insulin+ oral medications	224	10.8
Systemic co-morbidity		
Ischemic Heart Disease	122	5.9
Renal impairment	91	4.4
Peripheral neuropathy	4	0.2
Amputation done	4	0.2
Foot Ulcer	3	0.1
Hypertension	1327	63.8
Cerebral Vascular Accident	41	2.0
Hypercholesterolemia	306	14.7
Anemia	9	0.4

Table II: Visual status of patient based on status of the better eyes (N=2081)

Vision Status	n	%
6/6	360	17.3
6/9 to 6/12	934	44.9
6/18 to 6/60	627	30.1
<6/60	160	7.7

Table III: Distribution of severity of diabetic retinopathy (N=2081)

	n	%
No apparent DR	1482	71.2
Mild NPDR	352	16.9
Moderate NPDR	123	5.9
Severe NPDR	62	3
PDR	48	2.3
Advanced Diabetic Disease	14	0.7
	2081	100

Table IV: Distribution of severity of diabetes retinopathy among natives and non natives

Severity of Diabetes Retinopathy	Natives n (%)	Non natives n (%)
Normal	534 (77.2)	948 (68.2)
Mild NPDR	98 (14.2)	254 (18.3)
Moderate NPDR	26 (3.8)	97 (7.0)
Severe NPDR	17 (2.4)	45 (3.2)
PDR	15 (2.2)	33 (2.4)
Advanced Diabetic Disease	2 (0.3)	12 (0.9)
Total	692 (100)	1389 (100)

Table V: Univariable analyses for associated factors of diabetes retinopathy (DR) among patients with diabetes mellitus seen at public health facilities in Sarawak (N=2081)

Variables n(%)	Non-DR n(%)	DR	p-value[a]
Gender			0.594
Male	623 (43.3)	286 (44.5)	
Female	816 (56.7)	356 (55.5)	
Ethnicity			<0.001
Borneo natives	523 (36.3)	169 (26.3)	
Non-natives	916 (63.7)	473 (73.7)	
Type of Diabetes			0.229
Type 1	116 (8.1)	62 (9.7)	
Type 2	1323 (91.9)	580 (90.3)	
Duration of DM			<0.001
< 5 Yrs	1021 (71.0)	362 (56.4)	
5-10 Yrs	239 (16.6)	107 (16.7)	
10-15 Yrs	102 (7.1)	94 (14.6)	
15-20 Yrs	29 (2.0)	28 (4.4)	
> 20 Yrs	48 (3.3)	51 (7.9)	
Age group			0.035
<50	421 (29.3)	159 (24.8)	
>50	1018 (70.7)	483 (75.2)	
Treatment for Diabetes			0.027
Diet only	33 (2.3)	11 (1.7)	
Oral medications	1268 (88.1)	545 (84.9)	
Insulin+ oral medications	138 (9.6)	86 (13.4)	
Ischemic Heart Disease			0.032
No	1344 (93.4)	615 (95.8)	
Yes	95 (6.6)	27 (4.2)	
Renal impairment			0.001
No	1390 (96.6)	600 (93.5)	
Yes	49 (3.4)	42 (6.5)	
Peripheral neuropathy			0.056
No	1438 (99.9)	639 (99.5)	
Yes	1 (0.1)	3 (0.5)	
Amputation done			0.407
No	1437 (99.9)	640 (99.7)	
Yes	2 (0.1)	2 (0.3)	
Foot Ulcer			0.179
No	1438 (99.9)	640 (99.7)	
Yes	1 (0.1)	2 (0.3)	
Hypertension			0.721
No	525 (36.5)	229 (35.7)	
Yes	914 (63.5)	413 (64.3)	
Cerebral Vascular Accident			0.422
No	1413 (98.2)	627 (97.7)	
Yes	26 (1.8)	15 (2.3)	
Hypercholesterolemia			0.377
No	1234 (85.8)	541 (84.3)	
Yes	205 (14.2)	101 (15.7)	
Anaemia			0.872
No	1433 (99.6)	639 (99.5)	
Yes	6 (0.4)	3 (0.5)	
Visual loss			233 (36.3)
Normal 6/6	290 (20.2)	70 (10.9)	
Mild 6/9 to 6/12	667 (46.4)	267 (41.6)	
Moderate 6/18 to 6/60	394 (27.4)	233 (36.3)	
Severe <6/60	88 (6.1)	233 (36.3)	

[a] Chi-square test was applied

Table VI: Associated factors for diabetes retinopathy by using multiple logistic regression among patients with diabetes mellitus seen at public health facilities in Sarawak (N=2081)

Variables	regression coefficient	Adjusted Odds Ratio (95% CI)	p-value[b]
Ethnicity			
Borneo natives	0	1	0.001
Non-natives	0.349	1.418 (1.145,1.756)	
Duration of DM			
< 5 Yrs	0	1	
5-10 Yrs	0.265	1.303 (1.002,1.695)	<0.001
10-15 Yrs	0.920	2.509 (1.835,3.430)	0.049
15-20 Yrs	0.917	2.509 (1.835,3.430)	<0.001
> 20 Yrs	0.972	2.643 (1.725,4.049)	0.001
Ischemic Heart Disease			
No	0	1	
Yes	-0.665	0.514 (0.325,0.813)	0.004
Renal impairment			
No	0	1	
Yes	0.539	1.714 (1.097,2.677)	0.018
Visual loss			
Normal 6/6	0	1	
Mild 6/9 to 6/12	0.399	1.490 (1.100,2.017)	0.010
Moderate 6/18 to 6/60	0.798	2.221 (1.624,3.037)	<0.001
Severe <6/60	1.131	3.098 (2.042,4.700)	<0.001

b Backward logistic regression variable selection method was applied
Interaction and multicollinearity was checked
Model assumption were checked by Hosmer Lemeshow Test (p=0.486),Classification table (70.3%).

DISCUSSION

The prevalence of DR varies among populations but ranges between 25% and 40% [19] and in Malaysia it varies from 11.1% to 51.6% [20-23]. The status of DR among all the patients registered with DER in 2007 was 36.8% and among Sarawakian was 30.9%. This figure was comparable with the prevalence found in the Blue Mountain Eye Study (BMES) of 32.4% [24] but is lower compared to the Newcastle diabetic retinopathy study (35%), The Beaver Dam Eye Study (36.8%) and Singapore Malay Eye Study (35.7%) [25-27]. Non-proliferative diabetic retinopathy was the commonest form of DR noted among Sarawakians in our study.

Unlike the Wisconsin Epidemiologic Study of Diabetic Retinopathy [28] and studies in India[29, 30], which show higher prevalence of DR and more severe form of DR in men, in this study, there was no difference in the occurrence of DR between men and women.

Longer duration of DM has been shown to be the major risk factor for DR[30-33]. Patients with Type 1 DM may show evidence of retinopathy as early as 5 years after the onset of DM, and almost all patients with DM will show varying degrees of DR 20 years after the onset of diabetes [34]. Longer duration of DM leads to chronic hyperglycaemia which in turn causes increased activity of protein kinase C (PKC) and glycation of key proteins that lead to formation of advanced glycation end (AGEs) products. This increase activation of PKC results in enhanced permeability of retinal vasculature, alterations in retinal blood flow, basement membrane thickening and cellular signalling by vascular endothelial growth factors (VEGFs) leading to ocular neovascularisation [35,36]. Advanced glycation end products results in microaneurysm formation and loss of capillary endothelial parricides [37]. Our study also confirms that duration of DM was significantly associated with both any DR and severity of DR.

Presence of microangiopathy such as DR and nephropathy are closely related to the metabolic control of DM. Patients with an advanced retinopathy is more likely to develop diabetic nephropathy. Albuminuria is also a predictor of micro-angiopathy in other organs. The annual incidence of PDR in early nephropathy is 10-15% compared to only 1% in patients without nephropathy [38]. Dowse et al in his study found that 75 percent of subjects with macroalbuminuria had retinopathy [39]. Similar strong association between retinopathy and urinary albumin concentration were also demonstrated in other studies [40-41]. This is also shown in our study where patients with renal impairment were significantly associated with both any DR and severity of DR.

In conclusion, like other studies, longer duration of DM and presence of renal impairment were significantly associated with presence of DR. However our study shows that being a native and having ischemic heart disease protect a patient from having DR. Further studies to determine the effect of genetic and environment to the development of DR among Sarawakians are warranted.

Limitation of our study

The eye examinations were done by various categories of medical doctors ranging from medical officers to eye specialists who may give varying diagnosis in terms of severity of DR but should be able to differentiate the presence of DR and no DR. Our study also did not include HbA1c which is an important risk factor of DR. The database contains patients who were referred from primary care clinics to eye clinics. Although the referral criteria for natives and non-natives were the same in our study, we do not know if the pattern of attending the eye clinic differed among natives and non-natives.

ACKNOWLEDGEMENT

We would like to thank the Director General of health for the permission to publish this paper and the doctors, optometrists and paramedical staff who were involved in the Diabetes Eye Registry at Ministry of Health facilities in Sarawak. We would also like to thank all the statisticians involved in this study.

REFERENCES

1. Wild S, Roglic G, Green A , Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27(5): 1047-53.
2. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998 Sep; 21(9): 1414-31.
3. National Health Morbidity Survey 2006 (NHMSIII), Institute of Public Health, Ministry of Health, Malaysia.
4. Letchuman GR, Wan Nazaimoon W M, Wan Mohamad W B, Chandran L R, Tee G H, Jamaiyah H *et al.* Prevalence of Diabetes in the Malaysian National Health Morbidity Survey III 2006. Med J Malaysia 2010; 65 (3) 2010: 173-79.
5. World Health Organization, Facts and Figures. Available from www.who.int./diabetes/facts/world-figures/en/index6.html. Accessed January 12 2011.
6. Facts Related to Chronic Diseases Fact Sheet – Diabetes. Available from http://www.who.int/hpr/gs.fs.diabetes.shtml. Accessed 24 February 2011.
7. National Society to Prevent Blindness. Operational Research Department. Vision problems in the US: a statistical analysis. New York: National Society to Prevent Blindness; 1980: 1-46.
8. Patz A, Smith RE. The EDTRS and Diabetes 2000 (Editorial). Ophthalmology 1991; 98: 739-40.
9. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82:844-51.
10. Rohan TE, Frost CD, Wald NJ.Prevention of blindness by screening for diabetic retinopathy: a quantitative assessment. BMJ. 1989 Nov 11; 299(6709): 1198-201.
11. Dwyer MS, Melton IJ, Ballard DJ, Palumbo PJ, Trautmann JC, Chu C. Incidence of diabetic retinopathy and blindness: a population-based study in Rochester, Minnesota. Diabetes Care 1985; 8: 316-22.
12. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. Ophthalmology.1981 Jul; 88(7): 583-600.
13. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991 May; 98(5 Suppl): 766-8.
14. Mafauzy M. Diabetes control and complications in private primary health care in Malaysia. Med J Malaysia. 2005 Jun; 60 (2): 212-7.
15. Goh PP for the National Eye Database Study Group. Status of diabetic retinopathy among diabetics registered to the Diabetic Eye Registry, National Eye Database, 2007. Med J Malaysia. 2008 Sep; 63 Suppl C: 24-8.
16. The official portal of Sarawak government. Available from http://www.sarawak.gov.my/seg.php?recordID=M0001&sscontent=SSM0049. Accessed on15 February 2011.
17. P P Goh, H Elias, N Nor Fariza, I Mariam. National Eye Database – A Web Based Surveillance System. Med J Malaysia 2008; 63(Supplement C): 20-23.
18. American Academy of Ophthalmology. Preferred Practice Pattern: Diabetic retinopathy 2003. San Francisco, Calif: American Academy of Ophthalmology.
19. National Health and Medical Research Council. Guidelines for the Management of Diabetic Retinopathy. Commonwealth of Australia, 2008.
20. Shriwas SR, Rahman Isa AB, Reddy SC, Mohammad M, Mohammad WB, Mazlan M. Risk factors of retinopathy in diabetes mellitus in Kelantan, Malaysia. Med J Malaysia 1996 Dec; 51(4): 447-52.
21. Mafauzy M. Diabetes Control and complication in private health care in Malaysia. Med J Malaysia 2005; 60: 212-7.
22. Mafauzy M. Diabetes control and complications in public hospitals in Malaysia. Med J Malaysia. 2006 Oct; 61(4): 477-83.
23. Tajunisah I, Nabilah H, Reddy SC. Prevalence and risk factors for diabetic retinopathy-a study of 217 patients from University of Malaya Medical Centre. Med J Malaysia. 2006; 61(4): 451-6.
24. Mitchell P, Smith W, Wang JJ, Attebo K.Prevalence of diabetic retinopathy in an older community. The Blue Mountains Eye Study Ophthalmology. 1998; 105(3): 406-11.
25. Mitchell P, Moffitt P.Update and implications from the Newcastle diabetic retinopathy study. Aust N Z J Ophthalmol. 1990; 18(1): 13-7.
26. Klein R, Klein BE, Moss SE, Linton KL.The Beaver Dam Eye Study. Retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus. Ophthalmology. 1992; 99(1): 58-62.
27. Wong TY, Cheung N, Tay WT, Wang JJ, Aung T, Saw SM, Lim SC, Tai ES, Mitchell P.Prevalence and risk factors for diabetic retinopathy: the Singapore Malay Eye Study. Ophthalmology. 2008 Nov; 115 (11): 1869-75. Epub 2008 Jun 26.
28. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984 Apr; 102 (4): 520-6.
29. Ramachandran A, Jali MV, Mohan V, Snehalatha C, Viswanathan M. High prevalence of diabetes in an urban population in south India. BMJ. 1988; 297(6648): 587-90.
30. P Namperumalsamy, R Kim, T P Vignesh, et al. Prevalence and risk factors for diabetic retinopathy: a population-based assessment from Theni District, south India. Br J Ophthalmol 2009 93: 429-34.
31. 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 DM. N Engl J Med. 1993; 329: 977-86.
32. Varma R, Macias GL, Torres M, Klein R, Peña FY, Azen SP. Biologic risk factors associated with diabetic retinopathy: the Los Angeles Latino Eye Study. Ophthalmology 2007 Jul; 114(7): 1332-40.
33. Robyn J. Jonathan E. Alex H, *et al.* The prevalence of and factors associated with diabetic retinopathy in the Australian Population. Diabetes care 2003; 26(6): 1731-37.
34. Shah CA. Diabetic retinopathy: A comprehensive review. Indian J Med Sci. 2008 Dec; 62(12): 500-19.
35. Xia P, Aiello LP, Ishii H, Jiang ZY, Park DJ, Robinson GS, et al. Characterization of vascular endothelial growth factor's effect on the activation of protein kinase C, its isoforms, and endothelial cell growth. J Clin Invest 1996; 98: 2018-26.
36. Miller JW, Adamis AP, Aiello LP. Vascular endothelial growth factor in ocular neovascularization and proliferative diabetic retinopathy. Diabete Metab Rev 1997; 13: 37-50.
37. Wautier JL, Guillausseau PJ. Advanced glycation end products, their receptors and diabetic angiopathy. Diabetes Metab 2001; 27: 535-42.
38. Jensen T, Deckert T. Diabetic retinopathy, nephropathy and neuropathy. Generalized vascular damage in insulin-dependent diabetic patients. Horm Metab Res Suppl. 1992; 26: 68-70.
39. Dowse GK, Humphrey AR, Collins VR, Plehwe W, Gareeboo H, Fareed D, Hemraj F, Taylor HR, Tuomilehto J, Alberti KG, Zimmet PZ.Prevalence and risk factors for diabetic retinopathy in the multiethnic population of Mauritius. Am J Epidemiol. 1998 Mar 1; 147 (5): 448-57.
40. Collins VR, Dowse GK, Plehwe WE, *et al.* High prevalence of diabetic retinopathy and nephropathy in Polynesians of Western Samoa. Diabetes Care 1995; 18: 1140-9.
41. Gall MA, Rossing P, Skott P, *et al.* Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy, and large vessel disease in European type 2 (non-insulin dependent) diabetic patients. Diabetologia 1991; 34: 655-61.